

Textbook of Small Animal
Emergency Medicine

1st ed.

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Textbook of Small Animal Emergency Medicine

Volume 1

Edited by **Kenneth J. Drobatz, Kate Hopper,
Elizabeth Rozanski, and Deborah C. Silverstein**



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Drobatz • Hopper • Rozanski • Silverstein



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Textbook of Small Animal Emergency Medicine

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2 VOLUME-SET

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This edition first published 2019
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John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA

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Library of Congress Cataloging-in-Publication Data

Names: Drobatz, Kenneth J., editor. | Hopper, Kate, editor. | Rozanski, Elizabeth A., editor. | Silverstein, Deborah C., editor.

Title: Textbook of small animal emergency medicine / edited by Kenneth J. Drobatz, Kate Hopper, Elizabeth Rozanski, Deborah C. Silverstein.

Description: Hoboken, NJ : Wiley, 2019. | Includes bibliographical references and index.

Identifiers: LCCN 2018002995 (print) | LCCN 2018004342 (ebook) | ISBN 9781119028949 (pdf) | ISBN 9781119028956 (epub) | ISBN 9781119028932 (cloth)

Subjects: LCSH: Veterinary emergencies--Textbooks. | MESH: Emergencies--veterinary | Pets

Classification: LCC SF778 (ebook) | LCC SF778 .T49 2019 (print) | NLM SF 778 | DDC 636.089/6025 -- dc23

LC record available at <https://lcn.loc.gov/2018002995>

Cover Design: Wiley

Cover Images: (Top) © Jeffrey J Runge DVM, DACVS; (Bottom) © John Donges

Set in 10/12pt Warnock Pro by Aptara Inc., New Delhi, India

Printed and bound in Singapore by Markono Print Media Pte Ltd

10 9 8 7 6 5 4 3 2 1

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Dedication

I would like to dedicate this book to my friend Dave. He was a true friend and was like a brother to me. His influence throughout my life has shaped the person that I am.

Kenneth J. Drobatz

To the animals, students and house officers who teach me something new on a daily basis and have made my career so worthwhile. I will be forever grateful.

Kate Hopper

This book is dedicated to my parents (Chester and Patricia Rozanski) and my sister (Catherine McNamara), for their support and love and to my colleagues in the ECC department at Tufts University who were vital in supporting me during the time and efforts that this book required.

Elizabeth Rozanski

As Franklin D. Roosevelt once said, "I'm not the smartest fellow in the world, but I can sure pick smart colleagues." I would like to dedicate this book to the phenomenal (and smart!) colleagues who co-edited this book, as well as the dedicated and talented contributors who made it possible. I am honored to contribute to such a rewarding profession that is filled with so many inspirational and caring colleagues. In addition, I would like to thank everyone at Wiley, especially Mirjana Misina, for their assistance as well as my family, Stefan, Maxwell and Henry, who put up with my hours at the computer to make this possible!

Deborah Silverstein

Preface

In the early to mid 1980's, the *Journal of Veterinary Emergency and Critical Care* was published once or twice per year with very few manuscripts included. There just simply was not much clinical evidence for veterinary emergency and critical care. There was no emergency specialty and ICU was run mostly by anesthesiologists. This struck me as strange, because when would you really want a specialist? When a life is on the line! Yet, here veterinary medicine was, similar to our MD colleagues years before that, where emergency was filled in mostly by people who were moonlighting and not really specialists in this area.

Now, let's fast-forward to today. *JVECCS* is a highly respected and frequently published clinical journal. The specialty has exploded with 639 diplomates, 69 approved residencies, and 176 residents in training along with numerous specialty internships. There are rigorous standards for veterinary emergency and critical centers. The ACVECC is a financially strong and still rapidly growing college. The IVECCS is one of the most highly attended and respected continuing education meetings in the world. Yet, despite all of this, there is no rigorous, evidence-based emergency medicine textbook. There are numerous excellent clinical emergency manuals but no real formal textbook. Deborah Silverstein's and Kate Hopper's *Small Animal Critical Care* textbook provided a rigorous format of excellent information for practicing in the ICU and has been the "go to" book for many experts practicing ICU medicine. Yet, there is no similarly formatted textbook for emergency medicine.

This frustrated Dr Rozanski and me as we both primarily focus our practice on emergency medicine. We decided to try to fill this gap with this book. Recognizing the great success of Drs. Silverstein and Hopper's textbook, we combined with them to bring this textbook together. I thought that the combination of editors who practice the "front-end" of emergency and critical care with two who practice the "back-end" of emergency and critical care would provide a well-rounded and integrated container of information and hence this book has come to fruition.

When putting this book together, we instructed the authors to provide cutting-edge, evidence-based emergency medicine information and combine that with their anecdotal expertise. We wanted the information to not only be cutting edge but provide physiology and pharmacological principles that are rigorous but clinically relevant. In reading this book cover to cover, I am impressed by what these chapter authors have done. It is truly remarkable and it reflects the rigor and high standards that this specialty has developed. I cannot thank them enough for their conscientious efforts, time, and energy. All of us editors are extremely grateful.

This book will provide you with a wealth of useful clinical information backed by clinical evidence and sound pathophysiological reasoning. Being my passion, I feel this area of veterinary medicine deserves nothing less.

Ken Drobatz
February 2018

About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/drobatz/textbook

The website includes:

- PowerPoints of all figures from the book for downloading
- Video clips
- Additional figures that do not appear in the printed book

Section 1

Emergency Medicine Overview

1

Goals in Veterinary Emergency Medicine

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The 40-Year Evolution of Goals in Veterinary Emergency Medicine

The Patient

Progress in meeting the needs of the veterinary patient in an emergent care scenario has been exponential when we compare the last four decades.

In the late 1970s and early 1980s, with the advent of the first independently owned and staffed after-hours facilities, the level of patient care was enhanced greatly simply by the dedicated overnight presence of doctors and technicians performing triage and hands-on monitoring on behalf of the local practices. Pain management rose to the level of recognition and was ministered to with repeated doses of butorphanol. Sophisticated point-of-care testing involved the human eyeballing of azostix and ketodiestrips. A single-channel paper recorder for ECG tracing and evaluation represented state-of-the-art vital sign monitoring. The creation of radiographs required a hazardous materials license and diagnostic ultrasound had just been “discovered.” Ventilators came from the mothballed basements of hospitals and were (for) the Birds. Transfusion medicine involved the science of grabbing the nearest hospital cat walking by, type B ... say what? Titrating fluid therapy to the needs of the patient depended on applying the computer-generated algorithm of being able to count drops and multiply by 4 – “Say, anybody here remember how many drops per milliliter with a microdrip administration set?” And no ACVECC veterinary specialists or AVECCT VTSS to be found ... just a gleam in their mother’s (Becky Kirby) and father’s (Wayne Wingfield) eye, respectively.

Fast-forward to our current 21st-century world of dedicated 24/7 ER facilities staffed by seasoned emergency doctors working side by side with board-certified veterinary emergency and critical care specialists and veterinary technician specialists! Point-of-care testing can provide virtually instantaneous assessment of essential coagulation functions and serial measurements of critical parameters

including ionized calcium and lactate using microliter instead of milliliter samples. Syringe pumps are loaded with acronymic cocktails of analgesics such as MLK (morphine/lidocaine/ketamine) and patients are maintained on transdermal patches of fentanyl for longer term continuous pain management. Lipid emulsion infusions are utilized in the treatment of many acute toxicities and drug overdoses. Commercial veterinary blood banks provide immediate access to a variety of blood components, allowing tailored approaches for the patient requiring transfusion therapy. A-Fast and T-Fast ultrasound studies are performed routinely as triage tools in the busy emergency room. Transcutaneous monitoring of oxygen saturation and indirect blood pressure measurement have become required assessment tools in the triage of critically injured and ill patients presented for evaluation and treatment. Telemetry monitoring of heart rate and rhythm makes for more comfortable patients and increased efficiency of staff in monitoring multiple patients simultaneously. Constant-rate infusions of norepinephrine and vasopressin are used to stabilize patients following resuscitation from cardiac arrest and the effectiveness of cardiopulmonary resuscitation (CPR) is gauged by measurement of end-tidal CO₂ instead of fumbling to palpate the presence of femoral pulses. The practice of and approach to CPR as well as its instruction have been standardized for small animal veterinary patients through the RECOVER initiative. There is a multicenter trauma registry and project under way to codify our best practices for managing the injured patient. And the evolution continues ...

The Client and the Team

Just as the goals and capabilities for care of the patient have been sharpened over time in the veterinary emergency room, the expectations of the clients attached to those patients have also come into greater focus. Gone are the times when clients were simply happy to have you open for business and available for them in the after-hours

when their family veterinarian had gone home for the day. The care of the traumatized client has become increasingly important as a critical goal in the busy emergency center, especially as the costs of the sophisticated care have increased dramatically. Clients are often confronted with life and death choices for their beloved pets that involve the potential expenditure of hundreds if not a few thousand dollars over a matter of mere hours in situations of grave uncertainty with regard to prognosis.

The proper handling of these situations by the veterinary emergency team with appropriate empathy and communication skill often determines the satisfaction of the client experience to a greater extent than does the outcome associated with the medical management of the patient. The veterinarians and staff delivering services in the emergent situation need to be properly trained and engaged to ensure that the expectations of clients are properly ascertained and managed with no medical or financial surprises. Clients need to see, through behind-the-scenes tours and detailed communication, the sophistication and value of the care being provided to their pets. To maximize the client experience, veterinary emergency healthcare providers need to attend to details such as minimizing client wait times, being careful not to predetermine client choices (“x-raying the wallet”), communicating frequently and fluently in situations of great angst when patient dynamics are labile, delivering bad news in understandable terms and with empathy, and ensuring that the euthanasia experience, when necessary, is handled with great compassion and patience.

The excellence required in the delivery of patient care and the client experience in the realm of veterinary emergency medicine in the 21st century puts significant strain on veterinary healthcare personnel. The constant medical, psychological, and interpersonal stressors of the daily grind in the ER necessitate recognition and proactive action by hospital leaders. These leaders need to adopt a nurturing approach toward the team on several levels, including implementation of proven processes for all to follow that ensure efficiency, quality of care, teamwork, and excellence in client service. Ongoing training to ensure development of communication skills, combating of compassion fatigue and opportunities for advancement of team members are crucial to the successful delivery of today’s veterinary emergency care.

Principles of Primary Survey, Resuscitation, Secondary Survey and Definitive or Refined Diagnostics and Treatment of Veterinary Emergency Patients

From primary care clinics to large multidisciplinary referral practices, no veterinary hospital is immune to the need

for providing emergency veterinary care. The diagnosis and treatment of unforeseen illness or injury may occur after giving a routine vaccine or during an anesthetic procedure or a client may present with an acutely ill or injured pet. Each practice has different abilities (staffing, equipment, experience, etc.) to handle emergencies and the veterinary practice should outline its abilities as an emergency hospital to its clients and the public.

Organization and preparation are paramount in providing prompt and appropriate emergency care regardless of clinical setting. Every hospital should have established guidelines and trained personnel for telephone and in-hospital triage. Contact with the client often occurs prior to the patient arriving at the hospital and it is important to determine the nature and urgency of the pet’s problem and provide appropriate advice. It is also important to realize that most clients do not have the knowledge or training to accurately assess or describe a pet’s condition and all patients with potential emergency conditions should be evaluated by a veterinarian. Patients with traumatic injuries, seizures, difficulty breathing, or inability to rise must be seen by a veterinarian without hesitation.

In-hospital triage is used to identify and prioritize a patient’s need for immediate care. The ABCDEs are a reasonable systematic approach to this primary survey. This approach evaluates a patient’s airway, breathing, circulation, (dysfunction of the) central nervous system and (rapid whole-body) examination to identify patients that require life-saving emergent treatment. Following emergent stabilization, a complete physical examination (secondary survey) is then performed by the veterinarian (see Chapter 3).

Every practice should have rapid access to the basic supplies needed to support patient airway, breathing, and circulation. Emergency patients commonly need oxygen supplementation that can be delivered by several means: rigid mask, commercially available oxygen hoods, plastic wrap-covered Elizabethan collars, or nasal catheter/prongs. A laryngoscope with multiple blade sizes and multiple sized endotracheal tubes along with bulb syringes or a medical vacuum for airway suctioning should be available to establish and maintain a patent airway. Lidocaine instilled into a cat’s larynx will aid in preventing laryngospasm should intubation be required in that species. A stylet can be used to help with difficult intubations. Temporary tracheostomy packs should also be available in case intubation is not possible. The ability to provide positive pressure ventilation via bag valve devices, anesthesia circuits and/or mechanical ventilator should also be available for apneic or hypoventilatory patients. Pleural space disease often compromises a patient’s ability to oxygenate and ventilate effectively and

rapid identification and evacuation of the pleural space are required in these patients. Equipment for thoracocentesis should be readily available in prearranged kits including butterfly needles, extension tubing, syringes, and three-way stopcocks as these pleural conditions are life threatening.

The ability to gain rapid peripheral intravenous (IV) access is a paramount requirement in patients presenting to the ER. Intravenous access is required to maintain or re-establish effective circulating volume, safely and effectively administer medications and in some cases to rapidly transfuse blood products. Gaining peripheral venous access may be difficult in some patients (e.g. neonates, severely hypovolemic pets) and other means of venous access may be necessary such as intraosseous or jugular catheterization via cut-down procedure.

The primary patient care-related goal in the emergent setting is to promptly identify life-threatening conditions such as shock so timely, life-saving decisions on patient care can be made. It is important to serially monitor and record patient vitals and keep in mind your endpoints of resuscitation to help guide treatment. Additionally, eliminating ongoing active hemorrhage or seizures should be

among the first goals in emergency treatment. Secondary goals, that follow quickly, in concert with circulatory stabilization, include optimizing oxygenation, ventilation, electrolyte and acid–base status, pain management, and developing an appropriate definitive diagnostic and treatment plan.

It is important to note that in some instances, the primary goal may not be to normalize vital circulatory parameters, for example hypotensive resuscitation strategies in hemorrhagic shock due to internal bleeding. In humans, hypotensive resuscitation strategies reduce coagulopathies and the transfusion requirement in trauma patients with hemorrhagic shock [1]. Commonly used hemodynamic targets used during resuscitation include heart rate, blood pressure, pulse quality, mucous membrane color, and central venous pressure (CVP). Calculating shock index (HR/SBP) may also be a helpful triage tool in determining if patients are in shock [2]. Global markers of oxygenation should be used during resuscitation and include lactate, base deficit, central venous oxygen saturation ($S_{cv}O_2$) or mixed venous saturation (S_vO_2). Specific goals for initial therapy have been outlined for several conditions, most notably severe sepsis and septic shock with the Surviving Sepsis campaign [3].

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2

Triage

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Introduction

Emergency patients present with a wide range of problems and while some “emergencies” exhibit more or less stable vital signs, many cases are true emergencies requiring immediate action. In these latter cases, it is extremely important that the life-threatening problems are detected and treated as quickly as possible since animals with unstable vital signs often have no further compensatory reserves.

Busy emergency clinics must have a protocol for identifying critical patients in order to follow the fundamentals of emergency medicine: “*Treat the most life-threatening problem and the most critical patient first.*”

The concept that allows the differentiation between stable and critically ill patients is called triage. Triage is a system that originated during World War I to allow sorting of emergent patients according to their need for medical care [1]. It is derived from the French word *trier* which means “to sort.” Triage has become common in both human and veterinary emergency medicine.

In veterinary medicine, triage may be carried out at three different levels.

- On the phone with the owner, when, based on history and clinical signs, it must be decided whether the patient needs to be seen immediately or if a later appointment may be sufficient (*telephone triage*).
- In the waiting room, in order to decide whether the patient needs to be immediately stabilized or if the animal can wait for a short time (*waiting room triage*).
- During physical examination of the patient, in order to decide which problem is the most life-threatening and should therefore be addressed first (*primary survey, ABC*).

Telephone Triage

The definition of an emergency can vary greatly between the veterinarian and pet owner and not all problems must

be seen immediately. Small practices or very busy emergency clinics may not have the capability to see and treat all potential emergency patients immediately, requiring a system that allows them to identify if a patient is suffering from a serious problem that requires immediate care.

An emergency patient is defined as one exhibiting clinical signs that require immediate action in order to maintain life [2]. It is important to remember that some clinical situations and problems are not immediately life-threatening but may become so with time or under certain circumstances.

Table 2.1 summarizes the most important emergency scenarios reported by owners and their urgency. Using lists like Table 2.1 means that the owner is specifically asked about the symptoms that require an immediate consultation.

If an animal cannot be seen immediately, the owner is advised to closely observe the animal. If any additional problems occur or the patient deteriorates, the owner is advised to report those changes immediately.

Specific questions that should be posed during telephone triage are summarized in Table 2.2. Depending on the primary complaint, more specific questions are required. Knowledge of the most common clinical signs and possible complications seen with specific diseases are presumed for the staff involved in telephone triage.

First Aid and Transport

Once the pet owner agrees to bring in their animal for medical care, they are instructed where to find the clinic and what to bring (medical record, medications). They may also be instructed on how to transport and handle the patient. The owners are told how to place a muzzle on painful dogs or wrap scared or painful cats carefully in a towel. Emergency patients should be cautiously manipulated and, depending on the nature of the problem, be kept as quiet and immobile as possible (due to possible fractures) or restrained as little as possible (respiratory

Table 2.1 Telephone triage.

Triage level	Conditions
Immediate consultation recommended	<ul style="list-style-type: none"> • Apparent respiratory distress • Respiratory arrest or agonal breathing • Choking • Inhaled/aspirated foreign body • Cyanosis • Pale or white mucous membranes • Collapse, lateral recumbency • Loss of consciousness • Status epilepticus • Heavy bleeding • Distinct pain • Distended abdomen, retching, unproductive vomiting • Electric shock • Burns • Heat stroke • Acute poisoning
Consultation as soon as possible (within the next 1–2 hours)	<ul style="list-style-type: none"> • Foreign body in the throat without shortness of breath • Seizures • Painful animals • Paralysis/paraplegia • Severe vomiting or diarrhea, hematemesis, hematochezia • Trauma patients • Stranguria • Hemorrhagic vaginal discharge (exclude heat) • Acute deterioration of any problem • Loss of appetite in combination with lethargy • Ophthalmological abnormalities • Injuries, abscesses, bite wounds, fractures • Self-mutilation • Temperature $>39.5^{\circ}\text{C}$ (103.1°F) or $<36.5^{\circ}\text{C}$ (97.7°F)

distress). Cats should be transported in a transport cage, a box with air holes or wrapped in a cloth (contraindicated with respiratory distress) if no box is available.

In trauma patients, the owner may have already instituted first aid measures. Heavy bleeding can be stopped with a pressure bandage. Large open wounds should be covered with a clean cloth. Non-ambulatory trauma patients should be manipulated very carefully and secured in a lateral position. Penetrating objects should not ever be removed (see Chapter 189), but it must be ensured that the object will not penetrate further or cause additional injury during transport.

Following determination of the approximate arrival time, the emergency team is notified and the necessary preparations are made.

Waiting Room Triage

If possible, emergency patients are immediately examined upon arrival. If several emergencies are arriving at the same time or an emergency interrupts full consultation, then classic triage is applied. This involves identification of the most critical patients, that is, those with life-threatening problems, and among them, the one having the *most severe* life-threatening abnormalities. Therefore, in the emergency room, patients are seen based on their medical urgency rather than on a “first come, first served” basis.

Waiting room triage is common in human hospitals and becomes more and more important in veterinary emergency clinics as the increasing number of emergency patients causes waiting times for those with minor problems. Performing triage intuitively and without specific guidelines may lead to inconsistencies in triage decisions [3,4]. These problems have led to the development of human triage systems in combination with triage training programs. Several triage systems exist, with the Manchester Triage System (MTS) being most often used [5–8]. The MTS is based on clinical symptoms rather than diagnoses and is color coded. Each color is assigned a urgency level and maximal waiting time: red (immediate), orange (very urgent), yellow (urgent), green (standard), and blue (non-urgent) [5].

While triage systems are widely used in human medicine [1], they are not fully implemented in veterinary medicine even though several approaches exist [4,9,10]. Ruys et al. composed a list of veterinary triage discriminators and compiled a veterinary triage list with five categories based on the MTS [4]. Patients in the red category should be seen immediately, while patients triaged as orange, yellow or green have targeted waiting times of a maximum of 15, 60, and 120 minutes, respectively [4]. Patients in category blue are considered non-urgent and may have to wait for several hours if patients with more urgent triage discriminators present.

A short physical exam assessing the breathing (respiratory rate and effort), perfusion parameters (heart rate, pulse quality, mucous membrane color, capillary filling time), level of consciousness, and temperature, in addition to identifying any life-threatening injuries such as spinal fractures, arterial bleeding or open body cavities, is essential for the recognition of emergent patients. Animals with the following symptoms should be placed into the red and orange categories and therefore should be brought immediately to the emergency room for stabilization [4].

- Respiratory arrest, cardiac arrest
- Respiratory distress
- Loss of consciousness, stupor, lateral recumbency
- Status epilepticus, cluster seizures
- Decompensated shock

Table 2.2 Telephone triage questions.

Question	Possible additional questions	Action
Name and phone number of the pet owner?	Address if not a previous client	Prepare/find medical record
Signalment of the animal? Name, age, sex, breed, weight		
Main presenting complaint?	Beginning of the signs? Did signs become more severe? See also questions for specific complaints below	Life-threatening signs such as shortness of breath, loss of consciousness, massive bleeding, status epilepticus require immediate consultation. Owners should be asked to bring their pet in immediately
Vital signs of the animal?	Is the animal standing? Responding? If possible: heart rate and mucous membrane color? Any signs of bleeding? If bleeding, pulsatile or steady bleeding?	Coma, status epilepticus, white mucous membranes require immediate consultation. Trauma patients should be transported carefully
How is the animal breathing?	Respiratory distress? Cyanosis? Cough?	Patients with respiratory distress or cyanosis should be seen immediately. Patients with dyspnea should be allowed to choose their position and should not be confined
Pretreatment and medical history?	Is the animal receiving any therapy/medications? What medications and dosages were given?	Owner should bring package of any administered medications. Owner should bring the patient's record if available
General condition of the animal?	Any vomiting or diarrhea? Distended or painful abdomen? Can the animal urinate?	

- White, cyanotic, or severely hyperemic mucous membranes
- Bradycardia (cat <120, dog <40–60/min)
- Tachycardia (cat >240, dog >180)
- Irregular hearth rhythm
- Arterial hemorrhage
- Perforated or open body cavities
- Distended abdomen
- Hyperthermia >41 °C or history of heat stroke
- Hypothermia <36.7 °C
- Stranguria with enlarged and hard bladder (suggestive of urethral obstruction)
- Dystocia with extruding fetal parts
- Acute poisoning
- Snake bites
- Burns, chemical injury

In cases of doubt, the animal is brought to the treatment room and examined thoroughly.

Investigation and Stabilization of the Patient

The successful approach to emergency patients requires knowledge of the (patho)physiological fundamentals,

general stabilization measures, life-saving emergency procedures, and, last but not least, the ability to remain calm in stressful situations. It is extremely important to maintain an overview of the situation, especially during busy and sometimes chaotic emergency hours. A routine approach to the emergency patient, for example following the ABCD, allows rapid identification and stabilization of life-threatening problems.

During the initial minutes of presentation, the pertinent history, physical examination results, and preliminary diagnostic results should be processed simultaneously in order to gain all important information for successful stabilization. This simultaneous evaluation is called the *primary survey* and follows the *ABCD*: Airway, Breathing, Circulation, Disabilities. Compliance with the ABCD is useful in all kinds of emergencies and serves to concentrate on less distinct but potentially life-threatening problems while decreasing the risk of distraction by striking but non-lethal injuries.

History

Obtaining the medical history focuses on information pertinent to the presenting complaint and needs to be adjusted depending on the problem list. General information to be obtained from the owner of any emergency

patient includes signalment, primary problem/clinical signs of the animal, onset of symptoms, progression of symptoms, treatment prior to presentation, and pre-existing disorders.

Emergency Physical Examination

The emergency physical examination aims at rapidly evaluating the respiratory tract, circulation, central nervous system, and abdomen and is *not* a complete physical exam. A routine approach is highly recommended, either following the ABCs or beginning at the nose and ending with measuring the rectal temperature.

- Respiratory rate, type, noise
- Presence and type of respiratory abnormalities
- Lung auscultation
- Heart auscultation with simultaneous assessment of pulse
- Mucous membrane color, capillary filling time
- Rectal temperature
- Level of consciousness
- If non-ambulatory: cranial nerves, motor activity, spinal reflexes

- Short abdominal palpation
- External injuries

Emergency patients with apparent respiratory distress should receive supplemental oxygen by mask or flow-by and the physical examination should concentrate on the respiratory system, without additional stressful procedures such as abdominal palpation or measurement of rectal temperature [11].

The third level of triage takes place during the initial examination of the emergency patient when several problems must be prioritized for stabilization. The abnormal parameters are listed and addressed according to priority. Emergent patients with acute, life-threatening problems such as airway obstruction, anaphylaxis, terminal shock or coma can die within seconds if they are not immediately stabilized. Patients with additional abnormal vital parameters also require immediate stabilization, but slightly more time may be available to compose a stabilization strategy. The further management of the emergent patient therefore concentrates on the immediate stabilization of life-threatening problems and obtaining further information by means of targeted diagnostic tests (Table 2.3).

Table 2.3 Stabilization of life-threatening problems.

ABC	Problem	Emergency measure	Emergency diagnostics	Additional information
Airway/ breathing	Respiratory arrest	Intubation, mechanical ventilation with 100% O ₂ , CPR	ECG, ETCO ₂	Chapter 151
	Inspiratory dyspnea, upper respiratory airway stenosis	Remove any foreign bodies Intubation – if this is not possible, tracheotomy		Chapter 32
	Dyspnea	O ₂ , rest, analgesia	Localization of the problem for the purpose of specific stabilization measures	Chapter 4
	Paradoxical breathing, decreased lung sounds	Thoracocentesis		Chapters 44–46
Loss of consciousness	Coma	Intubation, O ₂	Glucose, HCT, electrolytes, acid–base status, ammonia	Chapter 20
	Status epilepticus	Antiepileptic therapy	Glucose, calcium, sodium, ammonia, urine toxin screen	Chapter 21
Circulation	Decompensated shock	O ₂ IV catheter Crystalloid +/- colloid bolus Analgesia	HCT, TP, lactate, ECG	Chapters 152–155
	Arterial hemorrhage	Pressure bandage Shock therapy Analgesia	HCT, TP, lactate	Chapters 167–170, 190
	Cardiac arrest	CPR, intubation, mechanical ventilation with 100% O ₂	ECG, ETCO ₂	Chapter 150

CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; ETCO₂, partial pressure of carbon dioxide; HCT, hematocrit; IV, intravenous; TP, total protein.

Emergency Stabilization

Maintaining adequate oxygen delivery to the vital organs is the principal goal of stabilization and also follows the ABCs: airway, breathing, circulation. Compliance with this order is important while taking into account the severity of the abnormality (e.g. tachypnea is less

severe than severe arterial hemorrhage even though B comes before C). The reader is referred to the appropriate chapters for more specific details. Table 2.3 briefly summarizes the most important life-saving emergency measures.

Following stabilization, a thorough physical examination should be performed.

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Section 2

Common Conditions in Emergency Medicine

3

Neurological Disorders

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Initial Management of the Acute Neurological Patient

When presented with a patient with obvious neurological abnormalities, it is important to remember the basic principles of emergency stabilization. A 10–15-second airway-breathing exam to rule out cardiopulmonary arrest (CPA) should be done first in any patient that is recumbent and unresponsive (see Chapter 150). Once CPA has been ruled out, a 1–2-minute primary survey targeted at identifying imminently life-threatening respiratory, cardiovascular or neurological abnormalities should be the next priority (see Chapter 2). Once these life-threatening issues have been identified and addressed, a full neurological assessment can be undertaken. Diagnosis and treatment of a range of common neurological emergencies are covered in Chapters 20–27. This chapter will focus on initial assessment and neuroanatomic localization in small animal patients with acute neurological disorders.

Neuroanatomic Localization

The emergency neurological exam is focused on rapidly localizing the source of neurological deficits, which will facilitate development of a complete differential diagnosis list and aid in the construction of diagnostic and therapeutic plans. Localization to one of 11 anatomic structures is the goal. Table 3.1 summarizes these 11 localizations.

Initial Assessment

The primary goal of the emergency neurological exam is to identify all acute neurological deficits and obtain a neuroanatomic localization. Once the lesion has been

Table 3.1 Neuroanatomic localizations.

Brain/cranial	Spinal cord segments	Peripheral
Forebrain	Cranial cervical: C1–C5	Peripheral nerve
Cerebellum	Cervical intumescence: C6–T2	Neuromuscular junction
Brainstem	Thoracolumbar: T3–L3	Muscle
Vestibular	Lumbar intumescence: L4–S3	

localized, the clinician can consider a prioritized differential diagnosis list and formulate an initial diagnostic and therapeutic plan.

A neuroanatomic localization is only possible after a complete neurological exam has been done. A full examination should include evaluations of level of consciousness, posture and body position, abnormal movements, ambulation and gait, and cranial nerves. The exam must be tailored to the patient, with care taken to prevent inducing additional injury. Patients with neurotrauma should be carefully assessed for evidence of unstable skull or spinal column fractures in which manipulation for assessment could lead to further injury (see Chapters 19 and 24).

The following is a brief review of the components and interpretation of the neurological exam. There are several recent textbooks with more thorough descriptions that the reader inexperienced in neurological examinations may consult [1–3].

Consciousness

Evaluation and documentation of a patient's level of consciousness must be meticulous in order to identify progression of signs during treatment. Patients that are unconscious and are not responsive to any stimulus, including painful

stimuli, are considered comatose and require aggressive stabilization to support the forebrain. Patients that are unconscious and are rousable only with painful stimuli (such as a hemostat clamped across a digit) are stuporous, while unconscious patients that respond to non-painful stimuli such as loudly clapping hands or vigorous shaking are obtunded. Inconsistent terminology (e.g. depressed, disoriented) has been used to describe patients that are conscious but are not as interactive or engaged as would be expected in a busy emergency room setting.

Posture and Body Position

Careful attention should be paid to posture and body position on the initial examination. The presence of a *head tilt* (rotation along the axis of the neck, indicative of vestibular disease), *head turn* (turning of the nose to one side, indicative of a forebrain lesion) or a *wide-based stance* (indicative of bilateral vestibular disease or cerebellar disease) should be noted. Patients in lateral recumbency may demonstrate a number of abnormal postures that must be correctly identified and differentiated, including *Schiff–Scherrington* posture (rigid extension of the thoracic limbs and neck with variable pelvic limb changes while the patient is in lateral recumbency consistent with a T3–L3 myelopathy), *decerebellate rigidity* (rigid extension of the thoracic limbs with relaxed pelvic limbs in all positions consistent with cerebellar injury; mentation is typically normal), and *decerebrate rigidity* (rigid extension of thoracic and pelvic limbs as well as the neck consistent with severe brainstem disease; mentation is typically abnormal). Persistent cervical ventroflexion may be a sign of metabolic disease, such as severe hypokalemia, while cats with dropped hocks may have diabetes mellitus and an associated peripheral neuropathy.

Abnormal Movements

Unexpected, repetitive, or abnormal movements should be noted and characterized. Myoclonus is a rapid contraction of a muscle group followed by immediate relaxation, and will look like a muscle jerk. Repetitive, generalized myoclonus may be seen in patients with tremor disorders (in which mentation remains largely normal) or in patients with generalized seizures (in which mentation is usually abnormal). In either case, these patients are at risk of life-threatening hyperthermia (see Chapter 147) and, in the case of seizures, secondary brain injury (see Chapter 21).

Ambulation and Gait

In all cases, the ability of the patient to ambulate should be evaluated as soon as possible after initial stabilization.

Cats stressed in the hospital will often not walk, so if the patient has normal mentation and is stable, place the cat on the floor in an enclosed room to evaluate ambulation. Fully observe voluntary motor function, proprioception and reflexes in each limb as well as the overall appearance of the gait.

Paresis is the presence of decreased voluntary motor function, while paralysis or plegia is the absence of voluntary motor function. The presence of paresis or plegia is rarely caused by forebrain lesions, and is most commonly associated with brainstem or spinal cord lesions. Care must be taken to differentiate involuntary motor function (such as exaggerated reflex activity stimulated by manipulation of the paws or limbs) from voluntary motor function. In smaller dogs and cats with normal thoracic limb function but significant pelvic limb deficits, “tail walking” can be used to evaluate motor function in the pelvic limbs. The patient’s hindlimbs are supported by holding the tail up and the patient is encouraged to walk on the thoracic limbs. The pelvic limbs are closely inspected while the patient walks for any evidence of voluntary movement. In larger dogs, supporting the patient under the pelvis or using a sling can accomplish the same goal, but this approach may make the assessment more challenging to interpret. In patients affected in all four limbs, the entire body may need to be supported directly or using two slings.

In ambulatory patients, the gait should be closely evaluated for evidence of crossing over of the limbs, especially while turning, or for uncoordinated movements. These movements are termed *ataxia* and indicate cerebellar, vestibular, or spinal cord localizations. Exaggerated movements, such as hypermetria in the limbs while walking or intention tremors while eating or drinking, are indicative of cerebellar disease. Circling while walking is a sign of intracranial disease, and the direction of the circling is generally towards the side of the lesion. Patients walking in very tight circles most commonly have vestibular disease, while those walking in wide circles with wall hugging most commonly have forebrain disease.

Postural reactions should be evaluated in all four limbs to identify deficits in conscious proprioception. Paw placement and hopping are most commonly used to assess proprioception in dogs, while cats are more challenging to assess and generally more consistently show deficits with the tactile placing test. When assessing tactile placing, it is important that the patient’s eyes are covered to ensure that proprioception and not vision is being assessed. The ascending sensory pathways, including the limbs, spinal cord, brainstem and thalamus, to sensorimotor cortex as well as the descending pathways through the spinal

cord to the effector muscles must be intact. Lesions in any of these pathways will lead to deficits in postural reactions.

Finally, spinal reflexes should be assessed in each limb and graded as normal, increased, decreased, or absent. The most reliable reflexes are the withdrawal reflex (which should be tested in all four limbs) and the patellar reflex. Note that in older dogs, the patellar reflex may be decreased in strength in the absence of acute neurological disease, so interpretation of deficits in this reflex in the absence of any other neurological deficits should be undertaken with caution. Additional reflexes that may be tested include: (1) thoracic limb – extensor carpi radialis, triceps; (2) pelvic limb – cranial tibial, quadriceps.

Cranial Nerves

A complete cranial nerve exam will aid in localization of lesions to the brainstem or vestibular system. Because brainstem lesions may also affect posture and gait, identification of cranial nerve deficits may help differentiate intracranial disease from spinal cord disease. Readers needing a more complete description of the cranial nerve examination are encouraged to refer to any of several recent, very thorough textbook chapters on this subject [1–3]. Table 3.2 contains a summary of neurological examination abnormalities and the associated cranial nerves.

Neurolocalization

Once all abnormalities on the neurological exam are identified, the most likely location of the lesion can be determined. This will be critical for the next steps, which include generating a list of differential diagnoses and formulating diagnostic and therapeutic plans. Table 3.3 summarizes the possible neurological exam findings in patients with various neuroanatomic localizations. It is important to remember that, depending upon the severity of the lesion, patients may not demonstrate all the abnormalities associated with a specific neuroanatomic localization. When evaluating the results of the neurological exam, the goal is to examine the pattern of abnormalities and identify the most likely neuroanatomic localization.

Approach to Differential Diagnoses

When dealing with a patient with acute neurological abnormalities, a systematic approach to differential diagnoses, which will ultimately guide the diagnostic

Table 3.2 Neurological exam findings associated with individual cranial nerve disorders.

Cranial nerve(s)	Exam findings
I. Olfactory	Loss of smell, challenging to assess clinically
II. Optic	Loss of vision, absent pupillary light response (PLR)
III. Oculomotor	Abnormal eye movements, absent PLR
IV. Trochlear	Rotary strabismus
V. Trigeminal	Absent palpebral reflex and facial sensation Masseter/temporal muscle atrophy Enophthalmos (pterygoid muscle paralysis)
VI. Abducens	Absent globe retraction (paralysis of retractor bulbi muscle) Medial strabismus (paralysis of lateral rectus muscle)
VII. Facial	Lip droop and/or facial droop Absent menace response and palpebral reflex
VIII. Vestibulocochlear	Head tilt, nystagmus, strabismus Ataxia, walking in tight circles, leaning Deafness
IX. Glossopharyngeal	Absent gag reflex
X. Vagus	Dysphagia
XI. Spinal accessory	Laryngeal paralysis Megaesophagus
XII. Hypoglossal	Dysphagia Unilateral tongue atrophy and/or deviation of the tongue

and therapeutic plans, is essential. Differential diagnoses and diagnostic and therapeutic plans for the most common neurological emergencies are presented in Chapters 20–27. The author recommends the use of the DAMNIT-V mnemonic to ensure that all categories of differentials are considered in each case, even if some specific differentials are missed. Table 3.4 enumerates the categories in this scheme and lists examples of differential diagnoses for neurological diseases in each category. This is not meant to be an exhaustive list, but to provide the reader with a framework for generating a differential diagnosis list once a neuroanatomic localization has been determined for a given patient.

Table 3.3 Neurological exam abnormality patterns for the major neurolocalizations. Bear in mind that all abnormalities do not need to be present in every patient.

Localization	Consciousness	Posture and body position	Ambulation and gait	Abnormal movements	Cranial nerves
Brain/cranial					
Forebrain	Abnormal	Decerebrate rigidity Head turn	Wide circling Proprioceptive deficits	Seizures	+/-
Cerebellum	Normal	Decerebellate rigidity	Tight circling Proprioceptive deficits	Hypermetria Intention tremors	Absent menace Anisocoria
Brainstem	Abnormal	Decerebrate rigidity	Proprioceptive deficits	None	Depends on location of lesion
Central vestibular	Abnormal	Head tilt	Ataxia	Hypermetria	V–XII deficits Nystagmus Strabismus
Peripheral vestibular	Normal	Head tilt	Ataxia	None	VII deficits Nystagmus Strabismus
Spinal cord					
C1–C5	Normal	Normal	Thoracic limbs: proprioceptive deficits. Normal to increased reflexes Pelvic limbs: proprioceptive deficits. Normal to increased reflexes	None	Normal
C6–T2	Normal	Normal	Thoracic limbs: proprioceptive deficits. Reflex deficits Pelvic limbs: proprioceptive deficits. Normal to increased reflexes	None	Normal
T3–L3	Normal	Schiff–Scherrington	Thoracic limbs: normal Pelvic limbs: proprioceptive deficits	None	Normal
L4–S3	Normal	Normal	Thoracic limbs: normal Pelvic limbs: proprioceptive deficits. Reflex deficits	None	Normal
Peripheral					
Peripheral nerve	Normal	Normal	Paresis/paralysis Proprioceptive deficits Reflex deficits	None	Normal
Neuromuscular junction	Normal	Normal	Paresis/paralysis Proprioceptive deficits Reflex deficits Stiff, stilted gait	None	Normal
Muscle	Normal	Normal	Paresis/paralysis Stiff, stilted gait	None	Normal

Table 3.4 DAMNIT-V approach to differential diagnoses for neurological emergencies.

Category	Examples of differential diagnoses
D: Degenerative	Intervertebral disk disease, degenerative myelopathy, storage diseases
A: Anomalous	Congenital malformations
M: Metabolic	Systemic diseases and endocrine diseases that can be associated with neurological abnormalities such as shock, hypothyroidism, diabetes mellitus, hypoglycemia, sodium disturbances, hepatic encephalopathy
N: Neoplasia	Primary nervous system neoplasia and metastatic disease
I: Infectious, Inflammatory, Idiopathic	Bacterial, viral, fungal, and protozoal disease Immune-mediated encephalomyelopathies Idiopathic epilepsy
T: Toxin, Trauma	Neurotoxins such as bromethalin, strychnine, pyrethrins/permethrins, organophosphates Skull fractures, vertebral fractures/luxations, contusion, hematoma, edema
V: Vascular	Fibrocartilagenous embolism, thromboembolic disease, hemorrhage

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4

Respiratory Distress

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Introduction

Respiratory distress represents a true emergency and is a major complaint of animals presenting to the emergency service. Prompt treatment is warranted to attempt to identify the underlying cause, to limit the sensation of difficult breathing and to provide diagnostic and therapeutic information for clients of affected animals. Some forms of respiratory distress are easily treatable or curable, while in others treatment options are much more limited.

For the clinician in emergency practice, success in patient management revolves around developing a knowledge base of potential causes of respiratory distress as well as “pattern recognition” of common emergent problems affecting dogs and cats. Respiratory distress may be further characterized by the location of the lesion or the underlying pathophysiological condition. Often, localization of the lesion can help to guide the clinician to the most likely cause. Specifically, respiratory distress may be localized to upper airway, lower airway, parenchymal or pleural space disease. Common pathophysiological causes for respiratory distress include anatomical abnormalities, airway collapse, pulmonary edema of cardiac and non-cardiac causes, infection, inflammatory, and trauma.

For the emergency clinician, the most appropriate first step is to localize the lesion and then to review specific differentials based upon signalment, history, and other physical examination findings. If equipment is available, ultrasonography is very beneficial in the emergency setting, including evaluation for pleural space disease, and screening assessment of cardiac chambers (see Chapter 182). Specific conditions and procedures are covered in subsequent chapters. Box 4.1 provides a summary of important questions to be used in the assessment of patients with respiratory distress.

Box 4.1 Key questions when evaluating a patient with respiratory distress.

- Does oxygen help?
- Signalment
- Any relevant past medical history?
- What has happened today?
- Is there hyperthermia or hypothermia?
- Is there loud breathing?
- Is there any cough or wheeze?
- Are there extra lung sounds?
- What does T-FAST/ultrasound show you?
- What should I tell the owner?

Does Oxygen Help?

While an understanding of potential causes of respiratory distress is mandatory, the first steps in the clinical evaluation of a patient presenting with respiratory distress are to provide a supplemental source of oxygen and to obtain a brief history from the client.

All emergency facilities should have a form of supplemental oxygen available. Supplemental oxygen may be provided via a variety of options, including flow-by, face mask, nasal oxygen, e-collar and cellophane wrap (“oxygen hood”), oxygen cage and intubation with intermittent positive pressure ventilation (IPPV) (see Chapter 181). Intubation and IPPV is the best option for providing high levels of supplemental oxygen, removing respiratory fatigue, and eliminating patient fear and anxiety although due to staffing demands, financial and emotional factors, it should not be undertaken lightly.

While supplemental oxygen is often helpful for all causes, most benefit is seen with parenchymal disease. Animals with pleural space disease benefit more from thoracocentesis, and animals with upper airway

obstruction benefit from sedation and/or intubation. Animals should not be placed on oxygen for more than a few minutes without being assessed for effusion or upper airway obstruction, as treatment of either of these is more beneficial than simple oxygen therapy.

Signalment

As with almost all diseases, signalment may provide useful clues, such as congestive heart failure in Doberman pinschers or upper airway obstruction in brachycephalic breeds. Younger animals are more likely to be affected with trauma or infection, while older animals are more likely to have degenerative or neoplastic diseases.

Any Relevant Past Medical History? What Has Happened Today?

During the initial stabilization of the pet, a history should be obtained from the owner. In some cases, the precipitating cause of the respiratory distress is straightforward, such as with trauma, while in other cases the onset may be more insidious.

On hot or humid days, particularly in early summer, heat stress may result in an increased likelihood of upper airway obstruction. Recent injections of long-acting glucocorticoids may be associated the subsequent development of congestive heart failure in cats [1]. Animals with pre-existing medical conditions, such as cardiac disease, neoplasia or megaesophagus, may also be predisposed to the development of respiratory distress due to progressive disease or aspiration pneumonia. Prior airway surgery or tracheal stents may predispose to later complications. Cats with a history of “hairballs” may have airway disease, and dogs being treated with prednisone or other hypercoagulable conditions may be predisposed to pulmonary thromboembolism.

Additionally, owners should be questioned as to past medical conditions and the patient’s history of routine veterinary care, including heartworm prophylaxis, and finally, the progression of the signs. Specifically, distress may be acute in onset or more progressive. In cats in particular, the development of respiratory distress may be preceded by anorexia, lethargy or abnormal behavior.

Is There Hyperthermia or Hypothermia?

Hyperthermia may be associated with inability to cool, which most commonly affects dogs with upper airway obstruction. Hyperthermia may also represent fever, which is most common with aspiration pneumonia, or,

much less likely, possibly pyothorax. Hypothermia usually represents decompensated shock, and is most often seen in cardiogenic shock in cats [2]. Occasionally, individuals are reluctant to measure rectal temperature in cats with respiratory distress, but in many cases it can provide a vital clue.

Is There Loud Breathing?

Upper airway diseases may be appreciated by loud stridorous or sterterous breathing, with an increased inspiratory time. Many dogs are hyperthermic on initial presentation due to decreased ability to cool as well as increased muscle activity. Upper airway obstructions can be either dynamic or fixed. Common dynamic obstructions include laryngeal paralysis and tracheal collapse, while fixed obstructions include extraluminal obstructions such as neoplasia or cellulitis and intraluminal obstructions such as laryngeal tumors or nasopharyngeal polyps. Both dynamic and fixed severe upper airway obstructions will also result in the development of airway mucosal edema and possibly everted laryngeal sacculles due to irritation from the increased air flow rates through a narrow lumen.

Emergently, upper airway obstruction should be suspected in a dog with loud, noisy breathing. Therapy for a suspected *dynamic* obstruction should include sedation and supplemental oxygen. Sedation is beneficial in the dynamic obstruction in reducing the anxiety associated with inspiration because with increased inspiratory effort, there is a resulting paradoxical decline in airway diameter. Hyperthermia should be treated by active cooling with room temperature intravenous fluids, and by placing the dog in a cool area. Due to airway swelling and edema, a single dose of short-acting anti-inflammatory glucocorticoid is advisable. If the dog has not improved within 15–30 minutes or if distress is worsening, more aggressive therapy is warranted. The dog should be heavily sedated for placement of nasotracheal oxygen or anesthetized and intubated. The emergency clinician should be competent to evaluate airway function and anatomy and to perform a tracheostomy if needed (see Chapter 180). Additionally, as many upper airway conditions require management and/or surgical intervention, the emergency clinician should be fluent in discussions with clients concerning long-term outcomes.

In cats, upper airway obstructions are less common but may be caused by nasopharyngeal polyps or infiltrative laryngeal diseases (neoplasia or granulomatous) [3]. Occasionally cats with severe pleural effusion will have the appearance of severe inspiratory distress; this should be excluded by ultrasonography if possible. If sedation for an oral examination for a cat with a suspected upper

airway obstruction is planned, then supplies should be collected ahead of time for an emergency tracheostomy. The laryngeal lumen of affected cats can be only a millimeter or two in diameter and may require an urgent tracheostomy. If biopsy of a laryngeal mass is performed in a cat, a tracheostomy is almost always required due to subsequent airway swelling.

Is There Any Cough or Wheeze?

Coughing is a response to the irritation of real or perceived foreign material (debris or mucus) within the airways while wheeze represents a high-pitched sound associated with airway narrowing. As a presenting complaint, cough is common in cats with airway disease and in dogs, cough is seen with chronic bronchitis, tracheal collapse and pneumonia, as well as with congestive heart failure (CHF). CHF-associated cough tend to be less productive and more dry. Additionally, dogs with CHF will also have tachypnea. Small breed dogs may have both chronic bronchitis and mitral valve disease. In dogs where CHF is the primary cause, they tend to have louder murmurs, tachycardia, and weight loss, while dogs with chronic bronchitis tend to have soft murmurs and sinus arrhythmia [4]. As CHF is more likely to be fatal than chronic bronchitis, if the underlying disease is unclear, it is better to try to start treatment with furosemide. In all cases of cough, thoracic radiographs will provide very useful information as to the cause of the cough.

Wheezing most often represents airway disease in cats, but laryngeal masses may also result in an audible wheeze. In dogs, wheeze is most commonly tracheal or airway disease.

Are There Extra Lung Sounds?

Auscultation of the thorax may document louder sounds or crackles. Abnormal lung sounds may be easily heard with parenchymal lung disease. It is wise to recall that it may be challenging to hear lung sounds in overconditioned or heavily coated animals or in a loud ER.

Common causes of parenchymal lung disease include pulmonary edema (cardiogenic and non-cardiogenic), pulmonary contusions, pneumonia, and neoplasia. Thoracic radiographs are very useful in determining the cause of the respiratory distress. The distribution of the pulmonary infiltrates may be very useful to help determine the underlying problem. In dogs, cardiogenic pulmonary infiltrates will most often surround the perihilar region, while in cats the distribution of pulmonary edema may vary. Non-cardiogenic pulmonary edema is usually caudal dorsally located. Bacterial pneumonias will typically have a cranioventral

distribution. Neoplasia will usually result in a nodular pattern, although metastatic disease can have variable radiological appearance. Other differentials include interstitial lung disease, thromboembolism, and atypical infections.

Heart failure in cats is usually appreciated by hypothermia combined with an increased respiratory rate and effort. A gallop, murmur, and/or jugular venous distension may be present. Due to the hypothermia, cats with CHF will commonly have slow heart rates (130–140 bpm) [2]. Heart disease in adult dogs is usually either chronic valvular disease or dilated cardiomyopathy. Treatment of heart failure includes furosemide, pimobendan, oxygen, vasodilators, and rate control (see Section 3C, Cardiovascular Disease).

Non-cardiogenic pulmonary edema may occur for a variety of reasons. In the emergency room, upper airway obstruction, seizures, and electric cord injury are common triggers for the development of non-cardiogenic edema (see Chapter 39). Non-cardiogenic pulmonary edema is typically high protein as a result of transient high hydrostatic pressure and/or permeability shifts in the capillaries, rather than purely hydrostatic forces as with cardiogenic edema [5]. There is no specific therapy that has been proven beneficial for hastening recovery from non-cardiogenic edema. The vast majority of dogs with non-cardiogenic pulmonary edema will rapidly improve within 24–48 hours although rare cases will progress to acute respiratory distress syndrome.

Pulmonary contusions are common after traumatic injury, particularly in dogs. Pulmonary contusions are typically straightforward to identify in the ER. Therapy includes rest and oxygen. There is no benefit of antibiotics, corticosteroids or diuretics in the treatment of pulmonary contusions.

Dogs with pneumonia may present with respiratory distress. Bacterial pneumonia is less common in cats. Therapy for pneumonia includes broad-spectrum antibiotics and in some cases physiotherapy, oxygen, and intravenous fluids. Ideally, a bacterial culture is performed prior to the institution of antibiotics but in the ER, antibiotic therapy should not be delayed if a culture cannot be promptly performed. Dogs that have been recently treated with antibiotics (within the last 30 days) are more likely to have multidrug-resistant infection and empirical antibiotic choices should be made with that knowledge.

Animals will infrequently present on emergency with dyspnea due to metastatic disease, although cough and lethargy are also common presenting complaints. Spontaneous pneumothorax may occasionally develop in a patient with pulmonary neoplasia. Treatment of suspected neoplastic disease is directed at supportive care. It is also important to exclude a recent travel history in dogs with a nodular pulmonary pattern as the systemic mycoses can mimic metastatic disease. Other less

common causes of pulmonary infiltrates include eosinophilic pneumonitis and pulmonary fibrosis.

What Does Point-of-Care Ultrasound Show You?

One of the major paradigm shifts in the last 20 years of emergency medicine has been the addition of ultrasound to the toolbox of the ER clinician (see Chapter 182). Ultrasound is very useful for evaluation of the pleural space and cardiac structure and function. Recent advances have also identified the utility of evaluating the lung parenchyma with ultrasound. While complete ultrasound and echocardiographic evaluation require advanced skills, the skills for screening ultrasound may be quickly gained. For animals with respiratory distress, evaluation for pleural effusion

and left atrial enlargement may be quickly performed bed-side and help direct therapy. Thoracocentesis will result in rapid improvement in clinical signs. Samples should be saved for cytological evaluation and bacterial culture if indicated.

What Should I Tell the Owner?

Respiratory distress is a frightening condition for the pet, and also for the owner. In some cases, there is an easy and quick resolution for the problem and in other cases more extensive diagnostics may be required. A systematic approach will improve the outcome. Emergency clinicians should avoid recommending euthanasia without a clear diagnosis as many affected animals will improve and may recover completely or adequately to have a good quality of life.

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5

Ventricular Ectopy

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Introduction

The cardiac conduction system is composed of the sinoatrial (SA) node, the atrioventricular (AV) node, the bundle of His, left and right bundle branches, and the Purkinje fibers. An arrhythmia is any heart rhythm that does not originate from the sinus node at a normal rate and at a regular interval. With respect to ventricular arrhythmia (VA), this originates from an ectopic focus located within the ventricular myocardium and distal to the bifurcation of the bundle of His.

Presentation

Animals experiencing VA can present asymptotically, for weakness, lethargy, collapse or apparent seizure activity. Depending on the frequency of the VA, physical examination can be relatively unremarkable other than occasional pulse deficits and an irregular cardiac rhythm. If the VA is more frequent, the heart rate can be very rapid with weak or absent pulses and the animal can present collapsed in lateral recumbency.

Diagnosis

Although a VA may be suspected based on the history and physical exam findings, an electrocardiogram (ECG) is required for definitive diagnosis. Ventricular premature complexes (VPCs) can occur as isolated complexes during sinus rhythm, as two consecutive VPCs (couplets) or as three consecutive VPCs (triplets). They do not utilize the normal cardiac conduction tissue and instead use muscle-to-muscle cell contact to spread depolarization, thereby slowing conduction velocity and increasing conduction time,

producing the classic “wide and bizarre” appearance of the QRS complex. They are classified as right bundle branch block morphology if there is evidence of a deep S wave in lead II, suggesting that the VPC originated from the left ventricle, or left bundle branch block morphology if the VPC is upright and wide in lead II, suggesting a right ventricular origin. They are further classified as uniform if there is only one morphological appearance of the VPCs or multifocal if there are several morphologies of VPCs present.

Ventricular tachycardia (VT) is defined as three or more consecutive VPCs with a rate exceeding a normal heart rate. The heart rate of animals with VT will be greater than 180 beats/minute in dogs and 240 beats/minute in cats. The rate differentiates VT from accelerated idioventricular rhythm (AIVR) which is a slower rate of continuous ectopic beats originating from the ventricle. However, whereas VT requires treatment, AIVR does not.

Causes

Ventricular arrhythmia can occur from a variety of both non-cardiac and cardiac causes and once diagnosed on an ECG, focus should turn to identifying the underlying cause.

Non-Cardiac Causes

Ventricular arrhythmias are rare in normal animals but common in hospitalized patients and are often associated with trauma, metabolic abnormalities, abdominal organ disease such as masses of the spleen and liver, gastric dilation and volvulus, autonomic imbalances, and systemic disease. Animals under general anesthesia, especially those in which barbiturates have been used, may also experience VA. In general, cats will rarely develop VA from non-cardiac causes.

Figure 5.1 Single lead II ECG of a Doberman pinscher displaying paroxysms of ventricular tachycardia and multiform ventricular premature contractions. The ventricular premature contractions have prominent S waves, indicating a right bundle branch block pattern suggesting a left ventricular origin.



Cardiac Causes

Structural heart disease from either congenital or acquired heart disease, trauma/inflammation, infarction, and neoplasia can all result in VA. VA is commonly associated with dilated cardiomyopathy (DCM) in Doberman pinschers, arrhythmogenic right ventricular cardiomyopathy (ARVC) in boxers and inherited ventricular arrhythmias in young German shepherds (IVAGSD). DCM is classically characterized by chamber dilation and impaired systolic and diastolic function in one or both ventricles. However, in some Dobermans the only abnormality identified may be VA (Figure 5.1). ARVC is a myocardial disease characterized by fibro-fatty replacement in the myocytes and VA but in most cases, the heart is structurally normal on echocardiographic evaluation and the only abnormality identified is the VA (Figure 5.2). In IVAGSD, the affected animal can experience life-threatening VT or ventricular fibrillation (VF) without any prodromal signs. The disease usually begins around 3–6 months of age and will spontaneously dissipate in surviving dogs around 2 years of age.

Although considered a less frequent occurrence, dogs with myxomatous mitral valve disease (MMVD) can also develop VA and this may be more common in dogs with

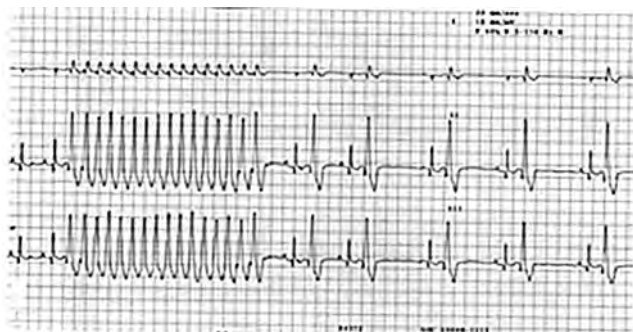


Figure 5.2 Lead I, II, and III ECG of a boxer with paroxysms of ventricular tachycardia followed by ventricular bigeminy. The ventricular premature contractions are wide and upright in lead II, suggesting left bundle branch block pattern indicating a right ventricular origin which is classic for boxer dogs with ARVC.

advanced cardiac remodeling and/or concurrent congestive heart failure.

Treatment

The decision to treat an animal with a VA is based on whether or not the patient is experiencing hemodynamic compromise from the arrhythmia or if the risk of sudden death is high. In general, animals with VT, multiform VA, or severe underlying cardiac disease are at the highest risk for sudden death and thus warrant therapy.

Class I Antiarrhythmics

Lidocaine

In dogs which require treatment for the VA, lidocaine is the drug of choice in both hospitalized patients and those under general anesthesia. Lidocaine is a class Ib agent; all class I antiarrhythmogenics are considered membrane stabilizers as they block a portion of the fast sodium channels which will result in a reduced action potential velocity in the atrial and ventricular myocardium. Lidocaine can only be administered intravenously due to extensive first-pass metabolism and 2 mg/kg is recommended as an initial bolus and repeated doses can be administered (Figure 5.3). As lidocaine has a short half-life, continuous-rate infusions (CRI) can be used for longer duration of action; dosages of 40–80 µg/kg/min are recommended; the authors typically initiate treatment at 50 µg/kg/min.

Side-effects of lidocaine are seen commonly with boluses greater than 6 mg/kg and include twitching and seizures. Side-effects are more commonly seen in cats which is why use of lidocaine in cats is not recommended. Mexiletine is an oral analogue of lidocaine which can be administered at a dose of 4–8 mg/kg PO every 8 hours. The main side-effects are anorexia and gastrointestinal upset so its use is not recommended in patients with pre-existing gastrointestinal disease or a poor appetite.

Procainamide

Procainamide is a class Ia antiarrhythmogenic agent and can depress conduction in normal and abnormal cardiac



Figure 5.3 Lead II ECG of rapid ventricular tachycardia, approximate rate of 300 beats per minute, terminated and converted to normal sinus rhythm with lidocaine.

tissue. In general, it is used for VA refractory to lidocaine and it may be more efficacious in patients with VA and hyperkalemia. Due to its short half-life, recommended dosages are 2–4 mg/kg PO followed by a CRI dose of 10–50 µg/kg/min. With rapid intravenous administration, procainamide can potentially be a dose-dependent cause of hypotension. However, due to lupus-like side-effects in people, it is increasingly difficult to obtain procainamide in the oral version and when available, it is typically cost prohibitive for veterinary patients.

Class II Antiarrhythmics

Beta Antagonists

The beta adrenergic blocking drugs are classified as class II antiarrhythmogenic agents and can be used for both supraventricular arrhythmias and VA. Unlike class I drugs, beta-blockers have indirect effects on stabilizing the cardiac cell membrane by reducing catecholamine secretion and associated catecholamine-induced arrhythmias. Beta blockade will also result in decreased myocardial contractility and myocardial oxygen consumption.

Atenolol is primarily a beta-1 antagonist with minimal beta-2 activity. It is typically the authors' first choice for antiarrhythmic control of a VA in cats and for use in dogs with subaortic stenosis. The dose in dogs is 0.5 mg/kg twice daily titrated upwards to 1 mg/kg orally twice daily. In cats, the dose initiated is typically 6.25 mg orally once to twice a day and is typically well tolerated in the authors' experience.

Esmolol is a beta-1 selective antagonist which has a very short half-life and can only be administered as a CRI (10–200 µg/kg/min) after a loading dose of 0.025–0.1 mg/kg IV given slowly over 1 minute; rapid administration of esmolol may cause pronounced negative inotropy and subsequent cardiovascular collapse.

Propranolol is a non-selective beta-blocker and can also be used for VA in both cats and dogs, especially VA from hyperthyroidism or pheochromocytomas. Propranolol has both oral (0.1–0.5 mg/kg q8h) and IV forms (0.02 mg/kg).

Beta-blockers should be used cautiously in patients with concurrent congestive heart failure or those with extensive cardiac remodeling due to their negative inotropic effects and ability to precipitate or worsen congestive heart failure.

Class III Antiarrhythmics

Sotalol

Sotalol is a class III antiarrhythmic agent, which also has non-selective beta-blocking properties. It is used mainly to reduce the risk of sudden death with VA as it increases the fibrillation threshold. Unlike other beta-blockers, sotalol may have fewer negative inotropic effects although caution is recommended in patients with congestive heart failure. A study found the use of sotalol provided superior arrhythmia control in boxer dogs with ARVC compared to mexiletine alone. However, sotalol was found to worsen the frequency of arrhythmias in IVAGSD cases and must be combined with mexiletine for these cases. Recommended dosages of sotalol are 1–3 mg/kg PO q12h.

Amiodarone

Amiodarone is a class III antiarrhythmogenic agent and can prolong the refractory period in the atria, ventricles, and AV junction. Amiodarone influences on the refractory period result in a marked antifibrillatory effect, so it is commonly used to reduce the risk of sudden death. Amiodarone has also been shown to have class I, II, and IV antiarrhythmic effects as well.

The effective dose of amiodarone in dogs is unknown, which is similar to humans where there is no established relationship between plasma concentrations and efficacy. The typical loading dose is 10–15 mg/kg orally twice daily for 7 days, followed by 5–7.5 mg/kg orally twice daily for 14 days and a maintenance dose of 7.5 mg/kg every 24 hours.

The use of amiodarone has been associated with numerous adverse effects in dogs including hepatotoxicity, positive Coombs test, phlebitis, and allergic

reactions. However, a recent study found the frequency of side-effects in dogs receiving amiodarone for supraventricular and ventricular arrhythmias was fairly low.

Other Antiarrhythmics

Magnesium Sulfate

Magnesium sulfate has been used in anecdotal cases of refractory ventricular arrhythmias in dogs with some success but no studies have been performed evaluating it for use in veterinary patients. In humans, studies evaluating magnesium salts for the treatment of VPCs in people have not been conclusive.

Defibrillation

In an emergency setting with cardiopulmonary resuscitation (CPR), defibrillation is the treatment of choice for VF and studies have shown higher rates of return of spontaneous circulation in dogs with VF after prompt defibrillation. Defibrillation is recommended in cases of VF lasting 4 minutes or less. There are sporadic case reports of the use of implantable cardiac defibrillators (ICD) in dogs with sustained VT and VF. However, these are challenging to place and are usually recommended where medical management has failed to reduce the risk of sudden death significantly.

6

Acute Abdomen

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History and Physical Examination

A complete history and physical exam are the most important steps in the management and diagnosis of a patient presenting with an acute abdomen. Often a brief history regarding the presenting complaint and duration of the current illness (time the patient was last normal) combined with a brief physical examination of the major body systems (cardiovascular, respiratory, and neurological) are performed as the triage exam to identify any life-threatening conditions (see Chapter 2). Common life-threatening conditions in patients presenting with an acute abdomen include hypovolemic or septic/distributive shock (see Chapters 152–155) and respiratory disorders from concurrent thoracic or pulmonary diseases.

Rapid volume resuscitation beginning with isotonic crystalloids is warranted in the patient with hypovolemic or septic/distributive shock. The author starts with one-quarter to one-third of the shock dose administered over 15 minutes (shock dose ~90 mL/kg in the dog and 66 mL/kg in the cat) followed by reassessment of the patient. Fluid boluses are continued until the patient is euvoletic. Life-threatening respiratory diseases should be rapidly identified and treated with oxygen support, thoracocentesis or intubation and positive pressure ventilation as needed (see Chapter 4).

Once the patient stabilization has begun, a thorough history should be obtained from the owner and a full physical examination should be performed with special attention paid to abdominal palpation. Focal areas of pain should be further examined with abdominal imaging to identify the source of pain.

Clinical Pathology

Collection of initial diagnostic samples, including blood for packed cell volume, total solids, glucose and

lactate, should be done at the time of catheter placement or during initial resuscitation if possible. Samples should also be collected for a complete blood count, serum chemistry, and urinalysis. Other blood work such as measurement of pancreatic lipase should be considered, depending on the history, physical examination and initial laboratory results. Species-specific pancreatic lipase measurement can be used to support or rule out pancreatitis. A bedside SNAP test is also available for dogs and cats (SNAP cPL for dogs and SNAP fPL for cats, manufactured by IDEXX). The reported sensitivity and specificity of these tests vary based on the method by which pancreatitis was diagnosed. Sensitivity and specificity of canine pancreatic lipase for the diagnosis of pancreatitis range from 21% to 82% and 71% to 100%, respectively [1,2]. Sensitivity and specificity of feline pancreatic lipase for the diagnosis of pancreatitis ranges from 54% to 100% and 63% to 91%, respectively [1,3].

Abdominal Imaging

Abdominal imaging is warranted in all patients presenting with an acute abdomen. The decision of whether to pursue radiographs or ultrasound as the first imaging modality depends on the most likely cause of the acute abdomen and availability of ultrasound. An abdominal focused assessment with sonography for trauma (aFAST) scan (see Chapter 182) can be accurately performed by clinicians with little ultrasound training to identify free fluid in the peritoneal and retroperitoneal spaces [4,5]. The aFAST focuses on four areas of the abdomen: the diaphragmaticohepatic site, splenorenal site, cystocolic site and hepatorenal site, with both longitudinal and transverse views being obtained at each site [4]. Serial aFAST scans can improve detection of free fluid in patients and should be performed in those where the index of suspicion

for free fluid is high but fluid is not identified on the first scan [6].

Abdominal radiographs are indicated in most patients presenting with an acute abdomen unless the cause was evident on physical exam or using the aFAST scan. A comprehensive review of potential radiographic abnormalities in patients presenting with an acute abdomen is beyond the scope of this review, but a few common abnormalities will be highlighted.

Loss of serosal detail should prompt the clinician to further evaluate the patient for free abdominal fluid through either ultrasound or abdominocentesis. Large-volume retroperitoneal fluid appears as loss of detail in the retroperitoneal space on abdominal radiographs, whereas streaking or mottling of the retroperitoneum may be seen with smaller volumes of fluid. Free gas in the peritoneal space (not associated with recent surgery) is most commonly caused by disruption of the gastrointestinal tract, or less commonly rupture of an abscess or necrotic mass that contains gas-producing bacteria, both indications for emergent surgical explore. Gastric dilation and volvulus is usually easily identified on a right lateral abdominal radiograph showing compartmentalization of the stomach and displacement of the pylorus dorsally. Bloat and food bloat are easily distinguished from gastric dilation and volvulus as the stomach will be distended with air or food, but not compartmentalized or displaced.

Obstruction of the gastrointestinal tract by foreign material or a mass is often identifiable on abdominal radiographs. Distension of the intestinal loops, especially resulting in two population sizes of intestines, is supportive of an intestinal obstruction. Moreover, using a lateral view, a ratio of intestinal width to L5 height of >1.6 in the dog and a ratio of intestinal width to the height of the cranial endplate of the second lumbar vertebra >2.0 on the ventrodorsal view in the cat are abnormal and should prompt the clinician to consider mechanical obstruction as a differential [7,8]. If gastrointestinal obstruction is suspected but not identified on radiographs, additional imaging should be pursued. Abdominal ultrasound is often better than radiographs at identifying gastrointestinal obstruction if performed by an experienced ultrasonographer [9]. If ultrasound is not available, an upper gastrointestinal study using barium should be performed.

Abdominal ultrasound is often useful in patients presenting with acute abdominal pain, but operator experience significantly affects the utility of this diagnostic modality. A full discussion of abdominal ultrasonography for the acute abdomen is beyond the scope of this chapter. Abdominal ultrasound is useful for identification of free abdominal fluid and may be more sensitive for diagnosing gastrointestinal obstruction and

differentiating obstruction from ileus than radiographs [9]. In particular, distension of the jejunal lumen >1.5 cm with normal wall layering is supportive of small intestinal obstruction [9].

Pancreatitis can be evident on abdominal ultrasound, especially when ultrasound is performed by an experienced ultrasonographer. Ultrasonographic findings of pancreatitis include an enlarged pancreas that can be hypo- or hyperechoic or have a mixed pattern of echogenicity. Cyst-like lesions can also be seen. The mesentery surrounding the pancreas is often hyperechoic and localized free abdominal fluid may be detected.

Obstruction or partial obstruction of the biliary tract characterized by dilation of the common bile duct and gall bladder enlargement can also be seen in patients with pancreatitis [10]. Dilation of the common bile duct to greater than 3 mm in dogs and greater than 4 mm in cats is consistent with biliary obstruction [11]. Other biliary tract causes of acute abdomen, including gall bladder mucoceles and gall bladder rupture, can often be identified using ultrasound. Gall bladder mucoceles are often described as having a kiwi-like pattern or stellate appearance. They are characterized by the presence of non-gravity-dependent biliary sludge which is organized. Gall bladder rupture can be identified by finding echogenic fluid free in the abdomen or around the gall bladder, hyperechoic fat near the gall bladder, or a mucocele protruding from the gall bladder or free in the abdomen [11].

Abdominal computed tomography (CT) is the gold standard diagnostic imaging modality in human medicine for people presenting with acute abdominal pain [12]. CT has also been shown to accurately differentiate surgical from non-surgical causes of acute abdominal pain in dogs [13]. While CT is likely superior to radiographs or ultrasound alone, limited availability and cost limit widespread use in veterinary medicine. In patients where a diagnosis is not obvious on radiographs and ultrasound, if available, CT is likely to provide additional information and should be recommended.

Collection of Peritoneal Effusion

If peritoneal effusion is detected on abdominal imaging (aFAST or ultrasound, or loss of serosal detail on abdominal radiographs) or suspected based on physical exam, a sample should be collected for analysis. Samples can be collected via ultrasound-guided abdominocentesis or using the four-quadrant technique (see Chapter 186).

For either method, the patient should be placed in left lateral recumbency to decrease the chance of accidental splenic aspiration. Sedation is usually not required and the author does not use a local block. Both closed and

open techniques have been described, but the author prefers the closed technique because the open technique can introduce free gas into the peritoneal space, potentially making the interpretation of radiographs more difficult. The area around the umbilicus or identified pocket of fluid should be clipped and prepped using a surgical scrub. A 20 or 22 gauge needle attached to a 3–6 cc syringe is used for fluid collection. The needle is slowly inserted perpendicular to the abdomen and advanced a few millimeters at a time. Following each advancement, the syringe is aspirated. If no fluid is obtained, the syringe and needle are advanced a few millimeters further and the syringe is reaspirated. The needle and syringe should not be advanced while being aspirated as the negative pressure can cause the omentum to be aspirated onto the end of the needle, potentially leading to a false-negative abdominocentesis. In addition, the needle should not be redirected once the abdominal wall is penetrated as this may increase the chance of lacerating an organ.

If the four-quadrant technique is being used, the four areas for abdominocentesis are 1–2 cm cranioventral, caudoventral, craniodorsal, and caudodorsal to the umbilicus.

Abdominocentesis is performed at each site until fluid is collected. If fluid is not obtained by the closed technique, conversion to the open technique can be done by removing the syringe from the needle and slowly backing the needle out; this may allow fluid to accumulate in the hub of the needle via capillary action. Rapid tapping of the abdomen with the free hand can sometimes facilitate capillary action drainage by creating vibration of the mesentery, resulting in intermittent patency at the tip of the needle.

Diagnostic peritoneal lavage (DPL) can be used to obtain a fluid sample in patients with known or suspected small-volume peritoneal effusion when abdominocentesis has been unsuccessful in obtaining fluid. Administration of analgesics often facilitates patient co-operation during a DPL. The patient is placed in left lateral recumbency and a large area around the umbilicus is clipped and prepped using surgical scrub. A local block is performed using 2% lidocaine followed by a stab incision either on the ventral midline at the level of the umbilicus or 2–3 cm lateral to the umbilicus to avoid the falciform fat. A peritoneal dialysis catheter or fenestrated 14 or 16 gauge over-the-needle catheter is advanced through the stab incision. Fenestrations in an over-the-needle catheter are made using a no. 10 scalpel blade. They should be small and smooth, not larger than 40% of the circumference of the needle and should not be placed directly across from one another as this will weaken the catheter. Once the catheter is in the abdominal cavity, it should be advanced over the needle. A drip set is attached to the catheter and, using gravity, 22 mL/kg of warm sterile

0.9% NaCl is infused into the abdomen. The patient is then rolled or the abdomen massaged to distribute the fluid throughout the abdomen. A syringe is attached to the catheter and fluid is retrieved from the abdomen. It is uncommon to aspirate large volumes of fluid following a DPL due to dispersion of the fluid in the abdomen.

Analysis of Peritoneal Effusion

Once peritoneal effusion has been collected, hematological, biochemical, and cytological analysis should be performed, depending on the appearance of the fluid.

Cytological analysis is indicated for every patient. Cytology can help identify patients with septic peritonitis (intracellular bacteria), neoplastic effusions, hemorrhage, and less commonly evidence of bile peritonitis (bile crystals). A direct smear for cytology will allow for estimation of cellularity of the fluid while cytology of a sedimented sample will likely increase the chances of seeing bacteria or abnormal cells.

Fluid obtained from a DPL should always be evaluated using a sedimented sample due to dilution from the infused fluid. Red-colored fluid should be placed in a clot tube or observed in the syringe for evidence of clotting. If the fluid clots, it was likely obtained from a vessel or organ. Peracute hemorrhage can also clot, though this is less likely. If the sample clots, abdominocentesis should be repeated to obtain a sample of the effusion. Non-clotting fluid likely indicates free peritoneal fluid, but a coagulopathy should also be ruled out. A packed cell volume and total solids should be obtained on any red-colored fluid to differentiate hemorrhage from serosanguineous fluid.

Biochemical analysis can be helpful in identifying the cause of peritoneal effusion. Comparisons of blood and fluid lactate and glucose can be used to support the diagnosis of septic peritonitis. A fluid glucose to whole blood difference of >20 mg/dL with the fluid glucose being lower is specific (dogs 100%, cats 100%) but may not be sensitive (dogs 41.2–100%, cats 86%) for a diagnosis of septic peritonitis [14,15]. Comparing plasma glucose to fluid glucose using a point-of-care glucometer may be more accurate for detecting septic peritonitis when a cut-off difference of >38 mg/dL is used (specificity 100%, sensitivity 88.2%) [15]. In addition, a blood to fluid lactate difference of >2 mmol/L with the fluid lactate being higher is supportive of septic peritonitis [14].

A uroabdomen can be diagnosed by comparing blood and fluid creatinine and potassium levels. Potassium and creatinine will both be higher in the fluid compared to the blood if the patient has a uroabdomen. Fluid that has creatinine levels twice as high as blood and potassium levels 1.9 times as high in cats and 1.4 times as high in

dogs is consistent with a uroabdomen [16,17]. Blood urea nitrogen is not useful as it is a small uncharged particle that easily crosses membranes and therefore quickly equilibrates between blood and peritoneal effusion. A diagnosis of bile peritonitis is supported by a bilirubin twice as high in the fluid as in the blood [18].

Samples obtained via DPL are diluted by the infused saline, so biochemical analysis is less likely to be diagnostic and other imaging techniques are needed to diagnose the conditions listed above.

Abdominal Surgery

The decision to pursue abdominal surgery often needs to be made quickly in the patient presenting for an acute abdomen. Indications for immediate abdominal exploratory include septic peritonitis, free gas in the abdomen without a history of a recent abdominal surgery, obstruction of the gastrointestinal tract, gastric dilation and volvulus, mesenteric volvulus, ischemic bowel, uroabdomen, bile peritonitis, uncontrollable hemorrhage, and abdominal abscess. In patients that cannot be medically stabilized, even when the cause of the acute abdomen has not been identified, abdominal exploratory can be used as both a diagnostic and therapeutic tool.

Nutritional Support

Nutritional support is key to recovery in patients presenting with an acute abdomen. Food should be offered early in the course of disease. If the patient refuses to eat, nutritional support should be initiated within 24–48 hours of hospitalization. Early enteral nutrition has been shown to be beneficial in critically ill humans [19,20]. In particular, early enteral nutrition may help decrease rates of infection and preserve the gut barrier function [20]. Enteral nutrition is recommended over parenteral nutrition due to decreased rates of infection and potentially shorter hospital stays in critically ill patients who are fed enterally [20].

Conclusion

A thorough history and physical exam are key in identifying the underlying condition in patients presenting with an acute abdomen. A combination of diagnostic imaging and laboratory data along with analysis of peritoneal fluid if present can help the clinician make a prompt diagnosis. When the patient cannot be medically stabilized, surgical exploration should be considered.

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7

The Collapsed Patient

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Introduction

Collapse is a sudden loss of postural tone (falling over or sudden weakness), often but not necessarily accompanied by loss of consciousness. Collapse, syncope or fainting is used somewhat interchangeably in veterinary medicine, but if the collapse episode is accompanied by a loss of consciousness, the term *syncope* should be used. Syncope is defined as “a transient loss of consciousness (TLOC) due to global cerebral hypoperfusion” characterized by rapid onset, short duration, and spontaneous complete recovery [1]. It commonly prompts a visit to the emergency room but by the time of evaluation, the patient is often “normal” again.

Depending on the underlying cause, syncope may have a benign disease course or represent aborted sudden death due to an arrhythmia. Severe heart rhythm disturbances are the most common cause of syncope in dogs and cats. However, up to 45% of syncopal events remain undiagnosed, but fortunately carry a relatively low mortality rate of 16% [2].

The evaluation of syncope in animals is often challenging, as owners may not definitively determine the loss of consciousness. Syncopal episodes are usually unpredictably sporadic, sometimes infrequent, and during intersyncopal periods the animals appear to be normal in behavior and activity level. Importantly, syncope must be differentiated from seizures. Seizures and certain metabolic diseases can also result in TLOC (Figure 7.1). The main tool in distinguishing the causes of collapse is observing characteristic clinical features of seizures and careful history taking of the events before, during, and after the collapse (Table 7.1).

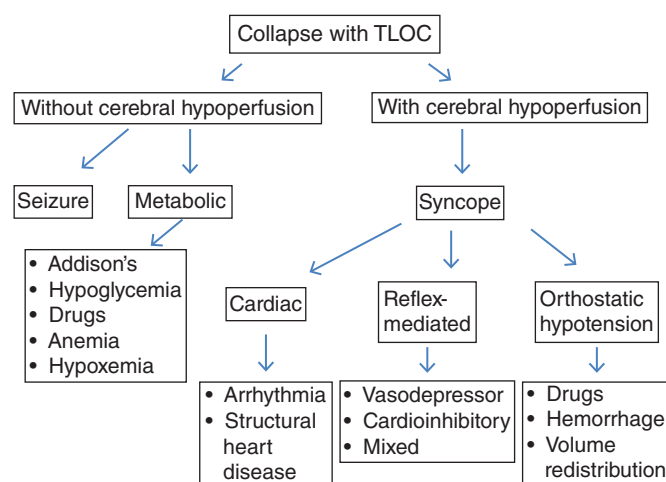


Figure 7.1 Causes of transient loss of consciousness (TLOC) in animals.

Pathophysiology of Syncope

Transient global cerebral hypoperfusion resulting in syncope is caused by an acute drop in systemic blood pressure. Blood pressure is determined by cardiac output (CO): the product of heart rate and stroke volume, as well as the systemic vascular resistance. Any condition leading to either a transient decrease in CO and/or a transient decrease in vascular resistance can thus result in syncope. Cessation of cerebral blood flow for 6–8 seconds or a sudden drop in systemic systolic blood pressure below 70 mmHg can cause syncope in humans, and this likely applies to animals as well.

Three principal mechanisms can produce a decrease in CO (Table 7.2): primary heart disease (structural or

Table 7.1 Differentiating causes of collapse.

Clinical features	Syncope	Seizure	Neuromuscular collapse*
Mentation	Normal	May be abnormal	Normal
Gait	Normal	Normal	Often abnormal
Alteration of consciousness	Yes	Frequent [†]	No
Tonic-clonic muscle activity	Rare	Usually	Variable depending on specific disease
Trigger events (excitement, activity, cough, gag, etc.)	Possible	Usually none	Variable depending on specific disease
Duration of episode	Seconds to few minutes	Minutes to hours	Varies
Prodromal phase	Very rare	Rare to common	Rare
Abnormal mentation after the event	Uncommon	Frequent	No
Urination/defecation during the event	Uncommon	Frequent	No
Response to antiseizure medication	No	Usually	No

* Neuromuscular causes include polymyositis, polyneuropathy, myasthenia gravis, narcolepsy, botulism, tick paralysis, hepatic encephalopathy, paraneoplastic syndromes, and central nervous system lesions

† Some seizures (e.g. simple focal/partial seizures) are not associated with alteration of consciousness.

electrical disorders); reflex-mediated bradycardia and hypotension, and decrease in venous return due to blood loss or redistribution of blood volume, also called orthostatic hypotension.

Causes of Syncope

Cardiac Syncope

Bradyarrhythmias caused by advanced atrioventricular (AV) block, atrial standstill or episodes of sinus

arrest due to sick sinus syndrome (commonly seen in middle-aged and older West Highland white terriers, female miniature schnauzers and cocker spaniels) (Table 7.3) and ventricular or supraventricular tachycardia are the most common causes of syncope in veterinary medicine (see examples in Table 7.2) (see Chapters 53 and 60). Cats can display seizure-like episodes (facial and whisker twitching, salivation, urination, defecation, disorientation, and syncope) secondary to high-grade AV block causing prolonged cerebral hypoperfusion (also called hypoxic convulsive syncope).

Table 7.2 Classification of syncope.

Category of syncope	Cause of syncope	Examples
Cardiac syncope	Bradyarrhythmia	Sick sinus syndrome, AVB: high grade 2nd or 3rd degree, atrial standstill
	Tachyarrhythmia	Ventricular tachycardia, atrial tachycardia, atrial fibrillation, OAVRT
	Structural heart disease	Aortic and pulmonic stenosis, pericardial effusion, pulmonary hypertension due to pulmonary thrombosis/embolism, heartworm disease, advanced degenerative AV valve disease, DCM, hypertrophic obstructive cardiomyopathy
Reflex-mediated syncope	Vasovagal neurocardiogenic	Mediated by emotion: stress, fear, pain (not documented in veterinary patients)
	Situational	Intense activity, excitement, coughing, urination/defecation, gagging/vomiting
	Carotid sinus hypersensitivity	Primary dysfunction of baroreceptors in carotid arteries, neoplasia in cervical region
Orthostatic syncope	Drug-induced hypotension	Acepromazine, hydralazine, amlodipine, nitrates, beta-blockers, diuretics
	Volume depletion	Dehydration, hemorrhage, redistribution

AVB, atrio-ventricular block; DCM, dilated cardiomyopathy; OAVRT, orthodromic atrioventricular reciprocating tachycardia.

Table 7.3 Breeds/species commonly affected with cardiac syncope.

Breed or species-related cause of syncope	Associated conditions	ECG findings
Miniature schnauzer, American cocker spaniel, West Highland white terrier	Bradyarrhythmia +/- tachyarrhythmia	Sick sinus syndrome: brady tachy arrhythmia, junctional or ventricular escape rhythm, sinus arrest
Boxer/Doberman*	Tachyarrhythmia	Ventricular tachycardia
Advanced cardiomyopathy in large breed dogs	Arrhythmia	Atrial fibrillation, ventricular tachycardia
Any dog with slow heart rate	Bradyarrhythmia	Advanced second or third degree atrioventricular block
English springer spaniel	KCNQ1 gene mutation	Long QT in sinus rhythm, biphasic T waves, presumed tachyarrhythmia as cause for collapse
Exercise-induced collapse syndrome (reported in Labrador retriever, Chesapeake Bay retriever, border collie, curly-coated retriever, Boykin spaniel and Pembroke Welsh corgi)	Dynamin-1 mutation, associated with acute hyperthermia	Presumed tachycardia
Cats with exertional syncope	Cardiomyopathy, left ventricular outflow tract obstruction, anemia	Normal to ventricular tachycardia
Cats or dogs with hypoglycemia	Hypoglycemia (insulin overdose), insulinoma, neonate	Normal
Older cats	Hyperthyroidism	Tachyarrhythmias to atrioventricular blocks

*Presumed to be ventricular tachycardia, but Boxers and Dobermans can collapse from reflex-mediated bradycardia and vasodilation as well. ECG, electrocardiogram; KCNQ1, potassium voltage-gated channel subfamily Q member 1.

Structural heart disease such as aortic/subaortic or pulmonic stenosis can cause syncope on exertion, when the CO cannot increase adequately to meet the oxygen demands of the brain and vital organs. It can also occur in patients with pulmonary hypertension if a massive pulmonary embolism obstructs blood flow, leading to reduced CO. Alternatively, the raised intraventricular systolic pressure may give rise to mechanoreceptor stimulation or activation of ventricular stretch receptors, resulting in reflex-mediated syncope. In addition, ventricular remodeling and scar tissue formation resulting from chronic pressure overload in dogs with severe ventricular outflow tract obstruction can cause ventricular arrhythmias, further predisposing to syncope.

Pericardial effusion is a common cause of collapse or weakness in dogs with tamponade from acute hemorrhage into the pericardial space, but there is no TLOC (see Chapter 54).

Reflex-Mediated Syncope

Syncope of different etiologies are included in this group (see Table 7.2), but they all share a common denominator of inappropriate and excessive cardiovascular reflexes relative to the triggering event. This autonomic dysregulation ultimately results in hypotension with (or without)

bradycardia, leading to cerebral hypoperfusion and syncope. Initially, hyperactivity of the sympathetic tone prompts an abrupt reflex sympathetic withdrawal and simultaneous vagal stimulation. If the syncope is mostly due to the resulting hypotension and not the bradycardia, it is called *vasodepressor*-type syncope, in contrast to the *cardio-inhibitory* type, where the bradycardia is the predominant cause of syncope. *Mixed* type includes syncope caused by an equal contribution of both mechanisms. Blood pressure monitoring during the event would be required to distinguish between the types of syncope.

Reflex-mediated (neurocardiogenic) syncope is thought to be caused by the Bezold–Jarish reflex (BJR). An initial drop in blood pressure due to a “perceived” hypovolemia (exacerbated in dehydrated patients) is sensed in the carotid sinus baroreceptors, resulting in augmented activity of efferent sympathetic fibers which leads to increased heart rate, contractility, and vasoconstriction. The strong contraction of the “underfilled” ventricle stimulates mechanoreceptors in the wall, sending impulses via afferent C-fibers to the medulla oblongata, resulting in a sudden withdrawal of sympathetic tone and simultaneous increased vagal tone. This triggers a paradoxical bradycardia and decreased contractility, resulting in a relatively sudden decrease in arterial blood pressure and syncope.

Examples of triggering events for reflex-mediated syncope are listed in Table 7.2. Pain, fear, or stress can elicit a *vasovagal syncope*, a condition not definitively documented in veterinary medicine. Intense activity, excitement, coughing [3,4], urination/defecation [5] or vomiting/gagging can result in a *situational syncope*, the second most common cause of syncope in veterinary medicine. Coughing that results in tussive syncope can be due to tracheal or bronchial disease and/or advanced mitral valve disease leading to atrial enlargement and compression of the mainstem bronchi.

This mechanism is likely also responsible for situational syncope observed in dogs with severe outflow tract obstruction, advanced degenerative AV valve disease [6], and/or pulmonary artery hypertension (see Chapter 59). The triggering event in those scenarios is a sudden increase in activity level or excitement resulting in tachycardia but a relative, inappropriate decrease in CO due to the structural heart disease and thus “empty” ventricle, setting off the BJR and cascade of events leading to syncope. Dogs with impending congestive heart failure may be at higher risk of reflex-mediated syncope and such episodes may subside with heart failure therapy.

Respiratory arrest, pale mucous membranes or cyanosis may be observed during severe and protracted bradycardia. Most episodes persist for only seconds to minutes. As with all reflex-mediated syncope, neurocardiogenic bradycardia is seldom fatal in isolation.

Neurocardiogenic bradycardia can also occur in otherwise healthy dogs, particularly in working dogs, following strenuous activity. Some Dobermans [7] and boxers collapse from reflex-mediated bradyarrhythmias [8]. In boxers, it is usually triggered by either exertion coupled with excitement or startle, and can occur without evidence of arrhythmogenic right ventricular cardiomyopathy. Since both conditions can co-exist in the same dog, a Holter recording is necessary to differentiate reflex-mediated syncope from primary arrhythmic causes (ventricular tachycardia) in these breeds.

Overstimulation of baroreceptors in carotid arteries can trigger a reflex-mediated syncope via afferent fibers of the glossopharyngeal nerve, resulting in bradycardia or prolonged asystole, called *carotid sinus hypersensitivity*. This is uncommon in veterinary medicine, but neoplasia in the cervical region has been associated with syncope in bulldogs after pulling on the leash or with swallowing [9].

Orthostatic Syncope

Commonly occurring in humans, orthostatic syncope is associated with low blood pressure while standing due

to inappropriate vascular tone or dehydration, without a change in heart rate. It can be diagnosed in people by means of an orthostatic challenge using a tilt-table test. For practical reasons, this type of syncope has not been documented in veterinary medicine.

Collapse or Syncope-Like Conditions

Many conditions can result in collapse and syncope-like signs (see Figure 7.1). Seizures and collapse from hypoglycemia or other metabolic/endocrine disease (e.g. Addison's disease) can result in a TLOC, but are not associated with cerebral hypoperfusion. Narcolepsy, a rare neurological disorder, can also cause syncope-like falling over, when dogs fall asleep abruptly while stimulated by food or excitement. However, these dogs can be awakened and there is no associated cerebral hypoperfusion [10].

Exercise intolerance or weakness from anemia, orthopedic or neuromuscular diseases (i.e. myasthenia gravis) should be differentiated from collapse (no TLOC). Patients with exercise intolerance are capable of exercising, but tire very easily and usually this gets gradually worse over time. Patients with collapse are able to exercise normally for a period of time but show an abrupt onset of weakness/collapse.

Exercise-induced collapse (EIC), described in the Labrador retriever, Pembroke Welsh corgi, Chesapeake Bay retriever, curly-coated retriever, and Boykin spaniel, is due to a mutation in the canine dynamin 1 (DNM1) gene [11]. Inherited in an autosomal recessive fashion, the dynamin 1 protein encoded by the DNM1 gene functions to maintain neural and neuromuscular transmission during high-intensity stimulation. Affected dogs display sudden hindlimb ataxia and weakness after 10–15 min of strenuous activity, but do not lose consciousness. They fully recover within minutes of resting. Genetic (DNA) testing for EIC can be performed to confirm a suspected diagnosis.

Border collie collapse (BCC) is a clinically very similar syndrome to EIC, seen in border collies and related breeds, who are negative for the DNM1 gene test. It is diagnosed by systematically ruling out all other disorders causing exercise intolerance and collapse and by observing characteristic clinical features, history, and laboratory test results in affected dogs.

Episodic falling syndrome (EFS), thus far only described in Cavalier King Charles spaniels, is an excitement- or exercise-induced hypertonicity of the limbs [12]. Dogs develop a hypermetric gait and fall over while remaining fully conscious. It is inherited in an autosomal recessive fashion and not caused by a muscular disease but a mutation of the BCAN gene,

which encodes proteins expressed in the central nervous system, responsible for regulation of brain function. Genetic (DNA) testing for EFS is available to confirm a suspected diagnosis.

Patient Evaluation and Risk Stratification

The initial evaluation consists of a careful history and physical examination to determine if the episode was syncope, collapse or a seizure (see Table 7.1). Distinguishing syncope from seizure activity may be difficult as both conditions are associated with TLOC. Disorientation after the event with slow recovery of normal consciousness is more common with seizures. However, protracted cerebral hypoxia resulting from cardiac arrhythmias may also be followed by a relatively slow recovery. Although usually associated with flaccid collapse, syncope due to arrhythmia can sometimes be associated with extensor rigidity and spontaneous urination or defecation, particularly in cats. Hypersalivation is rarely associated with syncope.

The role of the emergency clinician is to determine if a life-threatening cause of syncope is present (arrhythmia) and to provide treatment if indicated. Also, non-life-threatening causes of syncope, such as reflex mediated (e.g. tussive syncope), medication overdose or collapse, should be recognized as lower risk conditions, and the patient can be safely discharged from the emergency room and referred to a specialist. Animals that suffer from repeated episodes of syncope or seizures will likely benefit from hospitalization for further monitoring, diagnostics, and treatment, as indicated.

The San Francisco Syncope Rule is validated in humans [13] and proposes a risk stratification system of human patients with syncope who present to the emergency room using the following criteria (acronym CHEMA).

- Congestive heart failure history
- Hematocrit <30%
- ECG abnormal
- Shortness of breath
- Systolic blood pressure <90 mmHg

These criteria demonstrate high sensitivity and specificity for serious outcomes in people [14] and may be useful tools for initial risk stratification of the collapsed patient presenting to the emergency veterinarian.

Upon presentation to the ER, the following diagnostics should always be performed.

Blood Pressure

Abnormal if systolic blood pressure is <90 mmHg or >200 mmHg (see Chapter 63).

ECG

Can provide a definitive diagnosis of syncope with any of the following.

- Persistent bradycardia, <50 bpm (advanced AV block, atrial standstill, sinus pauses >6–8 seconds).
- Ventricular or supraventricular tachycardia.
- Pacemaker malfunction.
- Pre-excited QRS complexes: the presence of an abnormal accessory electrical conduction pathway between the atria and the ventricles may allow for the electrical wavefront to travel from the atria down this abnormal accessory pathway. The wavefront can thereby activate the ventricles prematurely, resulting in shortening of the PR interval and slurred upstroke (delta wave) of the R wave, making the QRS appear wide (pre-excited). Pre-excitation on the ECG suggests presence of atrio-ventricular re-entrant tachycardia (a type of supraventricular tachycardia), which can cause syncope.

Long-Term Monitoring

Long-term monitoring of ECG by 24–48h Holter or event recording is often required to document intermittent arrhythmias such as sick sinus syndrome or reflex-mediated bradycardia. In cases of very infrequent suspected but undocumented arrhythmias, a leadless loop recorder may be implanted subcutaneously [15]. Alternatively, owners can be instructed to acquire ECGs themselves during an “episode” using their smartphone and an ECG case (AliveCor™) and email it to the veterinarian for diagnosis.

In the ER, clinicians can easily use ultrasound to evaluate for pericardial effusion, enlarged atria or inadequate cardiac filling. A full echocardiogram is recommended in animals suspected of having a cardiac cause of collapse/syncope. Pericardial effusion, severe aortic stenosis or pulmonic stenosis, severe pulmonary artery hypertension, obstructive tumors or thrombi may be evident upon examination. Echocardiographic Doppler parameters may support a diagnosis of high preload and impending congestive heart failure (increased mitral E velocity, E/IVRT, E/E) in cases of advanced myxomatous mitral valve disease, severe dilated cardiomyopathy, and hypertrophic obstructive cardiomyopathy in cats and these should be considered predisposing conditions for reflex-mediated syncope.

Bloodwork

- Serum chemistry: check for electrolyte abnormalities (e.g. Addison’s disease) or hyperkalemia as a cause of bradyarrhythmias, and to rule out hypoglycemia.
- T4: to rule out hyperthyroidism as a cause for arrhythmias in cats.

- Cardiac biomarkers
 - Increased concentrations of NT-proBNP may aid in ruling in a cardiac cause of syncope/collapse and should prompt further testing, including an ECG and echocardiogram, but normal levels cannot rule out intermittent arrhythmias or reflex-mediated syncope.
 - Troponin (cTnI) has not been shown to independently identify cardiac causes of syncope, but in humans, there is an association of increased cTnI and seizures [16] and increased concentrations of cTnI post seizures have been found in dogs [17,18].
- Complete blood count: detect anemia/polycythemia.

- Neurological evaluation: if seizures are suspected.

Treatment

Treatment of the collapsed patient depends on the cause and is aimed at managing the underlying disorder. If an arrhythmic etiology is discovered, antiarrhythmic medication (Table 7.4) or pacemaker therapy is indicated. Management of reflex-mediated bradycardia in the absence of structural heart disease and syncope is difficult, but since the episodes are usually infrequent and

Table 7.4 Drugs for the treatment of cardiac syncope associated with arrhythmias.

Drug	Indication	Maintenance dosage	Frequency
Lidocaine	Acute, life-threatening ventricular arrhythmias	2 mg/kg bolus IV, over 1–2 min followed by CRI at 40–80 µg/kg/min	Repeat up to 4 times, if no effect or the arrhythmia recurs
Atropine	Sinus bradycardia, high-grade AV block, atropine response test	0.02–0.044 mg/kg IV, IM, SQ	
Procainamide HCl	Life-threatening ventricular and supraventricular arrhythmias	2–4 mg/kg (up to 20 mg/kg) IV SLOWLY over 10 min followed by CRI at 20–50 µg/kg/min	Repeat bolus 2 times (but negative inotrope and may cause hypotension)
Esmolol	Ventricular and supraventricular arrhythmias	25–100 µg/kg IV bolus followed by CRI at 10–200 µg/kg/min	Repeat 2 times PRN
Sotalol	Ventricular and supraventricular arrhythmias	Dog: 0.5–2.5 mg/kg PO Cat: 10–20 mg	q12–24h q12h
Diltiazem HCl	Supraventricular arrhythmias	0.05–0.25 mg/kg IV bolus, followed by CRI at 2–6 µg/kg/min	Repeat up to 3 times
Diltiazem XR (Dilacor)	Supraventricular tachycardia, atrial fibrillation	Dog: 3–4 mg/kg PO Cat: 30–60 mg total dose	q12h q12–24h (start with 30 mg q24h)
Cardizem	Supraventricular tachycardia	Dog: 0.5–1.5 mg/kg PO, increase PRN Cat: 7.5 mg/cat, increase PRN	q8h q8–12h
Cardizem CD	Supraventricular tachycardia	Cat: 6–10 mg/kg PO	SID q24h
Amiodarone HCl	Ventricular and supraventricular arrhythmias	2 mg/kg IV bolus slowly over 10 min followed by CRI at 0.8 mg/kg/h for 6 h	
Amiodarone	Ventricular and supraventricular arrhythmias	Dog: 10 mg/kg PO Dog: 5 mg/kg PO	q12h for 1 week (loading)* q24h* (maintenance)
Mexiletine	Ventricular arrhythmias	5–8 mg/kg PO	q8h
Hyoscyamine sulfate	Sick sinus syndrome Advanced heart block	0.003–0.005*** mg/kg PO	q8–12h
Propantheline bromide	Sick sinus syndrome	0.2–0.5 mg/kg PO, increase PRN	q8–12h q12h BID
Digoxin	Atrial fibrillation	Dog: 0.005–0.01 mg/kg PO**	q12h BID

*Recommended dose range in veterinary medicine is testimonial and variable.

** In dogs weighing less than 20 kg; 0.22 mg/m² in dogs weighing >20 kg.

***Consider if positive response to IV atropine test (0.044 mg/kg). Pacemaker implantation is the treatment of choice.

BID, twice a day (*bis in die*); CRI, continuous-rate infusion; IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); PRN, as required (*pro re nata*); SID, once a day (*semel in die*); SQ, subcutaneous.

Table 7.5 Drugs for the treatment of reflex-mediated syncope associated with high preload or pulmonary hypertension.

Drug	Indication	Maintenance dosage	Frequency
Furosemide	Overt or impending CHF	1.0–2.0 mg/kg PO	q8–12h
ACE-I	Overt or impending CHF	0.25–0.5 mg/kg PO	q12–24h
Enalapril		0.25 mg/kg PO	q12–24h
Benazepril			
Spironolactone	Overt or impending CHF Electrolyte control	1.0–2.0 mg/kg PO	q12h
Amlodipine	Afterload reduction, overt or impending CHF	Dog: 0.2–0.4 mg/kg PO* Cat: 0.625–1.25 mg/cat	q6–12h
Sildenafil	Pulmonary hypertension	0.5–1 mg/kg PO	q8–12h

ACE-I, angiotensin converting enzyme inhibitor; CHF, congestive heart failure.

* Initiate at 0.1 mg/kg and titrate up weekly while monitoring blood pressure. Target dosage is 0.4 mg/kg. Target systolic blood pressure is around 110–120 mmHg. If co-administered with an ACE inhibitor, initiate therapy once ACE inhibitor maintenance therapy has been established.

non-life-threatening, treatment may not be required. Pacemaker implantation may be helpful in some dogs if a bradyarrhythmia is documented during the event [19]. However, if hypotension occurs in conjunction with the bradyarrhythmia, pacing may not eliminate the collapsing episodes and it is difficult to predict which patients experience hypotension as a component of the syncopal event [2,16]. It is not advised to administer beta-blockers to “prevent” the initial triggering tachycardia, as this can cause exacerbation of bradycardia-related syncope, especially in cardiomyopathic Doberman pinschers [7].

Anticholinergic agents may be helpful in patients with documented supraventricular bradycardia during syncopal events, who appear to be atropine responsive. However, no studies have established efficacy in animals, nor humans. Boxers with ventricular tachyarrhythmias treated with sotalol who develop new or more frequent syncopal episodes may be experiencing reflex-mediated bradycardia. In some of these cases, pacemaker therapy is required in addition to antiarrhythmic medication to optimize patient care.

Reflex-mediated syncope associated with high preload (ongoing or impending congestive heart failure) in dogs with structural heart disease warrants “cardiac unloading” using diuretics (furosemide, spironolactone), positive inotropes (pimobendan), and ACE inhibitors. Animals with pulmonary hypertension may also benefit from sildenafil treatment (Table 7.5). Initiation of heart failure therapy may reduce the syncopal episodes, even if pulmonary edema is not evident on thoracic radiographs.

Cats with hypertrophic obstructive cardiomyopathy can experience exertional syncope as a result of left ventricular outflow tract obstruction and these patients usually respond favorably to beta-blocker treatment.

In people, reflex-mediated syncope related to fluid homeostasis is sometimes treated with fludrocortisone, midodrine, or selective serotonin reuptake inhibitors, as well as avoidance of dehydration. However, results are variable and these therapies are not standard of care yet [20].

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8

Global Approach to the Trauma Patient

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Introduction

Trauma accounts for roughly 10% of veterinary hospital admissions. Approximately 35% of these cases are documented to have serious injuries. The mortality rate, including euthanasia, is greater than 10% in this patient population [1–3]. Trauma, defined as a physical injury (i.e. burns, lacerations, or blunt trauma), results in initiation of the hypothalamic-pituitary-adrenal axis as well as immunological and metabolic responses in an attempt to restore hemostasis [4].

In veterinary patients, trauma can occur secondary to motor vehicle accidents, a fall from a height, animal–animal interactions, human–animal interactions or fire exposure. Injuries in a trauma patient may be limited to one organ system or multiple organ systems (polytrauma), either directly or indirectly. Polytrauma reportedly accounts for greater than 72.3% of patients admitted to an intensive care unit for trauma [2]. The initial approach to a trauma patient should involve a thorough evaluation and global approach to improve patient outcome (Figure 8.1). Veterinary staff should be well versed in evaluation of, and therapy for, the trauma patient.

Tissue oxygenation is dependent on the rate of tissue oxygen consumption (VO_2) and delivery of oxygen (DO_2). Shock occurs when VO_2 exceeds DO_2 , resulting in inadequate oxygenation and anaerobic metabolism (see Chapter 152). In the early stages of shock, tissue extraction of oxygen increases to meet demands. Over time, with continued blood loss, inadequate resuscitation or compensatory mechanism failure, a mismatch of VO_2 and DO_2 results in dysoxia. Dysoxia occurs when mitochondria can no longer support aerobic metabolism and ATP production fails [4,5]. Therefore, one of the primary goals in initial management of a trauma patient is to support DO_2 to prevent dysoxia.

Oxygen delivery is dependent on cardiac output (CO) and arterial content of oxygen (CaO_2). CaO_2 can

be determined by the oxygen content equation (see Figure 8.1). Early recognition of perfusion impairment and aggressive resuscitation are recommended. Long-term survival is dependent on the metabolic responses to trauma, early restoration and maintenance of tissue perfusion, and adequate tissue oxygenation [5].

Pathophysiology

Shock in the trauma patient may be characterized as hypovolemic, distributive, or hypoxic shock, depending on the type and degree of trauma (see Chapter 152). In these patients, maldistribution of blood flow can occur from catecholamine release, peripheral vasoconstriction, and release of vasoactive substances. In patients with severe blood loss or thoracic trauma, shock may be related to true hypovolemia or hypoxia. Continued microcirculatory perfusion failure may lead to decreased blood flow, sludging of blood, and increased cellular and platelet aggregation, further impairing capillary diffusion. Endothelial injury may occur following trauma and results in the exposure of endothelial tissue factor, which promotes the release of inflammatory mediators, stimulates a procoagulant response and results in further exacerbation of systemic inflammation.

Some inflammatory mediators such as cyclo-oxygenase and lipoxygenase stimulate the production of thromboxane and leukotrienes, respectively. The release of thromboxane results in further vasoconstriction and promotes platelet aggregation at the sites of injury. Production of leukotrienes and the activation of the complement cascade further stimulates the systemic inflammatory response through the mobilization and activation of neutrophils (see Chapter 159). Neutrophils release lysosomal enzymes and reactive oxygen species (ROS). ROS can cause further cellular damage, resulting in excessive endothelial tissue permeability, edema formation, and further impairment of oxygen diffusion from local

$$\text{CaO}_2 = (\underbrace{0.003}_{1} \times \underbrace{\text{PaO}_2}_{2}) + (\underbrace{1.34}_{3} \times \underbrace{[\text{Hb}]}_{4} \times \underbrace{\text{SO}_2}_{5})$$

Figure 8.1 Formula for oxygen content (CaO₂) in arterial blood.

- 1 Conversion factor
- 2 Partial pressure of oxygen in arterial blood
- 3 Hemoglobin oxygen carrying capacity (1.34 mL O₂/1gram Hb)
- 4 Hemoglobin concentration
- 5 Oxygen saturation

CaO₂-oxygen content in arterial blood

capillary beds. If DO₂ remains impaired, these cascades will perpetuate themselves, resulting in systemic inflammation which could lead to multiple organ failure (see Chapter 159). The primary goal of a clinician's approach to the management of the trauma patient is therapeutic interventions that target the optimization of DO₂.

Triage Evaluation and Intervention

Maintaining adequate oxygen saturation of hemoglobin (Hb) concentration is critical in supporting DO₂. Assessment of the respiratory system and rapid correction of abnormalities is critical to improving patient outcome (see Chapter 4). If there is any concern for impaired saturation of Hb, supplemental oxygen (see Chapter 181) should be provided until oxygenation can be further evaluated via arterial blood gas analysis or Hb oxygen saturation (pulse oximetry). In the event that oxygen saturation cannot be evaluated with these methods, thorough patient assessment, including mucous membrane color, respiratory rate, respiratory effort, heart rate, and thoracic auscultation, can help to subjectively assess respiratory function. Thoracic imaging (either radiographs or thoracic ultrasound) can be performed to further assess the trauma patient for pleural space disease or pulmonary contusions that may compromise oxygen Hb saturation.

The initial assessment of adequate cardiac output and circulating volume should include thorough evaluation of mucous membrane color, capillary refill time, pulse rate, and quality. The most common symptoms of decreased cardiac output and poor tissue perfusion include pale or gray mucous membranes, prolonged capillary refill time, tachycardia (or bradycardia in cats), and altered pulse quality (weak or bounding). The most common cause of

impaired tissue perfusion in the trauma patient is hypovolemia due to hemorrhage (see Chapter 153).

Pulmonary arterial catheter placement can provide an objective measurement of cardiac output, oxygen delivery, and oxygen consumption, but this is rarely necessary in a trauma patient. Less invasive measurements of cardiac output include direct arterial blood pressure measurement or indirect blood pressure measurement with Doppler or oscillometric techniques. Even if blood pressure measurement is within normal limits, peripheral perfusion may be inadequate to meet the oxygen demands of the peripheral tissues.

Immediately following triage assessment, venous access should be obtained (see Chapters 178 and 179). The cephalic vein may be preferable due to ease of access and familiarity, but additional sites include the lateral or medial saphenous veins and femoral veins. The jugular vein should be avoided unless absolutely necessary in patients with suspected head trauma to prevent an increase in intracranial pressure. In the event that venous access cannot be obtained percutaneously, a surgical cut-down or intraosseous catheter should be placed. Large dogs may require multiple catheters if rapid volume replacement is necessary. If possible, a sample of blood should be obtained at the time of catheterization for blood gas, packed cell volume (PCV), total protein (TP), lactate, blood glucose, and electrolytes analysis.

If impaired circulation is suspected based on physical examination, blood pressure management and/or laboratory data evaluation, fluid therapy should be initiated immediately. The blood volumes of the dog and cat are 90 mL/kg and 60 mL/kg, respectively (see Chapter 153). These volumes are commonly termed the shock dose of the dog and cat, although the full amount is rarely indicated. An initial bolus of 20–50% of the

shock dose should be administered rapidly. Following the initial bolus, repeat examination of perfusion parameters and blood pressure should be performed. At the discretion of the clinician, a minimum database (MDB; includes PCV (%), TP (g/dL), and serum glucose) or extended database (EDB; includes PCV (%), TP (g/dL), and venous blood gas, including lactate) should also be performed to determine the need for additional fluid administration. If impaired circulation is unresponsive to fluid therapy, further evaluation to identify causes of refractory shock is indicated. Non-responsive shock can occur due to continued hemorrhage or cardiogenic shock secondary to arrhythmias, pericardial effusion, myocardial depression, electrolyte abnormalities, impaired venous return (tension pneumothorax) or organ ischemia (torsion). The most common cause of non-responsive shock in the trauma patient is active hemorrhage. Potential sites of sustained hemorrhage include the peritoneal space, retroperitoneal space, pleural space, external hemorrhage, and around long bones (femur or humerus).

Initial assessment of the PCV and TP may aid in the diagnosis of active hemorrhage. As a result of splenic contraction in dogs with active hemorrhage, initial evaluation of the PCV and TP typically reveals a relative hypoproteinemia (TP <6.0 g/dL) and a PCV within the reference range. Following initial fluid resuscitation, the PCV typically decreases to less than 30% and the TP decreases to less than 3.5 g/dL. In patients with severe hemorrhage that cannot be stabilized with crystalloid fluid resuscitation, additional fluids should be considered including synthetic colloids, hypertonic saline, hypertonic saline and synthetic colloid combination, blood component therapy (plasma, pRBC), or whole blood (see Section 5). Following initial fluid resuscitation, continuous monitoring of perfusion and oxygenation is necessary. Trauma patients are in a dynamic state and therefore it is crucial to monitor trends and anticipate complications before they occur.

A third factor that affects oxygen delivery is hemoglobin (Hb) concentration. Hb is the primary carrier of oxygen within the vascular system. It has the capacity to carry 1.34 mL of oxygen per gram of Hb. Only a minimal amount of oxygen exists dissolved and unbound within plasma (0.003%). The PCV of the trauma patient gives a rough estimate of the Hb concentration (Hb in g/dL is roughly one-third of the PCV). As previously discussed, the initial PCV will drop quickly following fluid resuscitation. There is no specific PCV at which a trauma patient should be transfused. Rather than monitoring the number specifically, physiological perfusion and oxygenation parameters should be monitored closely. Clinical signs indicative of low hemoglobin and oxygen delivery include tachycardia, tachypnea, hypotension, bounding

or weak pulses, altered mentation, and cardiac arrhythmias. Blood component therapy should be initiated before the hemoglobin and PCV has reached a critically low point.

Further Evaluation

In addition to optimization of oxygen delivery, the trauma patient should be evaluated for end-organ compromise (renal or central nervous systems). A depressed mentation can be a result of poor cerebral perfusion or traumatic brain injury (TBI). Following initial fluid resuscitation, a thorough neurological examination should be performed to establish a baseline from which to evaluate progression and therapy (see Chapter 20). The Modified Glasgow Coma Scale (MGCS) is a scoring system that evaluates the motor activity, brainstem reflexes, and level of consciousness based on a score out of 18. A score of 18 indicates a neurologically normal patient. The MGCS can be used to predict a trauma patient's prognosis over time. Patients with a score less than 8 on initial evaluation have a 50% chance of survival at 48 hours. For every 1-point increase in the MGCS on presentation, the probability of survival increases [6].

In patients with TBI, altered mentation can occur as a result of direct tissue damage, hemorrhage, hematoma formation, cerebral edema, cerebral ischemia or hypoxia and increased intracranial pressure (see Chapter 19). The underlying injuries resulting from TBI can be classified into two main categories: primary and secondary injuries. Primary injuries occur immediately as a result of direct damage. Secondary injuries occur minutes to days following the primary injury. Secondary injuries are the result of physical or biochemical intracranial alterations and extracranial injuries [7].

Cerebral perfusion pressure (CPP) is equal to the difference between mean arterial pressure (MAP) and intracranial pressure (ICP). Therefore, in patients with altered mentation, it is imperative to maintain an appropriate MAP to support CPP. Therapeutic considerations include optimization of CPP, maintenance of adequate blood oxygen saturation, mannitol for treatment of intracranial hypertension (0.5 g/kg IV), mild elevation of the head (15–30° without kinking the neck), and hyperventilation.

Additional nursing care precautions should be taken with TBI patients. Sampling and indwelling catheter placement in the jugular vein should be avoided unless absolutely necessary. Tight collars and wraps should be removed from the neck. Care should be taken to avoid inducing a sneeze, cough, and vomiting.

Any trauma patient has the potential for urinary system damage from either impaired renal perfusion

or direct urinary system damage. Manifestations of renal hypoperfusion may not be evident until several hours following presentation. Potential abnormalities include direct renal injuries (avulsions, hematoma, contusions), ureteral rupture, bladder rupture, or urethral trauma. Even patients with lower urinary tract trauma may be able to pass urine. Regular monitoring of fluid accumulation within the peritoneal and retroperitoneal space is recommended. Abdominocentesis (see Chapter 186) and comparison of the peritoneal fluid creatinine to peripheral serum creatinine can be used to diagnose a uroabdomen (see Chapter 103). A fluid creatinine to serum creatinine ratio of $\geq 2:1$ is considered diagnostic of a uroabdomen [8]. In patients with a uroabdomen, additional imaging studies (contrast studies, ultrasound or radiographs) may be necessary to determine the site of tear/rupture (see Chapter 103).

Following thorough evaluation of perfusion, central nervous system, and renal function, the musculoskeletal and peripheral nervous system should be evaluated. A large case study of blunt trauma in dogs was performed in 2009 and reported that appendicular injuries were very common and recognized in 53% of patients [2]. A thorough oral examination including

visualization of the hard and soft palate, palpation for asymmetry and malocclusion for evaluation of oral trauma is recommended. A thorough examination of all cranial nerves and palpation of the orbit, globe, and skull should be performed. A rectal examination is necessary in every trauma patient. The pelvic canal should be palpated for fractures, instability, and evidence of frank hemorrhage. If at all possible, assessment of the patient's ability to ambulate should be performed.

The above systems should be monitored closely for the initial 24–48 hours following trauma, regardless of any perceived stability on presentation. The intensity of monitoring should be proportional to the status of the patient. Owners should be made aware that complications may not be detected until several days to months following trauma.

Diagnostic Imaging

Diagnostic imaging is an imperative part of the complete evaluation of a trauma patient. Imaging is never therapeutic and therefore should not be pursued prior to thorough physical examination and

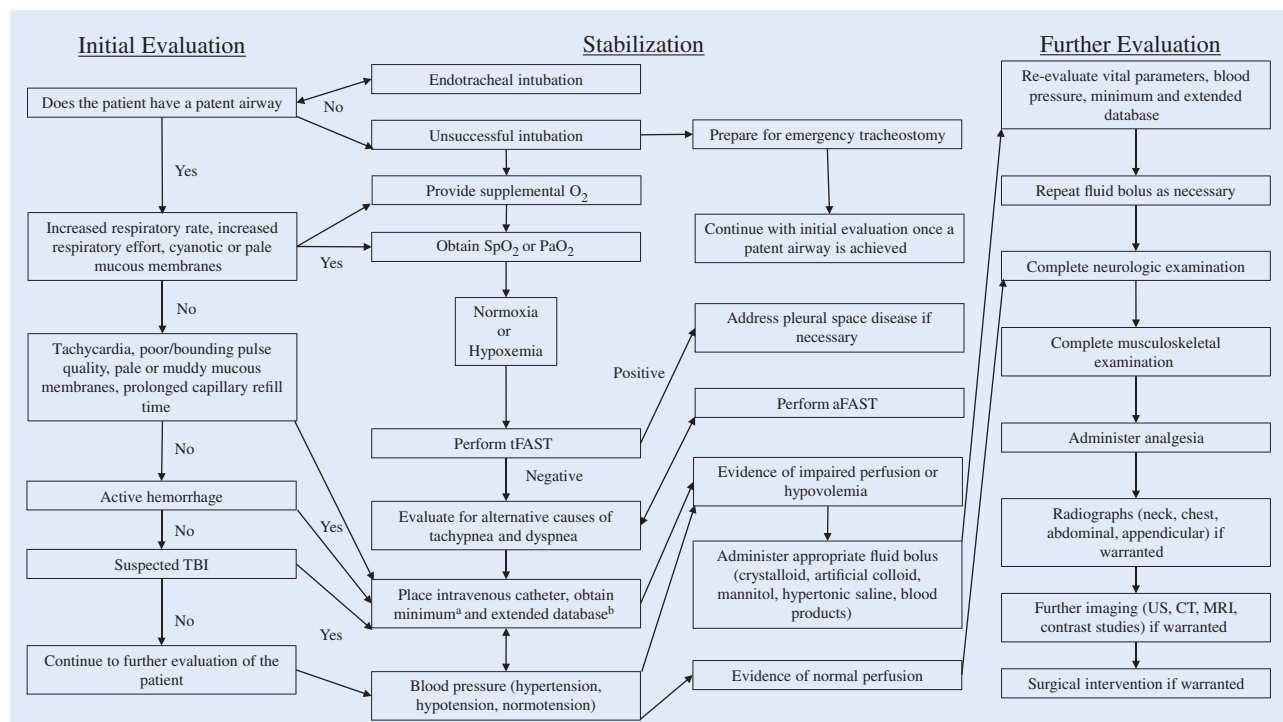


Figure 8.2 Algorithm for evaluation and stabilization of the small animal trauma patient. aFAST, abdominal focused assessment with sonography for trauma; CT, computed tomography; MRI, magnetic resonance imaging; TBI, traumatic brain injury; tFAST, thoracic focused assessment with sonography for trauma; US, ultrasound.

immediate stabilization of the patient. The availability of table-side ultrasound has improved the initial assessment of the trauma patient. Abdominal/thoracic focused assessment with sonography for trauma (aFAST/tFAST) can be utilized to evaluate a patient for thoracic and abdominal disease (see Chapter 182) [9–11]. Thoracic injuries occur in approximately 72% of trauma patients [2]. Thoracic injuries such as pneumothorax, contusions or diaphragmatic hernia can be documented based on the presence of absent glide sign, increased B-lines or abdominal contents within the thoracic cavity. Abdominal injuries occur in 12–50% of trauma patients [2] and can be qualified by evaluation of free fluid within the four quadrants of the abdomen (diaphragmatic-hepatic, hepatorenal, splenorenal or cystocolic) [9]. Based on the location of the free fluid, specific types of injuries are considered more likely (see Chapter 182).

Additionally, thoracic radiographs should be evaluated in every trauma patient to further assess the severity

of pulmonary contusions, rib fractures, and other pleural space diseases not diagnosed on physical examination or tFAST. Radiographs of the abdomen and appendicular skeleton are recommended based on physical examination findings. In patients with severe polytrauma, a full-body computed tomography (CT) scan may provide more accurate assessment of all injuries. This modality is ideal for patients that may require staged surgical intervention.

Conclusion

This chapter provides a general overview of the approach to a trauma patient. Trauma accounts for roughly 10% of veterinary hospital admissions [3]. Evaluation and stabilization of the trauma patient typically require a multisystem approach (Figure 8.2). For more detailed information, please see Section 4, Trauma and Resuscitation.

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9

Reproductive Emergencies

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Introduction

Reproductive emergencies in females often occur during and after estrus and during pregnancy. It is imperative that veterinarians recognize life-threatening complications and treat them accordingly. During pregnancy, saving the life of the dam should be the first consideration, followed by the neonates and then, lastly, saving the reproductive capacity of the dam. In males, reproductive emergencies include those of the penis (priapism), testicles (cryptorchidism, testicular neoplasia, testicular torsion), and prostate (prostatitis, neoplasia, benign prostatic hypertrophy). The reader is referred to Section 3G, (Reproductive Disorders).

Female Reproductive Emergencies

Many female reproductive disorders can be life-threatening and should be of strong consideration when evaluating the systemically ill, intact female animal. Although reproductive disorders occur primarily in intact female dogs and cats, incomplete ovariectomy can result in stump pyometra in the supposedly spayed animal.

Vaginal Discharge

There are several possible causes of vaginal discharge and the nature of the discharge as well as the reproductive status of the animal help determine the likely cause. Discharge evident at the vulva can be originating from the uterus, vagina, and/or vestibule so a full physical examination, including a vaginal examination, is often important in the evaluation of these patients.

Hemorrhagic Discharge

Hemorrhagic vaginal discharge is normal during the proestrus phase of the reproductive cycle. It usually persists for 6–11 days and is associated with swelling of

the vulva and growth of the mammary glands [1]. The vaginal discharge associated with vaginitis or an open pyometra (discussed further below) can be hemorrhagic in appearance and cytological evaluation should be performed if the fluid is at all unclear. Hemorrhagic vaginal discharge has been reported subsequent to anticoagulant rodenticide intoxication (or other causes of coagulopathy), in particular in the postpartum weeks. Coagulation testing is recommended if there is not a clear reason for vaginal hemorrhage. Vaginal foreign bodies and vaginal neoplasia can also cause hemorrhagic vaginal discharge, again highlighting the importance of a vaginal examination in these cases.

Purulent Vaginal Discharge

Purulent discharge evident at the vulva can occur with an open pyometra, metritis or vaginitis. Pyometra occurs during diestrus when progesterone levels are very high and is more common in older, intact dams. It is often preceded by cystic endometrial hyperplasia and can occur with an open cervix or a closed cervix, with clinical signs varying from mild abnormalities to severe sepsis [2]. Vaginal discharge is usually present with open cervix pyometra and these animals generally have somewhat milder clinical signs. Closed cervix pyometra in dogs tends to cause more severe clinical signs such as shock and sepsis. A diagnosis is made with a combination of clinical signs and abdominal radiographs or ultrasound.

The first line of treatment is ovariohysterectomy although efforts to stabilize critically ill animals prior to surgery are essential. For valuable breeding animals, medical treatment of open cervix pyometra can be attempted but the owner must be warned that a recurrence is likely. Pyometra in queens may be associated with minimal clinical signs, making diagnosis more challenging [3]. It is important to note that stump pyometra can occur in animals who have had an ovariohysterectomy. For this reason, pyometra should not be considered solely a

disease of intact animals (see Chapter 123). Metritis can also be a cause of purulent vaginal discharge in the postpartum animal.

Vaginitis describes inflammation of the vagina and/or vestibule. In comparison to pyometra, it is generally very irritating to the animal and often associated with licking, scooting, and rubbing of the vulva. Perivulvar dermatitis may be a consequence. It can occur in animals of all ages and has several potential causes although primary bacterial vaginitis is uncommon. Puppy vaginitis occurs in dogs less than 12 months of age and usually resolves without therapy, after the first estrus [1]. Other potential causes of vaginitis include vaginal foreign bodies, vaginal neoplasia, urine pooling, and urinary tract infections. Initial diagnostic tests include vaginal examination and vaginal cytology. Further work-up and treatment will be dependent on the clinical scenario. Systemic antibiotics are often not indicated and prevention of self-trauma is an important aspect of the management of these cases.

Swollen Vulva or Mass Lesion

Swelling of the vulva is normal during proestrus and estrus and in the periparturient animal. Vulvar swelling can also occur secondary to self-trauma in cases of vaginitis or perivulvar dermatitis. Mass lesions of the vagina and/or vestibule can make the vulva prominent with or without tissue protruding through the vulvar opening. Causes of mass lesions include neoplasia, vaginal fold hyperplasia, vaginal prolapse, and uterine prolapse.

True vaginal prolapse is rare and usually occurs in the periparturient period. It is recognized by swelling of vaginal tissue through the vulva with a urethral orifice located ventrally. In most cases, parturition can continue as normal and the prolapse will be self-resolving. Hysteropexy and/or cesarean section may be necessary if vaginal prolapse causes dystocia. Prolapse of a vaginal fold is more common than true vaginal prolapse. This generally occurs during proestrus or estrus. In most cases it will resolve during diestrus. Reoccurrence can be prevented by ovariohysterectomy. In both true vaginal prolapse and vaginal fold prolapse, the tissue may be dry, necrotic or ulcerated and treatment to keep the tissue moist and prevent trauma is important (see Chapter 125).

Uterine prolapse is a rare condition where the uterus prolapses through the cervix and vagina and is most commonly seen in the periparturient period. It may involve one or both horns and may lead to shock and death. A history of straining, either from labor or constipation, often precedes the prolapse. In cats, it can occur up to 48 hours after the last kitten is born. Treatment involves

cleaning the tissue and replacing it or surgical removal of necrotic tissue (see Chapter 125).

Reproductive Emergencies of the Pregnant Patient

Uterine Torsion

Uterine torsion has been reported in both dogs and cats and occurs secondary to an enlarged uterus, such as at term pregnancy, or the presence of fluid-filled uterine horn(s), such as pyometra or mucometra [4,5]. In the pregnant animal it can occur before parturition or as a cause of dystocia. Uterine torsion can occur unilaterally; as a result, the animal may birth some of the fetuses in a normal fashion. Clinical signs of uterine torsion may be as minimal as failure to proceed with parturition or it can lead to peritonitis and severe sepsis. Abdominal imaging will show an enlarged uterine horn(s). Diagnosis is confirmed on laparotomy and definitive treatment is ovariohysterectomy.

Dystocia

Dystocia is defined as delay or difficulty in expelling fetus(es) and is more common in older animals, especially brachycephalic breeds [6,7]. Causes can be maternal (uterine inertia, narrow birth canal, uterine torsion/prolapse), fetal (oversize, malpresentation or formation, death), and/or physiological (stress, hypocalcemia, body condition) [8].

As an emergency clinician, determining when an animal should be transported to a veterinary facility for evaluation of dystocia is an important decision. Chapter 118 reviews the key indications for evaluation. If dystocia is identified, a minimum database to assess for anemia, azotemia, hypocalcemia, and hypoglycemia is recommended. A full biochemistry and complete blood count would be ideal. Fetal heart rate is a monitor of fetal distress and fetal bradycardia (<180bpm) suggests that intervention is warranted.

Medical management of dystocia can include IV fluids, correction of hypocalcemia or hypoglycemia and possibly oxytocin. Cesarean section is indicated in some patients.

Reproductive Emergencies of the Periparturient Patient

Metritis

Metritis is an endometrial infection from retained placenta/fetus, necrotic uterine tissue, or a bacterial infection of the uterus. It is recognized in a bitch or queen that becomes systemically ill several days after parturition and a foul-smelling vaginal discharge is common. Normal lochia is greenish and does not have a foul odor. Fever, lethargy, and decreased milk production may also be present. Abdominal radiographs or ultrasound

may detect the presence of a retained fetus or fetal tissue. Metritis can lead to severe sepsis and may require aggressive intervention. Therapy includes IV fluids, antibiotics, and ovariohysterectomy if retained tissue is discovered (see Chapter 122).

Mastitis

Mastitis most commonly occurs postpartum but can occur in mammary glands following progesterone-induced hyperplasia [9]. It can be due to trauma from nursing or environmental factors or from hematogenous spread of bacteria. The most common bacteria isolated are *E. coli*, staphylococcal and streptococcal species. Clinical signs include swollen, warm, painful mammary gland or glands. There may be areas of necrotic tissue or abscesses. The dam may be anorectic, lethargic and febrile. Treatment includes antibiotic therapy and wound management (see Chapter 122).

Eclampsia

Hypocalcemia in the lactating female is more common in toy and small breed dogs and is rare in cats. Predisposing factors include calcium supplementation during pregnancy and large litters [10]. Clinical signs include anxiety, pacing, panting, whining, ataxia, muscle twitches or tremors, tetany, and possibly seizures. The dam may also develop hypoglycemia and hyperthermia. Diagnosis is ideally based on ionized calcium measurement and levels $<0.8\text{ mmol/L}$ are consistent with eclampsia [10]. Evaluation of body temperature and blood glucose is also important. Treatment includes intravenous calcium administration and other therapies as indicated.

Male Reproductive Emergencies

Paraphimosis and Priapism

Paraphimosis describes the inability to retract the penis into the prepuce. It is often the result of hair causing entrapment of the base of the penis. Tissue necrosis and trauma can occur if it is not addressed quickly. Treatment includes cleaning and lubrication of the penis to aid replacement in the prepuce. Any underlying causes should be addressed. In some cases, surgical narrowing of the preputial opening may be indicated. If necrosis of penile tissue occurs, surgery such as penile amputation with prescrotal or perineal urethrostomy for dogs and cats respectively, along with neutering, may be necessary.

Priapism is an inappropriate and persistent erection, not due to sexual stimulation and is a rare disorder in dogs and cats. Causes may include trauma, neurological

disease, mass lesions, and thrombosis. Without rapid therapy, ischemic necrosis can occur, necessitating penile amputation (see Chapter 126).

Prostate Disorders

Prostatic disease can present as an emergency, either as a result of the associated clinical signs such as tenesmus, dysuria, etc. or possibly due to severe systemic disease secondary to prostatic disease. The most common presentations for disorders of the prostate are tenesmus and urinary problems (dysuria, hematuria, straining to urinate). Benign conditions (benign prostatic hyperplasia and prostatic cysts) more frequently occur in sexually intact male dogs with the risk increasing with advanced age [11,12]. Physical examination may reveal a symmetrically enlarged, non-painful prostate. Treatment is castration.

Prostatitis and prostatic abscesses are serious health conditions that can lead to a rapid decline and sepsis if an abscess ruptures into the abdomen (see Chapter 87). These conditions are much more common in sexually intact males and these dogs are clinically ill. If the inflammation remains confined to the prostate, the dog may show tenesmus, stiff gait, hematuria, and stranguria. If the infection has spread (i.e. ruptured abscess), there will likely be clinical signs of sepsis including anorexia, lethargy, fever, hypotension, and tachycardia, along with the other signs. Diagnostics depend on the clinical presentation and may include abdominocentesis (if septic peritonitis has developed), urinary gram stain, urinary culture and susceptibility, abdominal ultrasound, abdominal radiographs as well as CBC and biochemistry panel. *Brucella canis* should be ruled out in suspected individuals. Avoidance of vigorous prostatic manipulation, particularly when abscesses are present, is warranted. Treatment includes antibiotics, supportive care, and surgical management when indicated.

Prostatic neoplasia can occur in sexually intact (adenocarcinoma) and neutered (urethral carcinoma, undifferentiated carcinoma) male dogs. There is an increased incidence with age (median age ~10 years) and these are locally invasive and frequently metastasize [12]. Clinical presentation often involves urinary abnormalities (hematuria, stranguria, incontinence), pain on palpation of the lower back, and tenesmus. Diagnosis is histological and treatment depends on the staging work-up (see Chapter 124).

Testicular Torsion

Although there are numerous testicular diseases of dogs and cats, testicular torsion is one of the few that

will present on an emergency basis. Dogs with testicular torsion often present with acute testicular, inguinal, or abdominal pain and may have systemic abnormalities (anorexia, lethargy, fever, etc.). If the descended testicle is affected, it is painful and enlarged on palpation. If an abdominal testicle is affected, a mass can often

be palpated. A brief report of testicular torsion in a cat described the cat to be behaving normally; a small swelling of the scrotum was noted without pain. The abnormality was identified on elective orchidectomy [13].

Testicular torsion is a surgical emergency and removal of the affected testicle is required (see Chapter 126).

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10

Anemia

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Introduction

Anemia is defined as a decrease in the red blood cell mass. This is identified by a packed cell volume (PCV), hematocrit (HCT), red blood cell count or hemoglobin (Hb) level below the normal reference range for the species. Decreased Hb results in decreased tissue oxygen delivery, and cellular ischemia [1]. Anemia is classified by causative mechanism (decreased erythropoiesis, hemorrhage or hemolysis) or by bone marrow response (regenerative or non-regenerative). Successful management of the anemic patient depends on a systematic diagnostic approach, supportive therapy with blood products and timely, effective intervention to treat or manage the underlying cause.

This chapter addresses the etiology of anemia in dogs and cats and the diagnostic approach to these patients. More detailed information on specific conditions and their management, including blood transfusion, is found elsewhere in this text (see Chapters 65, 66, 177).

Etiology

Anemia results from decreased erythropoiesis, hemorrhage or hemolysis (Box 10.1) [2,3]. In dogs, anemia is most commonly related to cancer and anemia of inflammatory disease [4]. These anemias are usually non-regenerative and tend to be mild or moderate in magnitude. With severe anemia, hemolytic causes are more common. In cats, most anemias are non-regenerative [5]. Bone marrow disorders are most common in this species, reportedly accounting for 53% of cases, while hemorrhage and hemolysis were seen in 21% and 11% of anemic cats, respectively. Infectious diseases and neoplasia were most common (22% and 20%, respectively) [6].

Consequences of Anemia

Anemia results in decreased tissue oxygen delivery and hypoxia. Acute and chronic compensatory mechanisms mitigate this effect and are responsible for some of the clinical findings in anemic patients.

Tissue oxygen delivery (DO_2) is a product of cardiac output (stroke volume $\times$ heart rate) and arterial blood oxygen content (CaO_2). Blood oxygen is composed primarily of oxygen bound to Hb, with a smaller proportion dissolved in plasma, as defined by the following equation:

$$\text{CaO}_2 = (1.34 \times \text{Hb} \times \text{SaO}_2) + (0.003 \times \text{PaO}_2)$$

where SaO_2 is the oxygen saturation of Hb and PaO_2 is the partial pressure of dissolved oxygen.

Thus, decreased Hb concentration has a significant impact on CaO_2 . Compensatory responses increase cardiac output to attempt to maintain DO_2 . Elevated sympathetic tone causes increased heart rate and myocardial contractility. Moreover, decreased blood viscosity results in increased venous return and decreased left ventricular afterload, thereby increasing stroke volume [7]. The decreased viscosity, together with anemia-induced vasodilation, leads to decreased peripheral vascular resistance. A redistribution of blood flow also occurs, with reduced flow to splanchnic vascular beds and associated sparing of circulation to the coronary and cerebral vasculature [8].

In the normal physiological state, DO_2 exceeds tissue oxygen consumption (VO_2) by approximately 400%. This supply–demand relationship is independent until a critically low DO_2 is reached and VO_2 then becomes limited by inadequate DO_2 , resulting in anaerobic metabolism and lactic acidosis. It is at this critical level that tissue ischemia and anemic shock ensue [1]. The magnitude of

Box 10.1 Causes of anemia classified by mechanism [2,3].**A. Decreased or ineffective erythropoiesis**

- Extramarrow disease
 - Anemia of inflammatory disease
 - Renal failure
 - Endocrine disease (hypoadrenocorticism, hypothyroidism)
 - Neoplasia
 - Iron deficiency
 - Starvation
- Intramarrow disease
 - Pure red cell aplasia
 - Immune mediated
 - Viral: parvovirus, FeLV
 - Congenital
 - Aplastic anemia
 - Infectious: Parvovirus, Ehrlichia, Anaplasma, FeLV/FIV
 - Drugs: estrogen, chemotherapy, griseofulvin, fenbendazole, albendazole, trimethoprim/sulfa, chloramphenicol, methimazole, phenylbutazone, quinidine, thiacetarsamide
 - Radiation
 - Idiopathic/immune mediated
 - Mycotoxins (cats)
 - Myelophthisis: neoplasia, fibrosis
- Tick-borne disease (ehrlichiosis, babesiosis, Rocky Mountain spotted fever)
- Bacterial infections
- Viral infection (FeLV, FIV, FIP)
- Neoplasia (particularly lymphoma)
- Alloimmune hemolytic anemia
 - Neonatal isoerythrolysis
 - Incompatible blood transfusions
- Heavy metal toxicity
 - Zinc
 - Copper
- Oxidative damage
 - Allium spp.: onions, garlic
 - Drugs: acetaminophen, cephalosporins, penicillins, sulfonamides, phenothiazines, procainamide, benzocaine, methimazole, propylthiouracil, dipyron, quinidine, phenazopyridine
 - Other: methylene blue, castor beans, propylene glycol, diabetes mellitus
 - Can be normal in cats
- Erythroparasites
 - Dogs: *Babesia canis*, *Babesia gibsoni*, *Mycoplasma haemocanis*
 - Cats: *Mycoplasma haemofelis*, *M. haemominutum*, *Cytauxzoon felis*, *Babesia felis*
- Microangiopathic
 - Disseminated intravascular coagulation
 - Hemangiosarcoma
 - Splenic or hepatic disease
 - Heartworm caval syndrome
- Inherited
 - Phosphofructokinase deficiency
 - Pyruvate kinase deficiency
 - Increased osmotic fragility
- Miscellaneous
 - Hypophosphatemia
 - Snake envenomation

B. Blood loss

- Trauma, surgery
- Bleeding disorder
- Ruptured neoplasm
- Gastrointestinal ulceration
- Ecto- or endoparasites

C. Hemolysis

- Immune mediated
 - Immune-mediated hemolytic anemia
 - Primary
 - Secondary
 - Live vaccines
 - Antibiotics (sulfonamides, penicillins)

anemia at which this occurs is variable. In experimental models, a HCT of 10–14% is suggested [9–11]. However, numerous factors in the clinical setting will affect this relationship, including concomitant disease processes or drugs that exacerbate reduced DO_2 (e.g. hypoxemia), alter oxygen consumption (e.g. sepsis, SIRS), or ameliorate the hemodynamic compensatory responses (e.g. decreased myocardial contractility, sepsis/SIRS, beta-blockers, vasodilators) [8]. Moreover, chronicity of disease has a significant impact on the HCT threshold.

Non-hemodynamic compensatory mechanisms occur with chronicity. Anemia results in increased 2,3-diphosphoglycerate (2,3-DPG) concentrations (marginally in species that contain low intraerythrocytic 2,3-DPG concentrations, i.e. cats, where chloride is the major effector molecule) [12,13]. This increases oxygen dissociation from Hb in the tissues, thereby increasing DO_2 . As a result, chronic anemia is better tolerated than acute anemia, and the need for intervention generally occurs at a lower HCT threshold.

Clinical Signs

Anemic patients are usually presented for progressive lethargy and weakness, which may culminate in an anemic crisis and collapse. Onset ranges from peracute to chronic. Inappetence and tachypnea may also be reported. Caregivers sometimes notice pallor, icterus or bleeding.

The severity of clinical signs is generally correlated with the magnitude of the anemia and with chronicity. Patients acutely affected by even moderate anemia can be decompensated, particularly where concurrent hypoperfusion or hypoxemia exacerbates tissue hypoxia. Conversely, patients with chronic anemia can generally tolerate a more severe anemia with fewer manifestations. Regardless of the rate of onset, tissue hypoxia is likely if the PCV is less than 12–15% [14].

Diagnosis

Diagnosis of the cause of anemia depends on a thorough history and physical examination, and laboratory assessment via PCV, complete blood count (CBC), reticulocyte count and blood smear examination. In some cases, these assessments will elucidate a definitive etiology. More commonly, they enable determination of the mechanism of the anemia and consolidation of a finite list of differential diagnoses, thus guiding focused diagnostic testing.

History

The signalment of the patient may be informative. Young animals are more likely to have congenital disease or blood loss due to parasites, whereas older animals are at greater risk of malignancies. The history should include detailed enquiries into medications, diet, travel, and past illnesses. Current drug therapy may predispose to immune-mediated disease, bone marrow suppression or thrombopathia. Dietary indiscretion (e.g. onions, zinc) can cause hemolysis, while travel to certain geographic locations should alert the clinician to the possibility of tick-borne or parasitic disease. The owner should be specifically questioned regarding signs of bleeding, including melena, hematuria or epistaxis, as well as any prior bleeding episodes. Given the prevalence of viral disease in anemic cats, detailed questions should be asked regarding exposure. The onset of clinical signs is often subtle and not obvious to the owner, but careful questioning may enable the clinician to determine chronicity.

Physical Examination

Pallor is the hallmark sign of anemia but must be differentiated from pallor associated with hypoperfusion by

assessment of perfusion parameters and confirmation of anemia (by PCV or CBC). Patients in an anemic crisis are typically obtunded, with marked pallor, tachycardia, bounding pulses, and tachypnea.

Physical examination should include a thorough search for evidence of hemorrhage: evaluation of body cavities, examination of the skin, mucous membranes and joints, as well as a rectal examination. The presence of icterus or splenomegaly is an important finding and should raise concern for a hemolysis, though neither is pathognomonic. Fever may result from inflammation, infectious disease, neoplasia or acute immune-mediated hemolysis. The clinician should actively seek evidence of neoplasia, infectious disease or immune-mediated disease (arthritis, uveitis or cutaneous lesions).

Laboratory Assessment

Anemia is rapidly assessed via PCV measurement. Confirmation of anemia should be followed by blood smear examination, CBC, and reticulocyte count.

Packed Cell Volume

A decreased PCV confirms anemia. PCV generally approximates HCT. The hematocrit is the percentage red blood cells, determined by automated hematology instruments by multiplying the red blood cell count by the mean cellular volume (MCV). The PCV is manually determined via microhematocrit centrifugation [15]. The PCV may be significantly higher than the HCT, however, in patients with macrocytosis, marked reticulocytosis or non-deformable red cells (e.g. spherocytosis). The plasma should be examined for evidence of hemolysis or icterus. Typically, a concurrent decrease in total solids (TS) suggests blood loss. In dogs with acute blood loss, the PCV may be normal or increased due to splenic contraction, and the decreased TS is an important early clue to active hemorrhage. Splenic contraction does not occur in cats.

Blood Smear Examination

Blood smear examination using a Romanowsky type stain (e.g. Diff-Quik) is likely the single most useful tool for evaluating anemia in the emergency setting. It permits assessment of the regenerative response (in dogs), and may elucidate an etiology (Table 10.1) [16]. Reticulocytosis is indicative of regeneration. Reticulocytes are recognized as larger, more basophilic erythrocytes, resulting in anisocytosis and polychromasia. Nucleated red blood cells are a less reliable indicator of erythroid hyperplasia, as they may be present in spite of a quiescent marrow (e.g. with neoplasia, lead toxicity, splenic disease). Regeneration cannot be accurately assessed on blood smear examination in cats. Due to the different forms of reticulocytes in cats (see below), the absence of

Table 10.1 Common erythrocyte abnormalities observed on blood smear examination, and associated causes.

Erythrocyte abnormality	Appearance on blood smear examination	Associated causes
Spherocytes	Small RBCs with lack of central pallor	IMHA, transfused blood, erythrocytic parasitemia, zinc toxicity, snake envenomation
Nucleated RBCs	Visible nucleus or nuclear fragment in erythrocytes	Accelerated erythropoiesis or can occur with lead toxicity, bone marrow pathology, hyposplenism, splenic disease, or heatstroke
Heinz bodies	Small round protrusions from cell margin composed of denatured hemoglobin. Generally seen as clear “blebs”	Oxidative damage
Eccentrocytes	Eccentric hemoglobin	Oxidative damage, particularly allium spp. toxicity
Schistocytes	RBC fragments; usually helmet or crescent shaped	DIC, hemangiosarcoma, heartworm caval syndrome, myelofibrosis, congestive heart failure, glomerulonephritis, chronic doxorubicin toxicity
Echinocytes	Spiculated RBC membrane, with regular interspacing	Artifact from slow drying, glomerulonephritis, lymphoma, doxorubicin toxicity, electrolyte deficiency, rattlesnake envenomation
Acanthocytes	Spiculated RBC membrane, with irregular interspacing	Hemangiosarcoma, portosystemic shunts, chronic liver disease, lymphosarcoma, glomerulonephritis, hepatic lipidosis
Keratocytes	Spiculated red blood cell fragments	DIC, hemangiosarcoma, heartworm caval syndrome, myelofibrosis, congestive heart failure, glomerulonephritis, chronic doxorubicin toxicity

DIC, disseminated intravascular coagulation; IMHA, immune-mediated hemolytic anemia; RBC, red blood cell.

identifiable reticulocytes does not exclude regeneration. Conversely, evidence of any degree of reticulocytosis on smear examination in a cat indicates an acute and profound regenerative response.

Erythrocyte morphology may confirm or suggest a cause. Microcytosis with a non-regenerative anemia suggests iron deficiency or myelophthisis. If hemolysis is suspected, erythrocytes should be evaluated for evidence of oxidative damage (Heinz bodies, eccentrocytes), immune-mediated destruction (spherocytes), physical damage (schistocytes) or parasitemia.

If the patient is bleeding, smear examination is essential to rapidly assess platelet numbers to assess for thrombocytopenia. A blood smear should be prepared using EDTA-anticoagulated blood. The feathered edge of the smear should be evaluated for platelet clumps that could contribute to a pseudothrombocytopenia. If clumping is not present, the platelet count can be estimated by multiplying the average number of platelets per high power field within the monolayer of the blood film by 15 000. An estimated count less than 30 000–50 000 can contribute to bleeding tendencies [17]. Evaluation of leukocytes enables assessment of white cell numbers and proportions, and may indicate a left shift, neoplastic changes or parasites.

Complete Blood Count

The CBC determines absolute cell numbers and red cell parameters. Depending on the technology, cell types are

typically distinguished based on size (impedance), granularity and/or light-scattering properties [18]. In cats, there is often considerable overlap between erythrocyte and platelet volumes, and impedance-based automated cell counters cannot resolve the cells into two distinct populations, resulting in inaccurate counts. Blood smear evaluation is recommended for verification of CBC results, particularly where in-house laboratory analyzers are used.

Red cell indices – MCV, mean corpuscular hemoglobin concentration (MCHC) and red cell distribution width (RDW) – may suggest the regenerative nature of the anemia but are neither pathognomonic nor particularly reliable, and do not preclude the need for a reticulocyte count. Non-regenerative anemia is typically normocytic and normochromic (normal MCV and MCHC) with homogenous cell volumes (normal RDW). Iron deficiency anemia is usually microcytic and hypochromic, but can be macrocytic in the early stages. Regeneration is suggested by red cell indices that demonstrate macrocytosis (high MCV), hypochromasia (low MCHC), and anisocytosis (high RDW). In one study, however, only 11.8% of canine regenerative anemias were macrocytic and hypochromic based on these indices [19]. Polychromasia was a more accurate indicator, highlighting the utility of blood smear evaluation when a reticulocyte count is not available. Similar findings in cats demonstrate little correlation between red cell indices and a regenerative response [5].

Reticulocyte Count

A reticulocyte count is essential in all anemic patients, to quantify the regenerative response. Reticulocyte counts are performed using supravital staining that enables visualization of ribosomes. A few drops of blood are mixed with an equal volume of 0.5% new methylene blue in physiological saline; 1000 red blood cells are counted and the percentage of reticulocytes recorded. This is uncomplicated in the dog where only one reticulocyte type exists. The cat, however, has two types of reticulocytes: aggregate reticulocytes, in which the organelles are coalesced into aggregates, and punctate reticulocytes, in which the organelles are present as small particles. Aggregate forms are released from the marrow and, after approximately 12 hours, develop into punctate forms that persist in the circulation for 9–20 days [16]. Aggregate forms therefore indicate active regeneration, whereas punctate forms indicate recent, cumulative regeneration. Since punctate forms are not recognizable on routine staining, the degree of regeneration may be underestimated in cats. If both forms are counted and not distinguished, active regeneration may be overestimated.

The degree of reticulocytosis must be interpreted relative to the degree of anemia, ideally by calculation of the absolute reticulocyte count, where absolute reticulocyte count = observed reticulocyte percentage $\times$ RBC number ($\times 10^3/\mu\text{L}$). In dogs, an absolute reticulocyte count exceeding $60\,000/\mu\text{L}$ is evidence of regeneration. In cats, aggregate reticulocytes counts exceeding $50\,000/\mu\text{L}$ are considered regenerative [16]. Alternatively, if the RBC number is not available, a corrected reticulocyte percentage can be calculated as follows:

$$\begin{aligned} \text{Corrected reticulocyte percentage} \\ = \text{Observed reticulocyte count} \times (\text{PCV}/\text{N}) \end{aligned}$$

where N is 45 in the dog and 37 in the cat. A corrected reticulocyte percentage over 1% indicates regeneration.

Diagnostic Approach

The essential first step in the diagnostic approach to the anemic patient is to ascertain the mechanism of the anemia: decreased erythropoiesis, hemorrhage, or hemolysis. This begins with determination of regeneration via reticulocyte count or, in the emergency setting, blood smear examination. The presence of regeneration indicates either hemorrhage or hemolysis. The absence of regeneration suggests decreased erythropoiesis. There are, however, three important exceptions:

- acute hemorrhage or hemolysis of less than 2–4 days duration

- concomitant disease that precludes an appropriate bone marrow response (e.g. renal failure)
- immune-mediated hemolytic anemia (IMHA) in which the immune response targets red cell precursors.

In these cases, the anemia will be non-regenerative in spite of a hemorrhagic or hemolytic etiology.

If the anemia is regenerative, the next step is to determine if it is due to hemorrhage or hemolysis. Several clinical clues can help in this differentiation. Blood loss is not always obvious, so a careful search must be made for evidence of bleeding. Physical examination can be augmented by focused assessment with sonography for trauma (FAST) scans to assess for cavitory hemorrhage [20] (see Chapter 182). In rare cases, hemorrhage and hemolysis can occur simultaneously, so documentation of one does not necessarily preclude the other. The serum protein concentration or TS is generally normal with hemolysis and decreased with hemorrhage. There are, however, exceptions: patients with concomitant hemolysis and protein loss or those with pre-existing hyperglobulinemia. Hemoglobinemia and hemoglobinuria indicate intravascular hemolysis. Splenomegaly and icterus usually suggest hemolysis, but are neither consistent nor specific findings.

Having determined the mechanism of the anemia, a comprehensive list of differential diagnoses can be constructed and prioritized such that efficient targeted testing can be initiated to determine a definitive diagnosis.

Decreased Erythropoiesis

Decreased erythropoiesis can result from extramarrow or intramarrow disease. Extramarrow causes result from a systemic disease that selectively depresses erythropoiesis. The pathogenesis of the suppression of bone marrow by extramarrow disease is multifactorial and is mediated by cytokines that result in decreased iron availability, decreased erythrocyte survival, and a decreased regenerative response to anemia [21]. The anemia is generally mild (HCT 25–35% in dogs, 20–25% in cats) and clinical signs of the underlying disease usually predominate. In contrast, intramarrow diseases, such as aplastic anemia, myelodysplasia, myeloproliferative disorders, and myelofibrosis, result from injury to the precursor stem cells and/or the marrow microenvironment. Depending on the precursor cells involved and the course of the disease, variable cytopenias are observed. The early stages of disease are usually characterized by granulocytopenia and thrombocytopenia, with mild to non-existent anemia. Neutropenia develops 5–6 days and thrombocytopenia develops 8–10 days after an intramarrow insult. Due to the long red blood cell lifespan, anemia is

generally mild or absent [22]. As the disease progresses, anemia becomes more predominant. The causes, diagnostic work-up, and management of non-regenerative anemia are covered in Chapter 66.

Hemorrhagic Anemia

Significant blood loss can occur externally, or internally into the pleural cavity, the peritoneal cavity, the retroperitoneal space or the fasciomuscular planes. Large volumes of blood can also accumulate in the gastrointestinal tract before melena is evident. If acute blood loss exceeds 30% of blood volume, signs of hypovolemia predominate: pallor, weak pulses, tachycardia, prolonged capillary refill time, and hypotension. PCV and TS are usually both decreased, although the PCV may remain normal initially in the dog due to splenic contraction and until fluid shifts occur (1–2 hours). Hemorrhagic shock constitutes a life-threatening emergency and must be addressed without delay (see Chapters 153, 189). When hemorrhage is identified in the absence of trauma, it is important to determine whether the bleeding is due to local factors or to a sys-

temic bleeding disorder. If any doubt exists, hemostatic testing is prudent.

Patients with low-grade chronic blood loss are generally not presented until they are severely anemic due to the depletion of iron stores. Since younger animals have smaller stores, they become anemic more readily than do adults, frequently from endo- or ectoparasitism. The anemia is variably regenerative and is usually microcytic and hypochromic; thrombocytosis may be present. Chronic blood loss in the adult is usually into the gastrointestinal tract. Even when parasites are identified in the adult, additional testing is indicated to eliminate the possibility of an additional cause of hemorrhage (e.g. neoplasia, ulceration).

Hemolytic Anemia

Hemolysis can be intravascular or extravascular, and acute or chronic. The associated anemia is almost invariably regenerative except in cases of immune-mediated hemolytic anemia in which red cell precursors are targeted. The causes, diagnostic work-up, and management of hemolytic anemia are covered in Chapter 66.

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11

Jaundice

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Definition

The term “jaundice” or “icterus” describes the yellow pigmentation of the skin, sclera, and mucous membranes as a result of abnormally elevated blood bilirubin levels (hyperbilirubinemia). These terms will be used interchangeably throughout this chapter.

Icterus is a physical abnormality of potentially serious hematological or hepatobiliary dysfunction. The normal serum bilirubin concentration in the dog and cat is approximately 0.1–0.3 mg/dL. Jaundice is not clinically detectable until serum bilirubin level reaches >2.5–3.0 mg/dL. By the time jaundice is visible in the tissues, it will also be detectable in the urine and serum. In the dog, bilirubinuria will often precede clinically detectable jaundice, whereas in the cat the appearance of bilirubinuria is usually accompanied by clinical icterus.

Physiology

Bilirubin is produced each day through the catabolism of heme molecules from senescent red blood cells. The heme group is cleaved in the reticuloendothelial system to form biliverdin, which is then oxidized to unconjugated bilirubin. A smaller proportion of bilirubin is produced from the destruction of maturing red blood cells in the bone marrow and from the hepatic hemoproteins. Unconjugated bilirubin is then released into the circulation where it is tightly bound to albumin and finally enters the liver.

The three phases of hepatic bilirubin metabolism are uptake, conjugation, and excretion into the bile [1]. Unconjugated bilirubin is rendered water soluble by its conjugation with glucuronic acid. If the excretion of conjugated bilirubin is impaired, it will regurgitate into the plasma and cause hyperbilirubinemia and subsequently

icterus. Since conjugated bilirubin is water soluble, it can pass through the glomerulus and enter the urine outflow where it will appear as bilirubinuria.

If the hepatobiliary tree is patent, conjugated bilirubin will enter the biliary canaliculi and eventually be stored in the gall bladder. It will then be emptied into the duodenum where it aids in fat emulsification and enhances the absorption of fat and other lipid-soluble substances. Once in the colon, bilirubin will be converted to stercobilin or urobilinogen, where the former will be excreted in the feces while the latter can be reabsorbed into the circulation and excreted in the urine, or it can be passively reabsorbed in the intestine and then enter hepatocytes for excretion in bile. The dog's renal epithelial cells can degrade hemoglobin to bilirubin, which lowers the renal threshold for bilirubin. Thus, in dogs with liver disease, bilirubinuria can be detected on urine dipstick before its serum concentration is increased. It is common to find small amounts of bilirubin in the urine of normal dogs. The cat's renal epithelial cells cannot convert unconjugated to conjugated bilirubin, therefore preventing bilirubin appearing in the urine of a normal cat [2]. Consequently, a positive urine bilirubin test result in the cat always reflects pathology in the hepatobiliary system or some ongoing hemolytic process.

Pathophysiology

The conventional classification of jaundice divides it into three basic categories: prehepatic, hepatic, and posthepatic (Box 11.1).

Prehepatic jaundice occurs from three basic processes: overproduction, decreased hepatic uptake, and decreased conjugation. Hemolysis is the most common cause of prehepatic jaundice in the dog and cat and it occurs because the destruction of red blood cells leads to

Box 11.1 Classification and selected clinical examples of icterus in the dog and cat.**Prehepatic***Hemolysis**Autoimmune* – immune hemolytic anemia*Congenital hemolytic disease* – pyruvate kinase and phosphofructokinase deficiencies*Infectious* – babesiosis, *Mycoplasma hemophilus**Toxic* – heavy metals (zinc in certain coins after 1982), acetaminophen (cats), certain mushrooms, *Allium* species (onions, garlic)*Traumatic* – microangiopathies**Hepatic***Inflammation**Infectious* – canine adenovirus, canine leishmaniasis, feline cytauxzoonosis, feline infectious peritonitis, bacterial hepatitis/cholecystitis and cholangiohepatitis, cholangiostasis of sepsis*Sterile* – lymphocytic/plasmacytic cholangiohepatitis, pancreatitis, adverse drug reactions*Parasitic* – liver flukes in dogs and cats (species varies with geographic locale)*Toxic**Plants* – mushrooms (*Amanita*), cycads (sago palm), others*Drugs* – methimazole, phenobarbital, sulfa drugs, imidazole drugs, xylitol, NSAIDs, others*Degenerative*

Cirrhosis, lipidosis, and other vacuolar disorders

Can include those that cause toxic and inflammatory hepatopathy

*Neoplastic**Primary* – hepatocellular carcinoma, hepatoma, hemangiosarcoma, lymphoma, mast cell tumor (MCT)*Secondary* – Pancreatic carcinoma, lymphoreticular neoplasia, MCT, several others**Posthepatic***Bile duct obstruction*

Primary or metastatic tumors

Cholelithiasis, choledocholithiasis

Gall bladder mucocele

Pancreatitis (acute or chronic)

Strictures

Parasites (flukes)

Duodenal obstruction

overproduction of heme, which exceeds the liver's ability to conjugate it and deliver it along the normal excretory pathway. The hemolytic disease can be a primary or secondary process leading to red blood cell destruction (see

Chapter 66). *Hepatic* jaundice represents direct liver pathology that can result from inflammation, toxicity, degeneration, infection, neoplasia, or a metabolic defect. *Posthepatic* icterus occurs from any lesion that can cause hepatic biliary outflow obstruction. These conditions include inspissated bile formation, inflammatory swelling or fibrosis, primary or secondary neoplasia, and parasitic causes. Acute pancreatitis can cause both hepatic (cholangiostasis – common) and posthepatic (fibrosis of the cystic duct – rare) jaundice. In most icteric patients, the effect of bilirubin on the body tissues is benign. The main exception occurs in brain tissue where very high levels of bilirubin (levels exceeding 20.0 mg/dL) can accumulate to cause *kernicterus*.

Evaluation of the Icteric Patient

The emergency clinician must perform a thorough history and physical examination in order to help determine the cause of the jaundice. In order to classify the onset of icterus as acute or chronic, the history should always include questions pertaining to the time of onset of the first noticeable clinical signs and the progression of those signs to the time of examination. The patient's environment should be described in search of possible exposure to toxic substances. Knowledge of any previous illnesses and past and present medications should be obtained in order to identify any possible adverse drug reactions.

When icterus is associated with direct liver pathology caused by the ingestion of toxic substances, the animal will usually have a history of inappetence, mental depression, lethargy, vomiting, and/or diarrhea for several days prior to the onset of jaundice, whereas icterus associated with a peracute hemolytic process will occur over a matter of a few hours accompanied by signs that include anorexia, weakness, mental depression, and sometimes vomiting.

Physical Examination

The physical examination begins with careful consideration of the presenting vital signs in order to assess for any immediate life-threatening condition such as hemorrhage and hypotension. Any acute cardiac, pulmonary, and encephalopathic abnormalities should be identified immediately and medically managed as soon as possible. Fever in the icteric patient can indicate global infection from sepsis or a more focal infection such as hepatitis, cholangitis, and cholecystitis. Fever can also accompany sterile conditions such as neoplasia, pancreatitis, and immune-mediated diseases.

Tachycardia, if present, is a cardiovascular response to moderate to severe anemia in icteric animals with

hemolytic disease but could also be secondary to sepsis/SIRS in animals with infectious causes of hepatic or hepatobiliary dysfunction. Heart rate elevation can also accompany sterile inflammatory conditions such as pancreatitis, lymphocytic-plasmacytic cholangiohepatitis, or neoplasia. The presence of tachycardia along with poor peripheral pulse quality should prompt the clinician to start immediate therapy for stabilization of the jaundiced animal. The same concern applies to cats when they are found to have hypotension and bradycardia.

Tachypnea without changes in respiratory effort can accompany changes in perfusion secondary to hemolytic anemia or in patients with sepsis/systemic inflammatory response syndrome (SIRS). It can also be present in the encephalopathic patient. Parenchymal pulmonary disease may be secondary to pneumonia caused by aspiration of gastric contents, especially when there is impaired consciousness. Any increased respiratory effort is an indication for thoracic radiographs while acknowledging that it can be caused by extrathoracic disease.

The mucous membranes should be evaluated for any signs of pigment change which can include hemorrhage, pallor, or jaundice. Icterus can be detected in the skin, sclera, and mucous membranes. Examination of the mucous membranes in a patient with acute intravascular hemolytic disease and marked anemia (packed cell volume <10%) will show very yellow mucous membranes caused by the accumulation of bilirubin in the absence of adequate numbers of red blood cells that would ordinarily contribute their red hue to the mucosa (Figures 11.1, 11.2). If anemia is absent or mild, the resulting ample red blood cell numbers superimposed over the jaundice will cause the mucous membranes to be orange colored (Figure 11.3). This latter condition most



Figure 11.2 Yellow sclera and pinna in another dog with immune-mediated hemolytic anemia.

often accompanies primary or secondary liver disease. This distinction on the physical examination might assist the examining clinician with formulating the initial differential diagnosis and diagnostic plan. The presence of any petechial or ecchymotic hemorrhages anywhere on the skin or mucous membranes signifies potentially life-threatening disease caused by a primary or secondary coagulopathy. Disseminated intravascular coagulation (DIC) is a potentially grave consequence to diffuse liver disease, and it can occasionally occur in a hemolytic situation.

Abdominal palpation can show evidence of pain in conditions such as pancreatitis, hepatitis, cholangiohepatitis or cholecystitis, bile peritonitis, or upper GI obstruction. Hepatobiliary neoplasia may or may not



Figure 11.1 Very yellow mucous membranes and sclera in a dog with immune hemolytic anemia with a PCV of 9%.



Figure 11.3 Orange-colored mucous membranes in a dog that has a hepatopathy with icterus and a PCV >30%.

cause palpable abnormalities. A detectable fluid line due to ascites can be caused by chronic liver disease, neoplasia, portal vein thrombosis or inflammatory disease. The caudal liver edge is rarely detected on palpation in a normal dog and cat, but infiltrative disease can usually cause palpable liver enlargement. The texture of the liver can be revealing where nodularity can reflect neoplasia or granulomatous inflammation (feline infectious peritonitis). Splenomegaly can occur from portal hypertension due to chronic liver disease, hyperplasia of the monocyte-macrophage system associated with immune-mediated disease such as immune hemolytic anemia, an infectious disease such as leishmaniasis, or neoplasia (hemangiosarcoma, MCT or lymphoma). Rectal examination may reveal melena which can be due to upper gastrointestinal ulceration, thrombocytopenia, or a hemorrhagic diathesis accompanying disseminated intravascular coagulation.

The central nervous system abnormalities that can be found in an icteric animal are diverse and can represent severe hypoxia caused by moderate to severe anemia, or reflect the effect of externally ingested hepatotoxins, hepatic encephalopathy in cases of liver failure or, more rarely, kernicterus. The clinical signs can range from mild to marked altered levels of consciousness and be accompanied by diffuse global sensorimotor involvements. The brain might also be adversely affected by any coagulopathic condition.

Kernicterus is an encephalopathic condition associated with large amounts of unconjugated bilirubin accumulating in the brain. The regions affected in the dog include caudate nucleus, globus pallidus, thalamus, deep cerebellar nuclei, and cortical gray matter [3]. Histopathological changes include neuronal necrosis involving the Purkinje cells, and Alzheimer type II astrocytes in the cerebrocortical gray matter [4]. Biochemical abnormalities in the brain caused by the unconjugated bilirubin accumulation include protein oxidation, lipid peroxidation, reduced cellular glutathione content, increased lactate dehydrogenase levels, and nitric oxide release [5].

Other physical examination abnormalities in an icteric patient can include lymphadenopathy associated with various forms of neoplasia or inflammatory disease, ocular fundoscopic abnormalities such as hemorrhage and chorioretinopathy, or mucosal hemorrhage that might accompany a coagulopathy.

Diagnostic Evaluation

The initial medical laboratory work-up should include a complete hemogram, serum biochemical profile, urinalysis, and fecal examination. The biochemistry profile may show elevations in alanine aminotransferase

(ALT) and aspartate aminotransferase (AST), two liver enzymes associated with hepatocellular injury or membrane leakage. The degree of aminotransferase elevation is not specific for a particular cause of hepatic injury and non-icteric patients can have considerably elevated elevations. Increases in alkaline phosphatase (ALP), serum gamma-glutamyl transferase (GGT), and bilirubin with or without elevation of the aminotransferases suggest intrahepatic or extrahepatic cholestasis. The presence of other metabolic abnormalities such as hypoglycemia, hyponatremia, hypokalemia, azotemia, and any acid-base abnormalities might not help narrow the differential diagnosis of jaundice, but will give further insight into the degree of illness of the patient. Biliary outflow obstruction can cause increases in the serum cholesterol concentration to levels exceeding 500 mg/dL.

A complete blood count will help identify hemolytic disease as the cause of jaundice, but if a low hematocrit or hemoglobin concentrations are noted without signs of hemolysis, further characterization of the anemia and red blood cell morphology is necessary in order to identify the cause of the anemia, such as anemia of chronic disease or hemorrhage (see Chapter 10). Cytauxzoonosis in cats can be diagnosed by detecting the small piroplasm organisms on three red blood cells. The liver produces all coagulation factors except factor VIII and von Willebrand factor so a full coagulation panel should be done initially if there is any evidence of hemorrhage. Coagulation defects can occur with disorders that impair hepatocyte ability to synthesize coagulation factors, or from interference with certain coagulation factor activation (factors II, VII, IX, X) because of biliary outflow obstruction and decreased vitamin K absorption. Furthermore, fibrinolysis can result from the liver's inability to clear fibrin split products as found in patients with DIC. The coagulation tests should include a platelet count, serum fibrinogen, prothrombin time (PT), and an activated partial thromboplastin time (APTT) or activated clotting time (ACT). Other coagulation tests might include fibrin split products, D-dimers, and thromboelastogram (TEG) (see Chapter 70).

Diagnostic imaging is an essential component of the medical evaluation of an icteric patient. The usual procedures include plain abdominal radiography and abdominal ultrasonography. Radiography might show evidence of pericholecystic gas consistent with emphysematous cholecystitis [6], a surgical emergency. Radiopaque choleliths [7] or mineralization of the biliary tree can also be identified in abdominal radiographs. Other findings such as hepatomegaly and decreased serosal detail consistent with abdominal effusion may be identified with radiography.

Abdominal ultrasound is very useful for assessing the hepatobiliary tree as it can detect dilation of the common bile duct consistent with biliary outflow obstruction, and pockets of fluid surrounding the gall bladder compatible

with gall bladder inflammation with or without perforation. Any effusion or parenchymal abnormalities can be aspirated for cytological and microbiological evaluations. Other tests that might contribute to the patient's diagnosis and medical management are blood ammonia levels, serology for infectious diseases where indicated, and full-thickness tissue biopsies where safe and indicated. Thoracic radiographs are important when searching for metastatic disease or to simply assess the heart and the lungs in any critically ill animal.

Treatment

The therapeutic approach to the icteric dog or cat will depend on the magnitude of the clinical signs at presentation. Dogs or cats with signs of shock and meeting the criteria for SIRS/sepsis should be immediately resuscitated (while avoiding fluid overload) with buffered crystalloid fluid therapy (see Chapters 152, 153, 155). Appropriate

antibiotics should be administered early when sepsis or parasitic infection is suspected (see Chapter 159).

Treatment of the jaundiced animal with normal cardiovascular, pulmonary, and neurological parameters is largely supportive in nature. Icteric animals secondary to hemolytic conditions should be promptly treated with cross-matched packed red blood cell transfusions when indicated (PCV usually <20%) (see Chapters 10, 66). Immunosuppressive doses of corticosteroids are also indicated in the icteric animal with immune-mediated disease. In patients showing signs of hemorrhage secondary to liver dysfunction and coagulation factor deficiency, fresh frozen plasma transfusions should be given in order to help restore normal coagulation. In cases where decreased vitamin K absorption is suspected, phytonadione (vitamin K1) at doses of 1–5 mg/kg per day by mouth or subcutaneously should be supplemented. Please refer to other sections of this book for more specific medical and surgical measures essential for treating the icteric patient.

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12

Ophthalmic Emergencies

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Proptosis

Proptosis is defined as a forward displacement of the globe to the extent that the eyelids are trapped behind the globe equator. This is virtually always secondary to trauma. However, the severity of the trauma necessary to induce proptosis varies dramatically based on species and skull conformation. Brachycephalic dogs can experience proptosis with minimal trauma, whereas mesocephalic and dolicocephalic dogs and cats usually require substantial trauma.

The diagnosis is straightforward and based on the characteristic clinical signs: the globe is protruding outside the palpebral fissure, often accompanied by lateral strabismus. This latter sign is due to the fact that the medial rectus muscle is often avulsed. Prognostic factors include skull conformation (brachycephalic dogs better, dolicocephalic dogs and cats worse), pupil reactivity, and severity of the trauma to the globe and periocular structures [1].

Unless there is severe trauma to the globe itself, the eyelids should always be replaced in front of the globe in the emergent situation. It is important to remember that the purpose of the procedure is to replace the eyelids in front of the globe. No attempt to “push” the eye back into the orbit should be made. Replacement requires general anesthesia and consists of placing vertical mattress sutures to return the eyelids to their proper position. After replacement, the eyelids are sutured together, usually for about 3–4 weeks (Figure 12.1). The tarsorrhaphy can usually be performed in such a manner that allows for topical treatment with antibiotic and atropine ointment. Broad-spectrum oral antibiotics and steroids (at an anti-inflammatory dose) should also be administered.

Eyelid Lacerations

The eyelids are highly vascular, which has two clinical implications: eyelid injuries are usually resistant

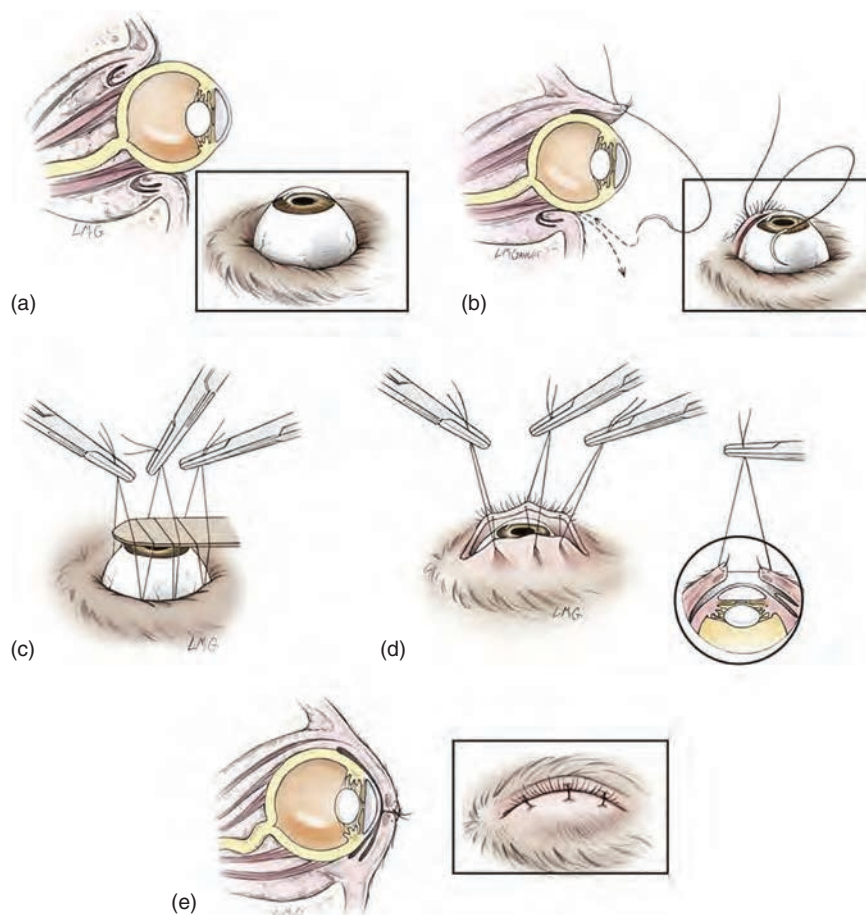
to infections, and they tend to heal quickly. While the eyelids are subject to a wide range of traumatic injuries, superficial abrasions require only minimal, “first aid” care. However, full-thickness lacerations require immediate repair to re-establish the adnexal–globe anatomic relationship. Careful examination for damage to the underlying globe, or secondary sequelae such as anterior uveitis, is important when assessing an eyelid laceration. Fortunately, most eyelid lacerations involve the lateral aspect of the adnexa, and so reconstruction of the lacrimal drainage apparatus is not necessary.

The diagnosis is easily made based on clinical signs. Surgical approach to a full-thickness eyelid laceration is a two-layer closure. Due to the highly vascular nature of the eyelids, minimal debridement is indicated. The first layer consists of the orbicularis muscle, which is the holding layer of the repair. Relatively small gauge (3-0 or 4-0), absorbable suture (such as polyglactin 910) should be used for this layer. The palpebral conjunctiva should not be sutured due to the danger of suture exposure to the cornea. The second layer is the skin. A soft, braided, non-absorbable suture such as 4-0 to 6-0 silk is ideal for this layer. Special care must be directed to the accurate apposition of the eyelid margin. This is especially important when the middle third of the upper eyelid is involved. Systemic antibiotics are indicated as well as either topical antibiotics and atropine (if a corneal ulcer is present), or a topical antibiotic/steroid combination in the absence of a corneal ulcer.

Corneal Lacerations

The most common causes of corneal laceration are fight wounds (particularly from cat claws) and penetrating plant material. The history and signs of corneal laceration are an acute onset of intense blepharospasm, epiphora, and miosis. On examination, a focal or linear corneal opacity is present, often in the dorsolateral quadrant.

Figure 12.1 Proptosis repair. (a) Globe proptosis. (b) Placement traction sutures of 2/0 to 4/0 nylon. Sutures should enter and exit at the lid margin and not on the conjunctival surface. (c) Placement of scalpel handle on a cornea lubricated with an artificial tear ointment. (d) Traction on the sutures and replacement of eyelids in front of the globe. (e) Completion of the sutures. Reproduced with permission of Elsevier.



The first question the emergency clinician should ask is whether the corneal wound is partial or full thickness. The answer to this question can be found in the anterior chamber. The presence of blood and fibrin in the anterior chamber is evidence of a full-thickness injury. On the other hand, the absence of these would indicate a partial-thickness corneal wound (Figure 12.2). If the laceration is judged to be full thickness, the clinician should next determine whether or not aqueous is leaking from the laceration. Signs of aqueous leakage would include a stream of aqueous coming from the laceration when stained with fluorescein (Seidel positive) and/or a shallow anterior chamber.

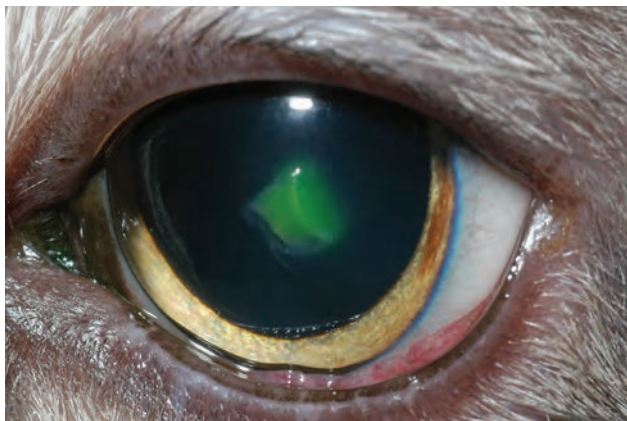
Finally, the clinician should attempt to determine whether or not the lens is also involved. Because of the severity of the miosis, tropicamide is often insufficient to allow for pupillary dilation. In such instances, a combination of 1% topical atropine and 2.5% phenylephrine will usually produce mydriasis. Signs of lens capsule rupture would include extruded lens cortex on the anterior lens capsule and focal cataracts under the corneal laceration. This is an important distinction to make as lens involvement can lead to persistent anterior uveitis.

Prognosis for corneal lacerations depends on:

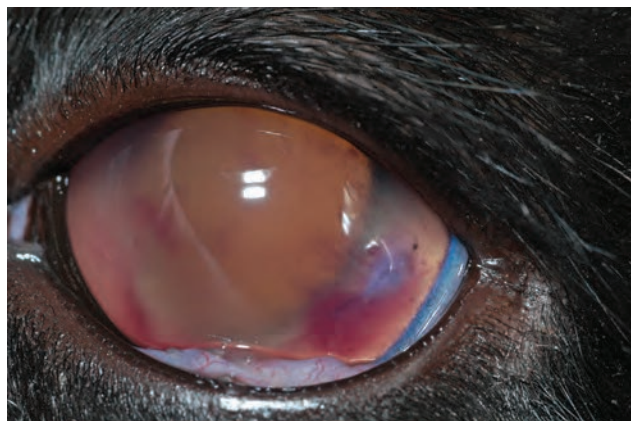
- length of the laceration (shorter better)
- location of the laceration (peripheral better, central worse)
- extension into sclera
- collapse of the anterior chamber
- lens involvement.

Partial-thickness corneal lacerations can be managed with topical antibiotics QID (fluoroquinolones preferred), and topical 1% atropine q12-24h. All full-thickness corneal lacerations should be referred to an ophthalmologist. While awaiting referral, or in instances where the client does not accept referral, medical management of a full-thickness corneal laceration would consist of:

- topical antibiotic q4–6h, preferably a fluoroquinolone
- oral broad-spectrum antibiotic
- systemic anti-inflammatory, either steroidal or non-steroidal
- topical 1% atropine
- Elizabethan collar
- strict cage rest.



(a)



(b)

Figure 12.2 Partial- and full-thickness corneal lacerations (a). Note the blood and fibrin in the full-thickness laceration (b).
Source: Courtesy of the Ophthalmology Service, School of Veterinary Medicine, University of California-Davis.

Deep Corneal Ulcers

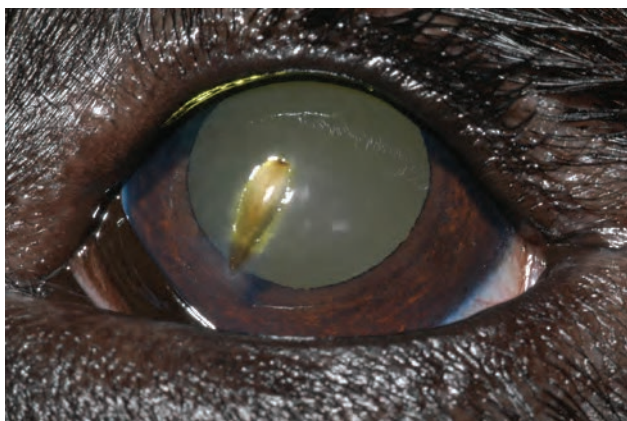
Corneal ulcers with significant or progressive stromal loss represent a risk of perforation. The most common causes of such ulcers are infection, exposure, and foreign bodies.

In addition to stromal loss, signs associated with an infected corneal ulcer would include cellular infiltrate and/or a melting component. All infected ulcers should be referred to an ophthalmologist. Such ulcers should have cytology and culture and sensitivity samples taken. While awaiting referral and the results of these tests, aggressive medical treatment should be initiated consisting of:

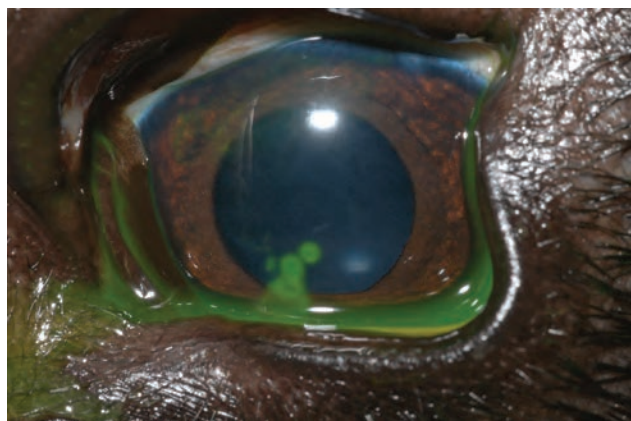
- topical antibiotics q2h, preferably a fluoroquinolone such as ciprofloxacin or ofloxacin, and either triple antibiotic or cephalazolin prepared from a recipe
- topical serum q2h
- oral broad-spectrum antibiotic
- Elizabethan collar.

Exposure corneal ulcers are found primarily in brachycephalic breeds and are characterized by a relatively small (~2–3 mm diameter), deep ulcer located either centrally or pericentrally. These ulcers usually have firm borders. While awaiting referral, these ulcers are best managed with frequent application of topical antibiotic ointment, usually q4h. Alternatively, a temporary tarsorrhaphy may be considered.

Corneal ulcers due to foreign bodies are often easy to identify. The foreign body is almost always plant material that is still located in the cornea or in the conjunctival cul-de-sac. In order to find the latter, topical anesthesia with proparacaine or tetracaine is followed by exploration with a cotton-tipped applicator. In the case of a foreign body lodged within the cornea, it must be determined whether or not the material penetrates only partially into the cornea or goes completely through the cornea into the anterior chamber (Figure 12.3). Frequently close



(a)



(b)

Figure 12.3 Corneal foreign body, before (a) and after (b) removal. Source: Courtesy of the Ophthalmology Service, School of Veterinary Medicine, University of California-Davis.

examination with magnification will allow this determination. Additionally, full-thickness penetrations will usually be accompanied with blood and/or fibrin in the anterior chamber. If there is any question over whether the foreign body penetrates into the anterior chamber, removal should only be attempted by an ophthalmologist. In most instances, once the foreign body is removed, the resulting ulcer can be treated as if it is uncomplicated with topical triple antibiotic BID-TID, and 1% atropine q12-24h.

Primary Glaucoma

Primary glaucoma is found mainly in pure-bred dogs, with cocker spaniels, basset hounds, beagles, and samoyeds being among the most common, although it can be found in others. With the exception of the beagle, primary glaucoma is characterized by a collapse of the iridocorneal angle, which leads to a peracute intraocular pressure spike. As such, the typical history of a primary glaucoma patient is acute onset of blepharospasm, epiphora, episcleral injection, corneal edema, mydriasis, and blindness.

The tentative diagnosis is confirmed with tonometry. Normal intraocular pressure (IOP) in dogs is 10–20 mmHg. Many primary glaucoma patients will have intraocular pressures over 60 mmHg. While awaiting referral, it is imperative that the IOP should be brought down as quickly as possible. This is accomplished by administering 20% mannitol IV (1–2 g/kg, given over 30 minutes). Mannitol reduces IOP by dehydrating the vitreous. Its effects are usually evident about 30 minutes after administration and are often dramatic; IOP frequently drops to 20 mmHg or less. With the IOP reduction, the classic signs resolve. Mannitol's effects can last for over 6 hours, but because the vitreous can only be dehydrated so much over the short term, it is usually only given once. Mannitol is highly irritating and may cause sloughing if it is injected extravascularly. Therefore, placement of an IV catheter is necessary. Due to its systemic effects, the cardiac and renal status of the patient should be evaluated before mannitol is administered. Oral glycerol has also been used to bring down the IOP, but frequently results in vomiting and is not as predictable in its effects. For these reasons, mannitol is preferred.

At the same time as the mannitol administration, topical antiglaucoma medication should be initiated, specifically a carbonic anhydrase inhibitor such as dorzolamide (TID), and a synthetic prostaglandin such as latanoprost (q2h until miosis is attained). These two types of medication work well together because they reduce IOP by different mechanisms; carbonic anhydrase inhibitors act to

decrease the production of aqueous, while prostaglandin analogues increase aqueous outflow [2,3].

Acute Anterior Uveitis

Anterior uveitis is the most common manifestation of systemic disease and as such has an almost endless number of potential causes. The minimum database for patients with anterior uveitis would include complete blood count, chemistry panel, urinalysis, and potentially tick titers, fungal titers, and other specific tests for systemic disease. However, because the intraocular structures are so delicate, in the emergency situation, it is necessary to prevent damage while trying to determine the underlying cause.

The cardinal sign of anterior uveitis is aqueous flare. This can best be evaluated using the slit beam setting on a direct ophthalmoscope head and magnification. The beam should not be apparent as it traverses the anterior chamber. If there is a hazy appearance to the beam, that is aqueous flare (Figure 12.4). Other signs consistent with anterior uveitis include blepharospasm, epiphora, episcleral injection, 360° corneal vessels, diffuse corneal edema, hypopyon, hyphema, and iridal hyperemia. Symptomatic treatment for anterior uveitis would include topical corticosteroids (in the absence of corneal ulceration), usually 1% prednisolone acetate q2–6h depending on the severity of the uveitis, topical 1% atropine (unless the IOP is above 20 mmHg), and a systemic anti-inflammatory, usually carprofen or meloxicam as oral steroids may be contraindicated by the possibility of infectious disease.

Anterior Lens Luxation

While lens subluxation and posterior lens luxation can lead to ocular problems, anterior lens luxation constitutes a true ocular emergency. The lens becomes unstable when some or all of the zonular attachments are lost. If the lens becomes completely free, it may move anteriorly into the anterior chamber. Glaucoma/buphthalmos and senility can lead to lens luxation/subluxation, but by far the most common cause of acute anterior lens luxation is heritable/breed related. In this group, terrier breeds are definitely overrepresented with the most common age of onset being the young adult. Signs of anterior lens luxation include blepharospasm, epiphora, the lens in the anterior chamber, indistinct pupillary border, and central corneal edema.

Due to the presence of the lens immediately behind the cornea, IOP can be difficult to measure accurately. It should be assumed that the IOP is elevated.

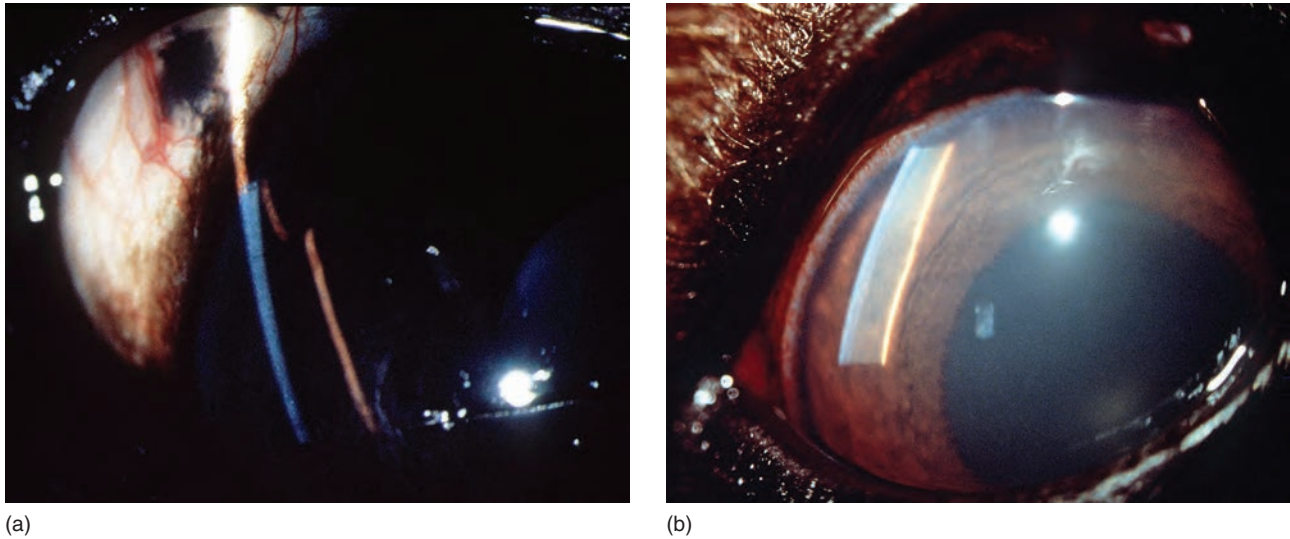


Figure 12.4 (a) Slit beam transversing normal anterior chamber. (b) Slit beam transversing anterior chamber with aqueous flare.
 Source: Courtesy of the Ophthalmology Service, School of Veterinary Medicine, University of California-Davis.

Immediate referral to an ophthalmologist is essential, but starting a topical antiglaucoma medication such as dorzolamide and a topical steroid (in the absence of corneal ulceration) can be beneficial while the patient is waiting for referral.

Acute Blindness

The three most common causes of acute blindness in dogs and cats are sudden acquired retinal degeneration syndrome or SARDS (dogs), ivermectin toxicity (dogs), and enrofloxacin toxicity (cats).

Sudden acquired retinal degeneration syndrome is characterized by a sudden onset of complete blindness without any other significant ocular signs in terms of pain or inflammation. At presentation, patients usually maintain pupillary light reflexes (PLRs), but they may be somewhat slow and incomplete. The dazzle response and menace reflex will be absent and the patient will behave as if blind. The fundus will appear unremarkable. The confirming diagnostic test is an electroretinograph, which will be completely extinguished (“flat line”) in a SARDS patient. There is no currently proven treatment.

The signs of ivermectin toxicity in dogs are similar to SARDS in that there is a history of acute onset of blindness, frequently with no or very subtle fundic lesions. The pupils are usually mydriatic and the PLRs are either absent or slow and incomplete. In all reported cases, the exposure to ivermectin has come

from association with horses who are being wormed, or dogs who are currently being treated with ivermectin for demodex [4,5]. Therefore, a careful history is necessary to differentiate ivermectin toxicity from SARDS. Suspicion of ivermectin toxicity can be confirmed by submitting serum for ivermectin levels. In reported cases, the serum ivermectin levels have exceeded 1000 ng/g (or 1000 ppb). Dogs with ivermectin toxicosis usually regain vision and normal PLRs over the next 7–14 days. Treatment with 20% lipid emulsion (Intralipid®) administered intravenously (1.5 mL/kg over 10 min in a bolus, then followed by 0.25 mL/kg/min for 90 min) has been reported to rapidly (within about 30 minutes) hasten the return of vision and PLRs (see Chapter 128) [5].

Enrofloxacin toxicosis in cats is characterized by mydriasis and blindness, often within a few days of starting the medication. Upon examination, there are signs of severe, diffuse retinal degeneration, specifically tapetal hyperreflectivity and retinal vascular attenuation. No age, breed, or gender association has been demonstrated. While cases have been reported with cats on the recommended oral dose, increased occurrence is correlated with higher doses, longer duration, and IV as opposed to PO administration. This condition is not painful and there is no evidence of inflammation. The prognosis for vision is poor, but may be slightly improved if the medication is stopped early in the course of the disease [6,7]. (Note: retinal detachment due to hypertension is another common cause of acute blindness in cats; see Chapter 63.)

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13

Vomiting, Regurgitation, and Diarrhea

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Differentiation Between Vomiting and Regurgitation

The most important initial step is to distinguish between vomiting and regurgitation, as many owners may confuse the two, and each has significantly different diagnostic and therapeutic plans. Obtaining a thorough history will often allow the clinician to make this differentiation. Coughing and retching secondary to respiratory disease may also be mistaken for gastrointestinal disease by owners. Regurgitation typically occurs immediately after eating or within several hours and can vary from undigested food to digested food to clear, frothy liquid. The presence of bile in the vomit, signs of nausea, including hypersalivation, depression, or discomfort, and active abdominal contractions are more consistent with vomiting. However, esophageal pain and distension can lead to signs of nausea as well as frequent and/or exaggerated swallowing.

Vomiting

Vomiting is the forceful ejection of upper GI tract contents, which can occur as a result of gastric, intestinal, or systemic disease.

Physiology of Vomiting

Vagal and sympathetic afferent pathways from the pharynx, esophagus, stomach, and proximal small intestine transmit impulses to the vomiting center (located in the medulla) when stimulated by irritation or overdistension, particularly of the duodenum. Vomiting may also be induced via stimulation of the cerebral cortex, vestibular system or chemoreceptor trigger zone (CRTZ), which then sends signals to the vomiting center. The CRTZ is located in the area postrema of the fourth ventricle. It

lacks an intact blood–brain barrier and is sensitive to endogenous substances or drug-induced stimulation.

Following stimulation of the vomiting center, a period of antiperistalsis, which causes distension of the upper GI tract, leads to the act of vomiting. This begins with a deep inspiration and closing of the glottis, and ends with a strong simultaneous contraction of the diaphragm and abdominal wall musculature followed by relaxation of the lower esophageal sphincter to allow expulsion of GI contents [1].

Differential Diagnoses

Causes of vomiting can be subdivided into primary gastrointestinal versus extragastrointestinal pathology. See Table 13.1 for a list of differential diagnoses.

Clinical Approach

History

Vomiting must be distinguished from regurgitation, as described above, and a description of the frequency and duration of signs and characterization of the vomitus should be obtained. Fresh blood or digested blood with a “coffee grounds” appearance is suggestive of hemorrhage within the upper GI tract, pharynx or nasal passages, but active gastric ulceration is the most likely cause in a vomiting patient. Other important historical information includes vaccination status, travel history, medication history, dietary indiscretion or recent diet changes, drug or toxin exposure, and any potential foreign body ingestion. The presence of other systemic signs should raise the possibility of an extra-GI cause for the vomiting.

Diagnosis

A complete physical examination with thorough palpation of the abdomen is of the utmost importance, along with assessment of hydration and hemodynamic status.

Table 13.1 Causes of vomiting.

Gastrointestinal	Extragastrintestinal
Dietary indiscretion	Uremia
Food allergy	Pancreatitis
Foreign body	Diabetic ketoacidosis
Neoplasia – focal vs infiltrative	Hepatic/hepatobiliary disease
Intussusception	Peritonitis
Viral (parvovirus)	Pyometra
Bacterial (<i>Campylobacter</i> , <i>Salmonella</i> , <i>Clostridium</i> spp, <i>Helicobacter</i>)	Prostatitis
Parasites	Drug or toxin induced
Inflammatory bowel disease	Hypoadrenocorticism
GI ulceration – NSAIDS, antibiotics, Chemotherapy	Hyperthyroidism
Uremic gastritis	Vestibular disease
Toxins	Heartworm disease (cats)
Constipation	Electrolyte disorders
Hemorrhagic gastroenteritis	Hepatic encephalopathy

The presence of any palpable effusion, organ distension, masses, or foreign bodies or pain on palpation should be noted. Oral examination may reveal evidence of systemic disease (e.g. ulcers) or a linear foreign body under the tongue. In cats, the thyroid gland should be palpated for nodules.

If hemodynamic instability is present, appropriate diagnostics and therapy should be implemented (see Chapters 169, 170, 172). Abnormalities in electrolytes and acid–base status may occur after protracted vomiting. Hypochloremic, hypokalemic metabolic alkalosis (in the absence of aggressive furosemide therapy) is strongly suggestive of vomiting due to a GI foreign body though severe vomiting from other causes must still be considered [2,3]. A complete blood count and serum chemistry should be performed in any persistently vomiting patient, with biochemical abnormalities typically being associated with extra-GI causes. A urinalysis performed prior to fluid therapy may distinguish prerenal from renal azotemia. Further testing may be required based on clinical suspicions.

Diagnostic Imaging

Abdominal imaging is the most important diagnostic in vomiting patients, with the choice of modality being dependent on several factors, including the chronicity of clinical signs. In the acute vomiting patient, it is essential to determine the presence of a surgical problem and

radiographs may be considered the first-line diagnostic. However, abdominal ultrasonography has been shown to have greater accuracy for identifying small intestinal obstruction than radiographs and is indicated in patients with equivocal radiographs and persistent or chronic vomiting [3]. Evaluation of the intestinal wall thickness and layering along with a thorough evaluation of the extraintestinal structures often has a higher yield in patients with chronic vomiting and helps determine the appropriate therapy. If ultrasonography is not available, barium studies and sequential abdominal radiographs may aid in diagnosis. Thoracic radiographs are also recommended as they may show evidence of misdiagnosed esophageal disease, thoracic neoplasia, or pneumonia and provide assessment of the heart and pulmonary vasculature [4,5].

General Treatment Guidelines

Management of a vomiting patient includes treatment of the underlying cause, management of electrolyte and acid–base disturbances and hemodynamic abnormalities, and symptomatic antiemesis when indicated. The general recommendation for stable animals with recent onset of vomiting is to withhold food for 24–48 hours [6], to rest the GI tract, decrease risk of aspiration, and prevent food aversions. Food always should be withheld from patients with suspected GI obstruction or those who do not tolerate feeding, but some vomiting patients may have a significantly quicker recovery with implementation of early enteral nutrition [7]. Antiemetics should be considered to decrease electrolyte, fluid, and acid–base disturbances (see Chapter 74).

Regurgitation

Regurgitation is the passive expulsion of food, water, or saliva from the esophagus or stomach. Animals with chronic regurgitation are at risk for aspiration pneumonia because the larynx does not close during regurgitation. Aspiration pneumonia is a significant negative prognostic indicator in patients with megaesophagus [8]. The majority of patients requiring hospitalization have aspiration pneumonia but in its absence, most patients are able to maintain good hydration. Persistent regurgitation of undigested food may lead to marked weight loss.

Differential Diagnoses

Regurgitation is seen more commonly in dogs than cats and is associated with esophageal and pharyngeal disease or as a manifestation of systemic illness. Causes of

Table 13.2 Causes of regurgitation.

Pharyngeal disorder	Neurological disorder
Cricopharyngeal achalasia	Central nervous system
Foreign body	<i>Brainstem lesion</i>
Neoplasia*	<i>Neoplasia</i>
Esophageal disorder	<i>Trauma</i>
Megaesophagus	<i>Distemper</i>
<i>Congenital</i>	Peripheral neuropathy*
<i>Acquired</i>	<i>Lead*</i>
<i>Primary idiopathic</i>	<i>Polyradiculitis</i>
<i>Secondary**</i>	<i>Polyneuritis</i>
Esophagitis	Dysautonomia*
<i>Vomiting</i>	Neuromuscular disorder
<i>Drug/chemical induced</i>	Myasthenia gravis*
<i>General anesthesia</i>	Botulism*
<i>Idiopathic</i>	Tetanus*
Foreign body	Tick paralysis*
Stricture	Acetylcholinesterase toxicity
Vascular ring anomaly	
Spirocercosis	Immune mediated
Alimentary disorder	Systemic lupus erythematosus*
Pyloric outflow obstruction	Polymyositis*
Gastric dilatation-volvulus*	Dermatomyositis*
Hiatal hernia	Endocrine
Pythium insidiosum	Hypothyroidism*
	Hypoadrenocorticism*

**Causes of secondary megaesophagus have an * after the cause. Hypothyroidism as a cause is controversial.

megaesophagus include congenital or acquired. Acquired can be divided into primary idiopathic or secondary megaesophagus. See Table 13.2 for a list of differential diagnoses of regurgitation.

Clinical Approach

History

Important historical information includes any predisposing factors for esophagitis (anesthesia, history of vomiting, drug exposure). Esophagitis is more likely to cause esophageal discomfort, evidenced as pain on swallowing (odynophagia), hypersalivation, repeated swallowing attempts, lip smacking, than animals with megaesophagus. Systemic signs such as lethargy, anorexia, vomiting, and diarrhea suggest a concurrent disease process or an

underlying cause for the esophageal disease. Aspiration pneumonia should be strongly considered in patients with coughing, nasal discharge, respiratory distress, fever or an acute decline in clinical status.

Diagnostics

Physical examination should include a thorough oral examination and palpation of the neck with evaluation of any masses, palpable esophageal dilation, or pain as well as thorough neurological examination to assess any deficits or neuromuscular abnormalities. Auscultation of pulmonary crackles may denote aspiration pneumonia, but should be differentiated from sounds of fluid in the esophagus.

Complete blood count and serum chemistry should be performed in any animal showing signs of systemic illness and are unremarkable in most patients with uncomplicated idiopathic megaesophagus. Additional testing for megaesophagus that may be considered includes a complete thyroid panel, adrenocorticotrophic hormone (ACTH) stimulation, acetylcholine receptor antibody test, lead level assay, serum creatine phosphokinase activity, and antinuclear antibody titer (ANA). Electromyography and nerve conduction velocity, and muscle and nerve biopsy may also be indicated.

Survey cervical and thoracic radiographs are recommended for initial evaluation. Plain radiographs should be evaluated for generalized or focal esophageal dilation, evidence of mass or foreign body, widening of the mediastinum, congenital abnormalities or aspiration pneumonia. Plain radiographs are often diagnostic, but more advanced imaging, including contrast studies, endoscopy or fluoroscopy, may be needed. Abdominal ultrasonography rarely provides useful information in animals with regurgitation [9].

General Treatment Guidelines

See Chapter 74 for more details.

Effective therapy is aimed at treatment of any underlying disease, as well as management of complications. The mainstay of treatment involves dietary modification with multiple food consistencies and formulas, as well as upright feedings. Bailey chairs, which can be purchased or made, keep the dog in an upright position while eating and then for an allotted time after eating. Gastrointestinal therapy with a histamine-2 receptor antagonist or proton pump inhibitor is recommended. Sucralfate may be indicated in esophagitis. Prokinetic agents such as metoclopramide and cisapride, which act on smooth muscle, are not beneficial in the canine esophagus, which is composed mostly of striated muscle, and may enhance lower esophageal sphincter tone. Cisapride may be more effective in cats, due to its larger effect on cholinergically

innervated muscle. There is limited information showing a beneficial effect of the parasympathomimetic agent bethanechol on esophageal motility of dogs with megaesophagus [10], and of improved gastric emptying of dogs treated with the COX-2 inhibitor celecoxib [11]. Some animals may need a permanent gastrotomy tube.

Animals with secondary aspiration pneumonia should be treated with broad-spectrum antimicrobials and may require supplemental oxygen and intensive care.

Prognosis

Congenital (idiopathic) megaesophagus carries a fair prognosis with adequate owner commitment, particularly with regard to nutrition. With appropriate management and prevention of aspiration pneumonia, improvement in esophageal motility is often seen. Acquired primary idiopathic megaesophagus is associated with a high morbidity and mortality rate, while secondary megaesophagus may have a better prognosis [8]. Esophageal foreign bodies can cause erosions, ulcers or an esophageal rupture, which may affect prognosis.

Diarrhea

Diarrhea is due to excess fecal water and is caused by decreased intestinal water resorption or increased secretion. It can lead to severe abnormalities in nutrient, acid–base, fluid, and electrolyte balance and may be associated with patient discomfort, local dermatitis, and potentially bacterial translocation if the integrity of the intestinal mucosa is altered. Diarrhea may be separated into small bowel and large bowel diarrhea with GI and extra-GI causes.

Gastrointestinal Causes

Dietary indiscretion (food intolerance) is one of the most common causes of acute diarrhea and is typically short term and self-limiting. Gastrointestinal parasitism, seen commonly in young patients, can cause severe clinical signs and may be associated with intussusceptions. Gastrointestinal disease and diarrhea may occur secondary to a variety of bacteria, although the role of pathogenic bacteria in GI disease remains controversial [12]. Viral infections such as canine parvovirus and feline panleukopenia, fungal and rickettsial infections also cause diarrhea. Hemorrhagic gastroenteritis (HGE) is commonly seen in dogs. The exact etiology is unknown, but bacterial endotoxins (*Clostridium* spp.), food hypersensitivity, and toxins have been suggested (see Chapter 79).

Inflammatory bowel disease (IBD) is one of the more common causes of chronic diarrhea in cats and

dogs and is characterized by a local immune-mediated reaction to normal dietary and bacterial components leading to an inflammatory focus within the intestine. IBD is characterized on histopathology by the type of inflammatory cell infiltrate (i.e. lymphocytic-plasmacytic). Primary or secondary lymphangiectasia can cause leakage of protein-rich and fat-rich chyle into the intestinal lumen due to abnormalities in permeability, leading to chronic diarrhea and severe weight loss. Protein-losing enteropathy leading to panhypoproteinemia can occur secondary to any GI disease and may necessitate aggressive diagnostics and therapy. Antibiotic-responsive diarrhea (formerly small intestinal bacterial overgrowth) is seen in young, large breed dogs and causes chronic illness. Neoplasia such as lymphosarcoma, adenocarcinoma, mast cell tumor, and GI stromal tumors can also cause significant diarrhea [13]. Many medications and toxins can also affect the GI tract and cause diarrhea.

Extragastrintestinal Causes

Systemic causes of diarrhea include hepatic/hepatobiliary disease, pancreatic disease, renal disease, endocrine disease, congestive heart failure (particularly right-sided) or other miscellaneous abnormalities. Diarrhea secondary to extra-GI causes is typically relatively minor and does not cause severe disease. Hypoadrenocorticism can cause waxing and waning GI signs, with some dogs having considerable amounts of bloody diarrhea (see Chapter 115). Hyperthyroidism can cause diarrhea in cats (see Chapter 116). The GI tract is the shock organ of the dog, and severe hemorrhagic diarrhea is seen commonly in critically ill patients in various forms of cardiovascular shock, as well as heat stroke. Systemic infections (including sepsis) can affect the GI tract and cause diarrhea [13] (see Chapter 159).

Clinical Approach

History

The approach to patients presenting with diarrhea should be based on the duration and severity of clinical signs as well as the signalment of the patient. Acute diarrhea is considered to be non-episodic and occurring for less than 7–14 days, whereas chronic is defined as episodic or not improved after 14 days. For cases of chronic diarrhea, historical questions may allow anatomic localization of the disease to either the small or large bowel, allowing more accurate formation of differential diagnoses and subsequent diagnostic testing. Volume and frequency of bowel movements are typically not as helpful, but weight loss is often seen in small bowel diarrhea with mucus and hematochezia being noted in large bowel diarrhea [14].

Dogs with HGE present due to vomiting with or without blood and bloody diarrhea or “raspberry jam” diarrhea (see Chapter 79).

Diagnostic Testing

The clinician must first assess the historical and physical examination findings in a patient presenting with diarrhea to determine, most importantly, if the diarrhea warrants diagnostics and/or treatment. In a stable patient presenting with acute diarrhea, limited diagnostics may be recommended (e.g. packed cell volume (PCV) and total solids (TS)) with only symptomatic/supportive treatment recommended. In any systemically ill patient, a complete blood count, serum chemistry profile, and urinalysis are indicated and often help to differentiate between GI and extra-GI causes of diarrhea; primary GI disease often does not cause biochemical abnormalities. Fecal flotation (with zinc sulfate for *Giardia* spp.) and fecal cytology are recommended, with additional testing including bacterial culture (*Salmonella* spp., *Campylobacter* spp., etc.) and parvovirus enzyme-linked immunosorbent assay (ELISA) if infectious disease is suspected. Endocrine testing (ACTH stimulation, total T4), trypsin-like immunoreactivity (in any patient with suspected exocrine pancreatic insufficiency), folate and cobalamin testing may be indicated as well as abdominal ultrasound [13,14]. Gastrointestinal biopsies are needed to diagnose inflammatory bowel disease and neoplasia (see Chapter 76).

Treatment

Treatment of diarrhea depends on the patient's clinical condition. It is very reasonable to attempt treatment for bacterial, dietary indiscretion or parasitic disease prior to performing advanced diagnostics. GI parasites may be treated with fenbendazole or other antihelminthic drugs. *Campylobacter* spp. may be treated with drugs such as erythromycin, enrofloxacin, tylosin, and cefoxitin [15] and *Clostridium* spp. may respond to metronidazole or ampicillin [16]. Antimicrobial therapy may be helpful in treatment of antibiotic-responsive diarrhea and those used most commonly include metronidazole, oxytetracycline, and tylosin [17]. Routine empiric use of antimicrobials may not be beneficial in stable dogs; no improvement in outcome was seen in aseptic dogs with hemorrhagic gastroenteritis treated with broad-spectrum antimicrobials [18,19] but broad-spectrum antibiotic therapy is recommended in treatment of immunosuppressive infectious disease (parvovirus) or where impaired GI permeability is suspected.

Probiotic supplementation is used commonly to treat suspected alterations in normal GI flora and has been shown to reduce the duration of clinical signs in dogs with acute gastroenteritis [20]. Treatment of IBD includes dietary therapy and immunomodulation. Large bowel diarrhea may be responsive to high-fiber diets and the anti-inflammatory effects of metronidazole.

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14

Dysuria

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Introduction

Diseases of the lower urinary tract, including the prostate or vagina, have characteristic clinical signs that are usually, but not always, present (Box 14.1) [1–5]. Often-times, multiple clinical signs are present and indicate the need for further evaluation of the patient. These clinical signs include dysuria, stranguria, pollakiuria, periuria, urethral obstruction, and hematuria. Dysuria localizes the pathophysiological process to the lower urogenital tract.

Alteration in Volume or Frequency of Urination

Dysuria

Dysuria is difficult urination often associated with pain. Painful urination in dogs and cats is not always easy to discern. Pain demonstrated may not be due to urological disease; for example, patients with lumbosacral disease or coxofemoral osteoarthritis may exhibit pain when posturing to urinate. Likewise, constipation or obstipation may be mistaken for dysuria.

Stranguria

Stranguria refers to slow and painful urination and can be associated with partial urinary outflow obstruction or inflammation of the lower urogenital tract. Causes of stranguria are the same as those for dysuria.

Pollakiuria

Pollakiuria is excessively frequent urination usually associated with passage of small volumes of urine. Often it is associated with inflammatory conditions, but may be due to decreased urine storage capacity.

Box 14.1 Problem-oriented rule-outs for diseases of the lower urinary tract and prostate.

D	Degenerative	Benign prostatic hypertrophy Urethral sphincter mechanism incompetency
A	Anatomic	Congenital malformations of bladder or urethra Congenital or acquired urethral stricture Ectopic ureter Detrusor atony Urinary bladder or urethral spasm Prostatic cysts
M	Metabolic	Urolithiasis
N	Neoplastic	Urinary bladder, urethra, or prostate (commonly transitional cell carcinoma or adenocarcinoma)
B	Behavioral	
I	Inflammatory	Urinary bladder polyps Lymphoplasmacytic cystitis or urethritis Eosinophilic cystitis
	Infectious	Bacterial or fungal cystitis or prostatitis Prostatic abscessation
	Idiopathic	Feline idiopathic cystitis
	Iatrogenic	Complications associated with cystocentesis, catheterization, endoscopy, or surgery
T	Trauma	Blunt or penetrating trauma
	Toxic	Certain drugs or environmental exposure, e.g. cyclophosphamide-induced sterile cystitis

Decreased Size of Urine Stream

Decreased size of urine stream is associated with partial urethral obstruction due to scar tissue, masses, clots or matrix-crystalline plugs involving the urethra or impinging on the urethra, urethroliths, prostatic disease, or urethral spasm.

Reflex Dyssynergia

Reflex dyssynergia is associated with a decreased urine stream during urination associated with spasm or premature closure of the urethra before the urinary bladder is empty and micturition is completed [6]. Typically, patients with reflex dyssynergia have normal urination at the beginning of micturition but while voiding, the urine stream diminishes, often to the point of “spurts” while the patient continues to attempt to urinate. This may be further characterized by intense abdominal compressions and even collapse or syncope. Often the patient will discontinue attempting to urinate, walk around for a short period of time, and then resume the process with similar results.

Urinary Obstruction

Dogs and cats with urethral obstruction attempt to urinate but are unable to pass urine. This must be differentiated from attempts at defecation (due to constipation or colitis). Most often, it is due to mechanical obstruction (e.g. uroliths or neoplasia), but may be due to functional causes (e.g. reflex dyssynergia).

Periuria

Periuria refers to inappropriate urination (literally, urinating around). It occurs with inability to retain urine due to irritation and inflammation of the lower urinary tract or to behavioral conditions.

Incontinence

Urinary incontinence (enuresis) refers to involuntary urination. This often occurs when the animal is relaxed or asleep due to loss of conscious control of urination. While awake, urination occurs normally. There are neurogenic and non-neurogenic causes of urinary incontinence; the most common cause is urethral sphincter mechanism incompetency that occurs in spayed female dogs. Female dogs and cats may leak urine when sitting, but when awake may have urethral sphincter dysfunction; however, this implies there is urine pooling in the caudal vagina.

Polyuria/Polydipsia

Polyuria/polydipsia are not typically associated with lower urinary tract disease, but imply either primary

renal or extrarenal disease influencing urine concentration and/or water intake. They may be associated with lower urinary tract signs such as incontinence or periuria, and if associated with bacterial pyelonephritis, may be associated with recurrent bacterial cystitis.

Alteration in Urine Consistency

Discolored Urine

Urine may differ from the normal yellow color with polyuric states (clear to light yellow), lipid or crystals (white), pigmenturia (red, brown, or black), or blue-green (certain bacterial infections) [7]. Presence of red blood cells in urine (hematuria) is associated with lower urinary tract disease, but may also occur with upper urinary tract disease (e.g. nephrolithiasis) or disorders of coagulation (e.g. acquired or congenital coagulation factor deficiency). When hematuria occurs due to lower urinary tract disease, other clinical signs of lower urinary tract disease are usually present. Hematuria occurring in the absence of clinical signs of lower urinary tract disease usually localizes the disorder to the upper urinary tract or to systemic disorders of coagulation. Dogs with prostatic disease may have hematuria without additional signs of lower urinary tract disease.

Malodorous Urine

Urine normally has an ammonia odor that is more intense with concentrated urine. Additionally, cats, especially males, excrete feline ((R)-2-amino-3-(4-hydroxy-2-methylbutan-2-ylthio)propanoic acid), which is converted by excreted peptidase, cauxin, to the pheromone 3-mercapto-3-methylbutan-1-ol that imparts a pungent odor to urine. A change in urine odor may occur with infection, hematuria, certain drugs (e.g. amoxicillin), and certain foods (e.g. asparagus).

Crystalluria or Small Uroliths in Urine

Microscopic crystalluria may indicate presence of or propensity to form uroliths, but may be normal and does not predict future urolith formation. Crystalluria by itself does not cause lower urinary tract disease. Additionally, crystalluria must be interpreted in light of urine sample collection and processing. Cooling urine from core body temperature to ambient or refrigeration temperature promotes *in vitro* crystal formation, thus creating artifactual crystalluria. If crystalluria is a concern, then urine should be collected and evaluated within 2h of collection. Passage of sand or small uroliths is abnormal, and should be collected and submitted for quantitative analysis in order for mineral identification. The animal

should be evaluated further for additional uroliths in all parts of the urinary tract by performing imaging studies.

Other Clinical Findings That May Be Associated With Lower Urinary Tract Disease

Abdominal Fluid

Abdominal effusion should be characterized as transudate, exudate, or modified transudate; however, abdominal effusion may be urine due to leakage from the urinary tract. For example, urinary bladder rupture secondary to urethral obstruction or trauma is associated with a uroabdomen (see Chapter 103).

Excessive Licking of Prepuce or Vulva

Excessive licking of the prepuce or vulva may occur with many disorders of the lower urinary tract, especially the distal part, but may also occur habitually. Excessive licking may cause trauma that is irritating, resulting in continued licking and a vicious cycle of cause and effect.

Blood Dripping from Prepuce or Vulva

The appearance of drops of blood or blood fluid from the prepuce or vulva suggests that the source is distal to the bladder. This occurs most commonly with prostatic disease (male dogs) or estrus (females), but may occur with diseases of the distal urethra, penis, prepuce, or vagina.

Prostatomegaly

In intact male dogs, prostatomegaly most often occurs due to benign prostatic hypertrophy and/or bacterial prostatitis. In this situation, the prostate is typically symmetrically enlarged and not painful unless acute bacterial prostatitis is present. With asymmetric prostatomegaly, prostatic cysts or neoplasia may be present. Prostatomegaly in male dogs castrated at least 6 months prior to examination nearly always indicates prostatic neoplasia with or without associated bacterial infection (see Chapter 135).

Purulent Discharge from Prepuce or Vulva

Pus dripping from the prepuce usually occurs from balanoposthitis, but may be observed with prostatitis. Purulent exudate from the vulva occurs most commonly in prepubertal female dogs due to puppy vaginitis. In adult female dogs or cats, purulent vaginal discharge may indicate infectious vaginitis or pyometra.

Painful Rectal Examination

Pain during a digital examination of the rectum is usually caused by disease of the rectum, anus, perianal area, bony pelvis, caudal lumbar vertebrae, lumbosacral area, or coxofemoral joints. Occasionally, it may be related to prostatic or intrapelvic urethral disease.

Painful Defecation

Pain during defecation is usually caused by disease of the rectum, anus, perianal area, bony pelvis, caudal lumbar vertebrae, lumbosacral area, or coxofemoral joints. It may occur with prostatic disease, especially if there is inflammation secondary to infection. Passage of ribbon-like stools is commonly observed with narrowing of the descending colon and may occur in animals with prostatomegaly, especially if prostatic neoplasia is present and has metastasized to iliac lymph nodes, resulting in both dorsal and ventral compression of the colon.

Painful or Abnormal Gait of Rear Limbs

Painful or abnormal gait in the rear limbs is often associated with musculoskeletal or neurological disease, especially lumbosacral disease or coxofemoral or stifle arthritis. It may occur with lower urinary tract disease such as prostatic or urinary bladder neoplasia that has metastasized to iliac lymph nodes or caudal lumbar vertebrae or with iliac lymphadenopathy due to extension of infection or inflammation from the urinary bladder or prostate.

Fever

Diseases of the lower urinary tract are uncommonly associated with fever. However, an elevated rectal temperature may be present with infection (prostatitis or pyelonephritis with cystitis).

Physical Examination Findings in Patients with Lower Urinary Tract Signs

A thorough physical examination should be undertaken in patients that present with signs of lower urinary tract disease, including a neurological examination. Palpation of the spine for pain is important, especially the lumbosacral area and joints. External genitalia should be evaluated and, when possible, a rectal examination to evaluate the prostate (male dogs) and urethra (male and female dogs) should be performed. A rectal examination requires sedation in cats. An assessment of bladder size should be performed to evaluate for distention. Observation of urination is helpful but often not possible in cats and some dogs; therefore, the clinician should query the owner as to their observations.

Additional Analytical Procedures in Patients with Dysuria

Patients with dysuria should undergo abdominal radiography in order to evaluate for urolithiasis, prostatic disease in male dogs, and to evaluate the regional spine and joints. Abdominal ultrasonography may be necessary to further evaluate the lower urinary tract for radiolucent uroliths and lower urinary tract cancer, but should not be relied on as the sole diagnostic imaging modality as a large segment of the urethra (particularly in male dogs and cats) is not visible. If clinical signs persist or if urethral obstruction or a uroabdomen is suspected, then contrast urethrocytography or urethrocytostcopy should be considered (see Chapter 97).

Urine should be evaluated for evidence of infection and the presence of blood, crystals, and neoplastic cells; a urine culture should be performed if a bacterial urinary tract infection is suspected. Urine collection may be difficult in patients that have dysuria as the urinary bladder may contain little urine. Ultrasonography may be used to facilitate cystocentesis or urinary catheterization may be performed. Administration of 50–100 mL of subcutaneous fluids or a diuretic with access to water, in addition to removing litter boxes in cats or not walking dogs, may allow for urine collection. The urinary bladder may be pharmacologically relaxed by administering a single dose of propantheline bromide (dogs: 7.5–30 mg PO; cats: 5–7.5 mg PO), which is a parasympatholytic agent that relaxes the detrusor muscle and promotes urine retention. Alternatively, amitriptyline (dogs: 2.2–4.4 mg/kg PO; cats: 0.5–1 mg/kg PO) promotes urine retention and also has a calming effect [6]. If the patient is showing systemic signs of illness (vomiting, anorexia, fever, etc.), then a complete cell count and serum/plasma biochemical analysis should also be performed.

Management of Patients with Dysuria

Management of patients with dysuria without urethral obstruction depends on the underlying cause(s) for the clinical sign(s). If a bacterial urinary tract infection is suspected, then empiric antimicrobial therapy may be initiated pending culture results or if urine cannot be collected for bacterial culture and susceptibility testing. The most common organism associated with bacterial cystitis in dogs and cats is *Escherichia coli*, which is a gram-negative rod occurring in an acidic urine pH. The next most common causative organisms are gram-positive cocci, such as *Staphylococcus* spp and *Enterococcus* spp, which are usually associated with an alkaline urine pH. Empiric therapy should only be used for the treatment of uncomplicated urinary tract infections; otherwise, a urine culture should be performed and results used to direct antimicrobial therapy. If empiric therapy is undertaken and clinical signs persist after 2–3 days, then either the wrong antimicrobial agent has been selected, a bacterial urinary tract infection is complicated by another disease process (e.g. uroliths), or a bacterial urinary tract infection is not present and further diagnostic testing is warranted [8].

In patients with dysuria, a urethral antispasmodic agent, such as prazosin (dogs: 1 mg/15 kg PO q8–24h; cats: 0.25–0.5 mg total dose PO q8–24h) or phenoxybenzamine (dogs: 5–15 mg PO q12h; cats: 2.5–10 mg PO q24h; or for dogs and cats: 0.25 mg/kg PO q12h), may be considered to aid in more rapid resolution of clinical signs. Amitriptyline, as mentioned before, promotes urine retention and has a sedative effect. There are other antispasmodic agents that may be considered such as oxybutynin, terazosin, etc. Administration of analgesic therapy should be considered in severely affected patient. For example, administration of a non-steroidal anti-inflammatory drug may decrease lower urinary tract inflammation [6].

Additional information may be found in Section 3F.

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15

Dermatological and Ear Disease

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Dermatological Emergencies

Alopecia, dermatitis, and otitis are in the top five reasons why dog owners visit their veterinarian [1]. Allergies and atopy are the two most common dermatological disorders affecting cats [2]. One of the larger US-based veterinary insurance providers listed otitis externa as a top claim for owner reimbursement [3]. There is likely more of an urgency to seek veterinary care in cases of dermatopathies because of the pain, discomfort, pruritus, and visualization of the lesions on a pet. Convenience of 24-hour care for non-life-threatening conditions, which is common in human medicine, is another likely factor prompting small animals with dermatological disease to receive care [4,5].

Some of the more common dermatological disorders which may present to the emergency veterinarian include pyotraumatic dermatitis, pyoderma, otitis externa, ectoparasites, and atopy. Most of the time, the aforementioned conditions are not life-threatening but with the continuing emergence and progression of bacterial resistance, secondary pyoderma from dermatopathies may cause systemic inflammatory response syndrome and associated organ dysfunction [6]. Ectoparasite infestations such as fleas can cause severe blood loss, requiring intensive management and transfusions. Vector-borne diseases from ticks and fleas can result in systemic illnesses such as anemia, thrombocytopenia, and leishmaniasis [7]. Emergency clinicians and specialists, who no longer practice general medicine, may not be familiar with recent advances in ectoparasite control and treatment of atopy. With regard to the “one health” concept in all disciplines of medicine, infectious pyoderma (MRSA) and ectoparasites, ticks in particular, are an important source of zoonotic disease.

Pyotraumatic Dermatitis

Another name for this disorder is hot spot or acute moist dermatitis. Pyotraumatic dermatitis is a self-inflicted lesion of alopecia, erythema, abrasions, and hemorrhage causing a superficial or deep infection [8] (Figure 15.1). These lesions may be simply moist with minimal bleeding or may be deep with marked hemorrhage. Biting, licking, and scratching secondary to pain or an itch cause the lesions. Allergies, otitis externa, dirt, irritative substances, other parasites (*Demodex* sp., *Cheyletiellia* sp., *Sarcoptes* sp.) and foreign bodies in the coat are some factors that can cause the irritation [9]. Flea bites and flea allergy are the most common causes of acute moist dermatitis in dogs but it is rarely seen in cats [10]. Heavy-coated dogs such as golden retrievers and German shepherds are more commonly affected [9].

Due to the appearance of the lesions, the persistent pruritus with self-injury and the rapidity of the problem,



Figure 15.1 Pyotraumatic dermatitis in a dog. Reproduced with permission of Kimberly Coyner.

pet owners are likely to seek emergency care. A presumptive diagnosis is made based on the acute history and clinical signs. Differential diagnoses to consider include dermatophytosis, demodicosis, *Malassezia* sp. and superficial pyoderma. Appearance of the lesion and tape cytology noting degenerate neutrophils, macrophages (suppurative inflammation), and mixed bacteria provide a more definitive diagnosis [11]. In a study of 44 dogs with pyotraumatic dermatitis, 66% had eosinophils present on histopathology and 57% had *Staphylococcus* sp. cultured from lesions [12].

The treatment plan for pyotraumatic dermatitis must address the pruritus which leads to self-inflicted skin injury and infection. Ectoparasites, otitis externa, and other aforementioned etiologies must be identified and treated (i.e. topical mitaban or oral ivermectin for demodicosis). Topical debridement is performed by clipping and cleaning the affected area using dilute antiseptic solution (dilute chlorhexidine 0.05–0.1% [13]). Sedatives such as acepromazine and benzodiazepines and analgesics including hydromorphone or butorphanol may be needed for large, painful lesions to perform debridement. Local anesthetics such as lidocaine gel should be considered for both superficial and deeper, more severe lesions prior to clipping. Topical drying agents or astringents (e.g. 5% aluminum acetate) are used with topical anti-inflammatory corticosteroids which may or may not contain antibiotics. These agents and sprays are used at least daily for 7 days.

Topical corticosteroid use (0.0584% hydrocortisone acetate) was found to be more efficacious than antibiotic-corticosteroid lotion (0.1% prednisolone, 0.5% neomycin sulphate, 0.5% sulfur, 3% zinc oxide) [14]. Short-term, oral corticosteroids should be reserved for dogs with severe pruritus by using 0.05–0.1 mg/kg of

injectable dexamethasone sodium phosphate or 0.5–1.0 mg/kg prednisolone orally daily for 5–10 days [11]. Systemic antibiotics (cefadroxil, 22 mg/kg PO B-TID; cefovecin 8 mg/kg SQ; clavulanate amoxicillin 22 mg/kg BID) are used for patients with deep pyoderma, papules and in cases with a poor response with only corticosteroid treatment [15]. Use of fluoroquinolones such as enrofloxacin is not recommended as they may increase the risk of methicillin resistance [11].

To assist in wound healing and stop self-trauma, an Elizabethan collar, topical dressing or T-shirt should be placed as needed [16]. There is generally a good to excellent outcome if the underlying cause and acute pruritus are controlled [13].

Pyoderma

Pyoderma or cutaneous infections are a common problem in dogs and atypical in cats [17]. Populations of bacteria present in the skin can be classified as resident bacteria and transient bacteria. Resident bacteria are normal commensals that successfully multiply and thrive on normal skin. Transient bacteria may be cultured from normal skin or may be part of a pathological process, acting as secondary invaders. Table 15.1 lists resident and transient bacteria noted in dogs and cats. Unlike pyoderma in humans, there are very few virulence factors such as hemolysin production which account for infection [18].

A recent report by Tanabe et al. reported that staphylococcal enterotoxins are unlikely to act as virulence factors and only 7.6% of isolates from dogs with pyoderma have demonstrable enterotoxins [19]. However, *Staphylococcus* spp do have some virulence characteristics which enhance infection such as the production

Table 15.1 Resident and transient skin bacteria of dogs and cats.

Resident bacteria		Transient bacteria	
Dog	Cat	Dog	Cat
<i>Micococcus</i> spp	<i>Micococcus</i> spp	<i>E. coli</i>	B-hemolytic streptococci
<i>Staphylococcus</i> spp (coagulase negative)	<i>Staphylococcus</i> spp (coagulase negative)	<i>Proteus mirabilis</i>	<i>E. coli</i>
<i>Clostridium</i> spp	A-hemolytic streptococci	<i>Corynebacterium</i> spp	<i>Proteus mirabilis</i>
<i>Staphylococcus</i> spp (coagulase positive)	<i>Staphylococcus</i> spp (coagulase positive)	<i>Bacillus</i> spp	<i>Bacillus</i> spp
A-hemolytic streptococci		<i>Pseudomonas</i> spp	<i>Staphylococcus</i> spp (coagulase negative)
<i>Acinetobacter</i> spp			<i>Staphylococcus</i> spp (coagulase positive)
			<i>Pseudomonas</i> spp

of damaging enzymes (proteases and thermonuclease), production of Protein A and toxic shock protein, along with toxins such as enterotoxins A, B, C, D. Additionally, certain resident bacteria can bind to fibrinogen and can form biofilms [20].

Of all the bacteria that could possibly cause pyoderma, *Staphylococcus pseudointermedius*, formerly *Staphylococcus intermedius*, is the most prevalent. This bacterium is a facultative anaerobic, gram-positive, coagulase-positive coccus. It is a resident bacterium which can become pathogenic, and can be cultured from up to 41% of dogs [21]. *S. pseudointermedius* is a highly resistant organism which can survive in low-humidity, high-heat environments and is tolerant of many antiseptic medications. This potentially pathogenic bacterium has become a very important factor in antibiotic resistance, falling into the MRS (methicillin-resistant *Staphylococcus*) group of pathogens. There are numerous reports of staphylococcal pyoderma resistance to commonly used antibiotics like clindamycin and even to more aggressive antibiotics such as the aminoglycosides and vancomycin [22–24]. It appears that not only most (if not all) B-lactam antibiotics but also many of our “bigger gun” antibiotics are ineffective against MRS. Complicated, drug-resistant MRS is discussed in Chapter 137).

Other, less common isolates include *Staphylococcus aureus* and *Staphylococcus schleiferi* which account for up to 8.3% and 28%, respectively [25]. Primary colonization sites of resident and transient bacteria are the nasal mucosa, oral mucosa, genitourinary region, and perineum. These bacteria can be transferred to other skin areas through grooming [26].

Small animal pyoderma is believed to be secondary to abnormal “host factors,” such as endocrinopathies, some other underlying dermatopathy, i.e. external parasites or allergy, and differences in the stratum corneum. Common underlying causes of secondary pyoderma are listed in Table 15.2. The development of pyoderma is

Table 15.2 Common underlying causes of canine pyoderma.

Condition	Examples
Dermatological abnormalities	Follicular dysplasia (congenital alopecia) Primary seborrhea
Hypersensitivity	Atopy, flea allergy, food allergy
Endocrinopathy	Hyperadrenocorticism, hypothyroidism, diabetes mellitus
Ectopic parasites	Fleas, demodex, sarcoptic mange
Immunodeficiencies	IgA deficiency of GSD, severe-combined immunodeficiency, retroviral infection, altered phagocytosis, Pelger–Huet anomaly, glucocorticoid use

multifactorial, including factors of bacterial pathogenic properties, underlying disease and its effect on skin defense mechanisms and finally, the host immunological response. Canine skin is more prone to infection due to a compact stratum corneum, diminished intracellular lipids, higher pH, and lack of lipid follicular plug [27]. Bacterial pyoderma is classified based on lesion depth as outlined in Table 15.3. Dogs with surface and superficial pyoderma are likely to present to the emergency service because those infections are less chronic than deep infections which are more likely to have been undergoing therapy.

Clinical signs of pyoderma vary according the depth of infection, degree of pruritus, breed, and location (haired skin, mucocutaneous junction, non-haired skin, skinfolds). Similar to demodex, pyoderma has a wide range of lesion appearance (Figures 15.2 and 15.3 are of a dog with papules from pyoderma due to *Staphylococcus pseudointermedius*). Superficial pyoderma lesions may be generalized or localized. They may appear as papules or pustules, crusts, discoloration, scales, or epidermal collarettes, and have raised tufts of hair (longer coated animals) similar to urticaria, commonly affecting the trunk, abdomen, and axilla [28]. Superficial bacterial infection of the hair follicle is the most common form of superficial pyoderma and different breeds will have varying manifestations of infection. English bulldogs, for example, are more likely to have dark, reddened, malodorous pyoderma affecting skinfolds of the muzzle and tailbase.

Table 15.3 Pyoderma classification based on lesion depth.

Surface pyoderma
• Pyotraumatic dermatitis
• Skinfold dermatitis
• Cutaneous bacterial overgrowth
Superficial infection
• Impetigo
• Mucocutaneous pyoderma
• Superficial bacterial folliculitis
Deep pyoderma
• Folliculitis and furunculosis
• Pyotraumatic folliculitis
• Nasal folliculitis and furunculosis
• Muzzle folliculitis and furunculosis
• German Shepherd dog folliculitis, cellulitis, and furunculosis
• Subcutaneous abscess
• Acral lick furunculosis
• Pedal folliculitis and furunculosis



Figure 15.2 Superficial pyoderma along the dorsum of a dog caused by *Staphylococcus pseudintermedius*. Reproduced with permission of Kimberly Coyner.

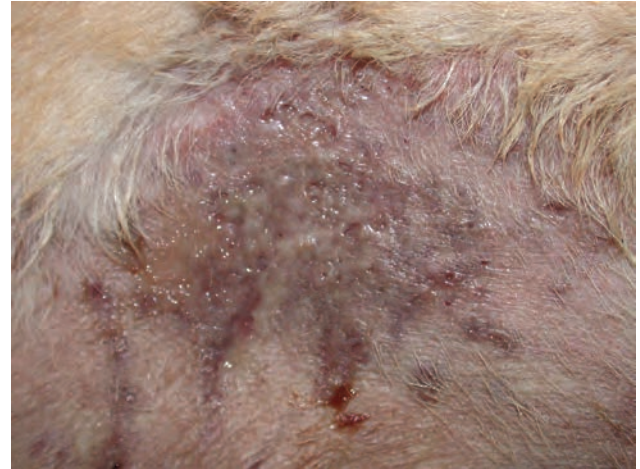


Figure 15.4 Deep pyoderma in a dog. Reproduced with permission of Kimberly Coyner.

Cocker spaniels can have pyoderma manifested as crusts and scaling, similar to seborrhea [29].

Lesions associated with deep pyoderma include “canine acne” or pustules, bullae, nodules, and fistulae of the chin, furunculosis, which may be focal to multifocal areas of alopecia, and crusting, most commonly affecting pressure points such as the lateral elbow. Furunculosis can affect the paws, causing erythema, pustules, bullae, and swelling of the interdigital regions. Finally, there have been reports of furunculosis occurring post bath or post grooming with lesions of swelling, erythema, draining tracts, and marked pain [30]. Figure 15.4 shows secondary deep pyoderma affecting a forelimb of a dog with atopy.

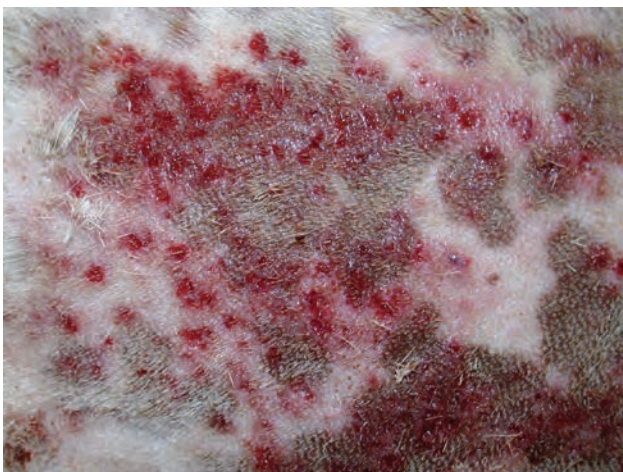


Figure 15.3 Close-up of superficial pyoderma from the dog in Figure 15.2. Reproduced with permission of Kimberly Coyner.

Diagnosis of pyoderma includes ruling out concomitant and/or primary etiologies which led to the infection. Skin scrapings, especially deep scraping, are necessary to identify *Demodex* mites. Hair follicle culture for fungal disease and tape cytology should also be performed. Identification of suppurative inflammation with intracellular cocci will support the diagnosis of superficial pyoderma. Deep pyodermas more often have pyogranulomatous inflammation with a paucity of infectious organisms present. Cases suspected of having deep pyoderma should have cultures performed. In dogs or cats who present with non-recurrent, superficial infection supported by suppurative inflammation without rod-shaped bacteria, culture is not necessary. However, for patients with recurrent infection, cytological identification of rod-shaped bacteria, deep infection and those who are not responding to empirical antibiotics, culture is necessary. Techniques for culture include aspirating purulent material from pustules, submitting tissue biopsy, and swabbing underneath scales or crusts [31]. Differential diagnoses for superficial pyoderma include *Malassezia* dermatitis, *Demodex*, other ectoparasites, dermatophytosis, and pemphigus if epidermal collarettes are present [32].

Both superficial and deep pyoderma will require antimicrobial administration, in addition to identifying and addressing the underlying cause, such as fleas. Topical treatments using ointments and shampoos are often used in conjunction with systemic antibiotics and discussion of these many options are beyond the scope of this chapter. For uncomplicated, bacterial dermatitis, empirical antibiotics which may be used are listed in Table 15.4.

Table 15.4 First-tier antibiotic options for treating uncomplicated pyoderma.

Drug	Dose
Clindamycin	11 mg/kg QD
Cephalexin	22 mg/kg TID or 33 mg/kg BID
Cefadroxil	22 mg/kg BID
Amoxicillin trihydrate with clavulanate acid	14–22 mg/kg BID
Trimethoprim/sulfonamide	20–30 mg/kg QD to BID
Erythromycin	10–15 mg/kg TID
Doxycycline	5–10 mg/kg BID

Superficial bacterial dermatitis should be treated for a minimum of 3 weeks. Recurrent and deep pyodermas may respond to some of the first-tier antibiotics but in cases that fail to respond to appropriate first-tier antibiotics or when culture notes resistance to all first-choice antibiotic options, second-tier antibiotics may be considered which are listed in Table 15.5.

Use of second-tier antibiotics requires at least 6 weeks of therapy and antibiotic choice should, ideally, be based on appropriate culture and sensitivity testing using mean inhibitory concentration (MIC), mutant prevention concentration (MPC), and mutant selection window (MSW). MIC is the minimal level of antibiotic needed to inhibit bacterial growth [33]. For complicated infections and MRS, MPC may be used as an adjunct test to measure *in vitro* bacterial resistance or susceptibility. MPC reflects the lowest concentration of an antibiotic needed to stop the growth of the least susceptible microorganism present. It is the upper boundary of MSW. This methodology has been used to help identify reasons for

Table 15.5 Second-tier antibiotic options for complicated pyoderma (refractory, resistant, deep).

Drug	Dose
Cefpodoxime	5–10 mg/kg QD
Cefovecin	8 mg/kg SQ repeat in 2 weeks
Cefadroxil	22 mg/kg BID
Choramphenicol	33–50 mg/g B-TID
Enrofloxacin	Superficial: 5 mg/kg QD–BID Deep: 10–15 mg/kg QD
Marbofloxacin	5 mg/kg QD
Orbifloxacin	2.5–7.5 mg/kg QD
Rifampin	5–10 mg/kg BID

bacterial resistance occurring in fluoroquinolones. It was determined in one study that high doses of this antibiotic class minimize selection of resistant mutants while use of traditional doses increases the selection of resistant mutant bacterial strains of *S. pseudintermedius* [34]. Finally, MSW is a range of antimicrobial concentration extended from MIC that determines the levels needed to stop the growth of the least susceptible, single-step mutant. Antibiotic concentrations within MSW select for higher mutant populations of the bacteria in question whereas concentrations above MSW (MPC or higher) help restrict resistant mutations [35].

Otitis Externa

Otitis externa is a syndrome characterized by inflammation of the external ear canal [36]. It is a common problem affecting cats and dogs, accounting for 10–20% of veterinary visits, with pure-breds having a higher incidence than mixed breeds [37]. One ear or both ears may be affected with varying degrees of inflammation ranging from mild to severe. Additionally, otitis may be acute or chronic, having secondary bacterial, fungal or both bacterial and fungal infection simultaneously. Certain breeds are overrepresented in otitis such as shar-pei, cocker spaniel and German shepherd. Both cocker spaniels and German shepherds were more likely to have infections with rod-shaped bacteria than cocci. Rod-shaped bacteria were more likely noted in dogs with endocrinopathies while yeasts were more often noted in dogs with allergies [38].

Unlike otitis in dogs, up to 80% of otitis in cats is due to infection by the ear mite *Otodectes cynotis*. These infections and subsequent otitis are most often noted in young cats, especially those housed in multicat facilities such as a shelter. Adult cats with otitis and concurrent mite infection often have a history of being housed in a kennel or shelter. Even a small number of infecting mites can cause a serious otitis from an Arthus-type reaction to the mite's biting of the epidermis [39]. Predisposed cat breeds noted with increased incidence of otitis include Persians and Himalayans [2]. Topical treatment options for *Otodectes cynotis* include topical selamectin, pyrethrin, and fipronil. Non-approved oral or injectable agents that are used topically against *Otodectes cynotis* include oral ivermectin and topical aural ivermectin [40]. Newer products used for ectoparasite control of fleas and ticks in dogs and cats have shown excellent efficacy against *Otodectes*. A single topical or oral dose of fluralaner was nearly 100% effective to rid the mites [41]. Similarly, a single 2.5 mg/kg dose of afoxolaner was very effective in treating *Otodectes* in dogs with >98% successful elimination of the mites [42]. Both of these products are extra-label use for this parasite.

Table 15.6 Primary causes, predisposing factors, secondary causes, and perpetuating factors of otitis externa.

	Most common examples
Primary causes	
Hypersensitivity	Atopy, food allergy, flea allergy
Parasites	<i>Demodex</i> , <i>Otodectes</i> , <i>Sarcoptes</i>
Keratinization disorders	Primary seborrhea, altered cerumen production
Foreign objects or material	Grass awns, hair, medications
Immune-mediated disease	Lupus, pemphigus
Predisposing factors	
Excessive moisture	Swimming, bathing
Breeds	Shar-pei, GSD, cocker spaniel
Obstruction	Feline nasopharyngeal polyps, neoplasia
Systemic issues	Immunosuppression, catabolic state, endocrinopathy
Conformation	Hair in otic canal, stenotic canal, pendulous pinnae
Secondary causes	
Bacteria	<i>S. pseudintermedius</i> , <i>S. epidermidis</i> , <i>P. aeruginosa</i> , <i>Proteus</i> spp, <i>E. coli</i> , B-hemolytic <i>Streptococcus</i>
Yeast	<i>Malassezia pachydermatis</i>
Perpetuating factors	
Progressive anatomic changes	Hyperkeratosis, fibrosis, stenosis, hyperplasia, excessive discharge
Treatment effects	Irritation from medications, trauma/inflammation from cleaning

Otitis externa etiology is categorized using the PPSP acronym, which stands for primary causes, predisposing factors, secondary causes, and perpetuating factors. Table 15.6 gives classification etiologies and examples of each. Primary causes include parasites such as *Otodectes cynotis*, atopy, endocrinopathies and immune-mediated disease such as pemphigus vulgaris. Predisposing factors are those which increase the risk of otitis and include ear conformation (pendulous ears), obstruction from masses or polyps, and excessive moisture from swimming. Secondary causes are those which are the main targets of treatment – bacteria and yeast opportunistic or secondary infections. Secondary bacterial pathogens include *Staphylococcus* and *Pseudomonas* spp in the cases of resistant, chronic otitis. Both *Candida albicans* and *Malassezia pachydermatis* are common secondary yeast pathogens [43].

As otitis progresses, perpetuating factors account for inability of the inflammation/infection to resolve without

intervention. Examples of perpetuating factors include fibrosis and epithelial changes affecting secretions [44]. It is important to view otitis externa as a syndrome affecting the skin, not as an isolated problem with the ear. While it is not necessarily the responsibility of the emergency clinician to identify and treat primary causes or predisposing factors of otitis, the pet owner should be made aware of the complexity of otitis so there is appropriate follow-up with their family practitioner or a dermatologist.

Diagnosis of otitis externa is not difficult. In most cases, the owner will state their pet “has an ear infection” due to scratching, erythema, swelling, head shaking, malodor, discharge, and pain. Physical exam often notes purulent or ceruminous (brown, waxy) exudate from the affected ear as well as swelling, erythema, and pain during palpation (Figure 15.5). In severe cases, otoscopic exam is difficult due to the pain and narrowing of the external ear canal, requiring sedation. The entire epidermis, especially mucocutaneous junctions and areas between the toes, should be thoroughly checked for lesions (crusts, alopecia, papules, collarettes, pustules) consistent with pyoderma, atopy, and mites or other external parasites like fleas. While the immediate concern is the otitis and associated symptoms, treatment will likely fail if primary and predisposing factors are ignored. Additionally, evidence of endocrinopathies should be assessed such as changes in thirst, urination, appetite, body condition, and weight.

Confirmation of secondary infection is accomplished by examining exudates from the ear cytologically using both routine Diff-Quik staining and gram staining of samples. Use of Diff-Quik with or without initial acetone dip and Gram-Quik stain was found to be highly reliable in detecting micro-organisms [45]. Note that bacteria and yeast can colonize and contaminate cytological stains. It is advised that stains be changed soon after

**Figure 15.5** Severe otitis externa in a dog. Reproduced with permission of Kimberly Coyner.

exposure to ear exudates or a separate set of stains be kept for use in cases of suspected otitis. Samples should be submitted for culture but it should be noted that it is typical for multiple isolates of bacteria to be present.

There is a population of non-pathogenic, normal microbial and fungal flora in the ears of healthy dogs and cats. *Malassezia* were noted in both normal dogs and those with otitis. That same study noted that *Malassezia* were more likely to be cultured from dogs with increased cerumen, dogs with atopy and those with other dermatopathies like pyoderma. Additionally, other saprophytic fungi such as *Penicillium* and *Aspergillus* spp can be cultured from normal dogs although cytological evidence of saprophytic fungal organisms was not found [46]. Bacterial isolates from healthy dogs include numerous *Staphylococcus* sp., including *S. pseudintermedius*, *S. epidermidis* and *S. schleiferi*. One report found 13 different species of bacteria in the external canal of 68.3% of healthy dogs, and of the isolates noted, 39% were identified as *S. pseudintermedius*, 25% *S. epidermidis*, and 28.6% were “unidentifiable” [47]. A similar study noted positive bacterial cultures in 78.8% of healthy beagles from different regions of the external ear canal. In that report, *S. pseudintermedius* was isolated from 57.7% of normal ears [48].

The most common bacterial isolates from dogs with otitis include *Pseudomonas aeruginosa*, *Staphylococcus pseudintermedius*, *Proteus* sp., *beta-hemolytic streptococci* and *Escherichia coli* [49]. Over 60% of dogs with bilateral otitis may have different isolates from each ear and have more than one species of bacteria positively cultured. However, the majority of dogs with otitis externa will culture positive for *Malassezia pachydermatis* and *S. pseudintermedius* [50].

Successful treatment of otitis externa requires the identification and management of primary causes (atopy, external parasites), manageable predisposing causes (removal of excessive hair from ear canal, thorough drying of ear canal after a swim or a bath) and antimicrobial/antifungal medication for the secondary infection. It is unlikely, during emergency examination for a pruritic ear, that a complete dermatological history and work-up will always be performed. However, it is important for the emergency clinician to, at the very least, obtain swab samples from the external otic canals for cytological examination and culture. Additionally, minimal dermatological work-up (skin scraping, flea comb, tape cytology, and sampling for DTM culture) for patients with pruritus or other skin lesions should be performed. Patients who are so pruritic that they are causing themselves harm by scratching or violent head shaking will need medications to stop that process. Commonly, topical ear cleaning, antihistamines, short-acting glucocorticoids, and topical antimicrobial/antifungal/anti-inflammatory ointments

are used to accomplish this. Again, photographs and samples should be provided to the family practitioner and/or dermatologist prior to initiating treatment.

The tympanum should be assessed prior to using or prescribing a topical therapy as certain medications may cause ototoxicity. In cases in which there is too much inflammation or exudate to visualize the tympanum, less toxic medications should be used. There is debate among veterinary dermatologists as to the true danger of ototoxicity from topical medication, since studies using topical agents considered ototoxic may or may not result in hearing loss or vestibular syndrome [51,52].

There are many topical ointments available to treat otitis and most contain combinations of antibacterial agents, antifungal agents, and glucocorticoids. Medication contents of different formulations should be reviewed prior to use, making sure the clinical picture, cytology of ear swabs and culture results (if available) correspond to the active ingredients. In general, dogs and cats with otitis should receive (1) adequate analgesia prior to cleansing or flushing, (2) topical ear cleaning using 0.9% saline and/or an ear cleaning agent (cases of marked cerumen and exudate may require use of a ceruminolytic agent), (3) antibiotic/antifungal agent or a combination of antibiotic, antifungal and anti-inflammatory ointment. Systemic antibiotics are indicated for patients with otitis media, ulcerative otitis externa, chronic/severe otitis externa and those who do not tolerate topical treatment well. Options of topical medications for ear cleaning are provided in Table 15.7. Table 15.8 lists topical combination medications containing antibiotic, antifungal, and anti-inflammatory ingredients.

Similar to pyoderma, *Staphylococcus* spp isolated from cases of otitis externa exhibit resistance to many first-tier, systemic antibiotics routinely used for pyoderma. In one study, 48 staphylococcal strains were identified and showed resistance to at least two antibiotics such as erythromycin, lincomycin, amoxicillin/clavulanic acid, and tetracycline [53]. There was little to no resistance of *Staphylococcus* spp to amikacin, rifampin, ciprofloxacin, ceftriaxone, cefoxitin, and cefaclor [54]. *Pseudomonas* spp have resistance to topical treatments. In one study of eight topical antiseptics, only three showed *in vitro* effectiveness against *Pseudomonas* spp [55].

In conclusion, otitis externa is a common complaint affecting dogs and cats. It is a syndrome that has predisposing and perpetuating factors which lead to secondary infection which is commonly due to *Staphylococcus* spp. and *Malassezia*. The majority of cats with otitis externa likely have *Otodectes cynotis* as a primary factor and elimination of the parasite typically results in resolution of the problem. Dogs tend to have an underlying disorder which can affect not only the ears but also other regions of the epidermis. While the goal of the emergency

Table 15.7 Topical agents commonly used to treat otitis externa.

Product/trade name and manufacturer	Active ingredient	Indication	Special considerations
Otoclean (Schering-Plough)	Salicylic acid 0.23% Lactic acid, oleic acid	Ceruminolysis	Most effective ceruminolytic agent*
Cerumene (Vetquinol)	25% squalene	Ceruminolysis	Ototoxic, primarily for in-hospital use
KlearOtic (Dechra)	22% squalene	Ceruminolysis	Ototoxic
Corium-20 (Virbac)	<i>tert</i> -Butyl alcohol and denatonium benzoate	Ceruminolysis	
Malacetic otic (Dechra)	Acetic acid, boric acid, surfactant	Ear cleaning and drying	
Epi-Otic Advanced (Virbac)	Salicylic acid, disodium EDTA, docusate sodium	Ear cleaning and drying	EDTA is bactericidal and more effective than gram(-) isolates
Epi-Otic cleanser (Virbac)	Lactic acid, salicylic acid, chitosanide, docusate sodium	Ear cleaning and drying	
Nolvasan Otic (Pfizer)	Isopropanol and inert ingredients	Ear cleaning	
Oti-Clens (Pfizer)	Propylene glycol, malic acid, benzoic acid, salicylic acid	Ear cleaning	
TrizEDTA (Dechra)	Tromethamine (Tris)-EDTA, deionized water	Ear cleaning Tris-EDTA increases cell wall permeability of <i>Pseudomonas</i> spp (more susceptible to antibiotics)	
OtoCetic Solution (Vedco)	Boric acid, acetic acid	Antiseptic and ear cleaning	Acetic acid is effective against <i>Pseudomonas</i> spp
DermaPet Ear Cleanser (Dechra)	Acetic acid, boric acid	Antiseptic and ear cleaning	Acetic acid is effective against <i>Pseudomonas</i> spp
Hexadene flush (Virbac)	0.25% chlorhexidine	Antiseptic	Ototoxic to cats, ototoxic to dogs? <i>Pseudomonas</i> spp resistance

*Robson DC, *et al.* *In vitro* ceruminolytic activity of 24 ear cleaners against standardized synthetic canine cerumen. Proceedings of the 24th North American Veterinary Dermatology Forum, Savannah, 2009, p. 217.

Table 15.8 Topical antibiotic, antifungal, and anti-inflammatory medications for otitis externa.

Product/trade name and manufacturer	Active ingredient	Indication	Special considerations
Tresaderm (Merial)	Neomycin sulfate, thiabendazole, dexamethasone	Bacterial otitis <i>Malassezia</i> otitis	Anti-inflammatory glucocorticoid
Otomax (Intervet/Schering-Plough)	Gentamicin sulfate, betamethasone, clotrimazole	Bacterial otitis Fungal otitis	Aminoglycoside Ototoxicity Inactivated by debris (canal must be clean)
Baytril Otic (Bayer)	0.5% enrofloxacin, 1% silver sulfadiazine	Bacterial otitis	Better gram(-) spectrum
Surolan (Vetquinol)	Miconazole, polymyxin B, prednisolone	Bacterial otitis Fungal otitis	Good activity vs <i>Pseudomonas</i> spp Inactivated by debris (canal must be clean)
Posatex (Intervet/Schering-Plough)	Orbifloxacin, posaconazole, mometasone	Bacterial otitis Fungal otitis	Anti-inflammatory glucocorticoid
Claro (Bayer)	florfenicol, terbinafine, mometasone furoate	Bacterial and Fungal otitis	Single use effectiveness

clinician is to relieve signs of pruritus, pain and infection, the underlying condition must be investigated at some point for proper therapy of otitis externa. Generally, topical therapy is employed and systemic medications are reserved for chronic, ulcerative, and resistant bacterial otitis.

Ectoparasites

The primary ectoparasites resulting in dermatological conditions are mites, fleas, and ticks. Two main species of mite will be discussed: *Demodex* sp. and *Sarcoptes* sp. *Demodex* mites are normal inhabitants of canine skin and are transmitted during birth or nursing. Mites are not always noted during microscopic studies of healthy dogs [56].

Demodex canis is the primary species that can cause dermatopathies in dogs. It is an obligate hair follicle parasite and measures 200–300 µm, having four pairs of short legs. In dogs, there are additional species of *Demodex* which may cause problems: the long-bodied *Demodex injai* measuring 350–400 µm, and a short-bodied *Demodex cornei* which is approximate 150 µm in length [57]. In cats, there are three described species of *Demodex* mites: *Demodex cati*, *Demodex gato*, and a third, still unnamed *Demodex* sp. [58]. Pure-breeds are more commonly affected than mixed breeds, with certain breeds having much higher incidence such as shar-pei, Scottish terrier, Great Dane, English bulldog and Boston terrier [59].

Sarcoptic mange in pets, livestock, and humans is caused by the mite *Sarcoptes scabiei*, which has at least 100 mammalian varieties which are somewhat species specific. *Sarcoptes* spp are highly contagious and not normal inhabitants of canine skin. The infectious species in dogs is *Sarcoptes scabiei* var. *canis* which has a 17–21-day life cycle and can survive for up to 3 weeks in the environment [60].

Since *Demodex* mites are commensal organisms, generalized *Demodex* infection can be the result of numerous factors such as age, altered skin structure, breed, nutritional status, endocrinopathies, estrus cycle, and immune status. Of all the aforementioned factors, the main reason dogs develop *Demodex* infections is immune dysfunction in both adults and juvenile dogs [61]. Gene studies in collies and beagles link an autosomal recessive gene to the infection. Humoral immunity and antibody function appear normal in dogs with generalized demodicosis; however, multiple studies have identified altered cell immunity, primarily affecting T-cells [62]. Dogs with generalized demodicosis had lower CD4+ T-cells, decreased interleukin (IL)-2 production and elevated IL-10 production or what is called “T-cell exhaustion” [63,64]. *Demodex* mites induce an elevation

of transforming growth factor (TGF)-beta and inhibit tumor necrosis factor (TNF)-alpha mRNA expression. Changes in the aforementioned inflammatory signaling molecules, overproduction of IL-10, which is an inhibitory cytokine, and diminished lymphocyte blastogenesis may explain why adult dogs may develop generalized demodicosis [61,64].

Immune suppression through chemotherapy agents such as azathioprine and high-dose prednisone, along with naturally occurring hyperadrenocorticism, can result in mature dogs developing generalized demodicosis. Hypothyroidism and neoplasia are also noted in adult dogs with generalized demodicosis, but in around one-half of adult-onset cases, no other underlying disorder is found [65].

Canine demodicosis may be generalized or localized. Generalized demodicosis is more common in younger dogs but adults with endocrinopathies or other causes of immune dysfunction may develop it. Localized demodicosis lesions are typically found on the muzzle, especially the commissure of the mouth. These lesions are typically partially alopecic with mild erythema and may be pruritic. Luckily, most puppies with localized infection have an excellent prognosis with spontaneous resolution taking place over 6–8 weeks [59]. There is also a localized form of *Demodex* which affects the feet called demodectic pododermatitis. These lesions are erythemic, with sometimes a moist dermatitis, and cause lameness due to pain. Pododemodicosis is considered as serious as generalized demodicosis.

Generalized *Demodex* lesions are characterized as poorly circumscribed regions of alopecia and erythema that progress in size and worsen in severity over time, sometimes being fatal [62]. Figure 15.6 is of a dog with severe demodicosis with secondary pyoderma. Since the



Figure 15.6 Demodicosis with secondary deep pyoderma in a dog. Reproduced with permission of Kimberly Coyner.

mites inhabit the hair follicles, hyperkeratosis and folliculitis are commonly noted during examination. Other lesions may be nodular and crusting is also frequently noted.

Demodex injai causes different lesions from *Demodex canis* and *Demodex cornei*, characterized by a dorsal, oily seborrhea of the lumbar region [66]. It is more prevalent in terrier breeds such as Jack Russell, West Highland white and Scottish terriers. *Demodex cornei* infections cause lesions similar to *Demodex canis* [67]. Therefore, demodicosis can appear similarly to many dermatopathies including pyoderma, contact allergy, all forms of seborrhea, dermatophytosis and endocrinopathies such as hypothyroidism.

It is recommended that all skin lesions of dogs be tested for demodicosis by performing a deep skin scrape, meaning that the epidermal layer is scraped until capillary bleeding occurs; trichograms and surface biopsies are less sensitive [68]. Deep skin scrapings are the diagnostic test of choice [69]. Alternately, acetate tape impression while squeezing the skin may also be used for diagnosis [70]. If demodicosis is suspected and the aforementioned diagnostic tests do not find the organisms, a skin biopsy should be performed. Demodicosis, especially caused by *Demodex injai*, may sometimes only be diagnosed by biopsy confirmation of mites in the sebaceous glands and/or hair follicles [71]. A diagnosis is made by identifying numerous adult mites or a high ratio of immature parasites, such as ova and larvae, to adults.

Treatment of canine demodicosis is determined by severity and form of infection. Localized demodicosis is self-limiting and treatment is not recommended. Most affected puppies will have resolution of the lesions by the time they reach sexual maturity. After initial diagnosis, it is recommended that any progression of the lesions be examined immediately to be certain that a localized condition is not becoming generalized.

Pododemodicosis and generalized demodicosis require treatment. Conditions contributing to immune dysfunction such as endocrinopathies, resistant MRS infection, and use of immunosuppressants should be identified and addressed.

There are many available treatments which are listed in Table 15.9. Topical application of amitraz, which is FDA approved, may be used weekly or bimonthly at a concentration of 0.025%. Some recommend higher concentrations and more frequent topical application for improved rate of cure [72]. Oral treatment using macrocyclic lactones is the current recommendation for generalized demodicosis [70]. These antiparasitic agents affect invertebrate GABA activity. This entire class of drugs will cause harm in dogs who have MDR 1 gene mutation which commonly affects collies, Shetland sheepdogs, and Australian shepherds along with any cross-breeds. Pure-breeds or mixed breeds suspected of MDR 1 mutation should be DNA tested prior to using oral macrocyclic lactones. These medications include ivermectin, doramectin and milbemycins. Of all the available products, ivermectin (0.3–0.6 mg/kg/day), milbemycin oxime

Table 15.9 Treatment options for generalized demodicosis in dogs.

Drug	Dose and route	Side-effects
Amitraz 0.025%	Weekly or every 2 weeks, topical	Depression, vomiting, diarrhea, bradycardia, polydipsia, polyuria
Ivermectin 1% injectable	Day 1: 0.05 mg/kg (50 µg/kg), PO	Ataxia, mydriasis, blindness, tremors, vomiting, seizures, coma, death
Ivermectin 1% oral liquid	Day 2: 0.1 mg/kg (100 µg/kg), PO	
Ivermectin tablets/ chewable: 55 µg, 68 µg, 136 µg, 165 µg, 272 µg	Day 3: 0.15 mg/kg (150 µg/kg), PO	
	Day 4: 0.2 mg/kg (200 µg/kg), PO	
	Day 5: 0.3 mg/kg (300 µg/kg), PO	
	Day 6 and on: increase by 0.1 mg/kg (100 µg/kg) every 3–7 days to reach the final target dose of 0.6 mg/kg/day	
Moxidectin 1% solution	0.2–0.4 mg/kg/day, PO (start with 0.05 mg/kg, PO and gradually increase dose as described for ivermectin)	Lethargy, vomiting, ataxia, inappetence, tremors, seizures
Moxidectin 2.5% spot-on formulation with 10% imidacloprid		
Milbemycin oxime tablets: 2.3 mg, 5.75 mg, 11.5 mg, 23 mg	1–2 mg/kg/d, PO	Ataxia, trembling, vomiting, lethargy

(2 mg/kg/day) and moxidectin (0.4 mg/kg/day) had good efficacy in treating generalized demodicosis [73]. Prognosis in dogs with generalized demodicosis is fair to good. In one study of 34 dogs, only five did not respond to therapy [74].

Feline demodicosis due to *Demodex cati* should be considered as a differential diagnosis in cats with generalized dermatitis and/or otitis externa. Siamese and Burmese are predisposed to developing generalized demodicosis [60]. Lesions noted in cats with *D. cati* include alopecia, erythema, seborrhea, scales, papules, and pustules. Similar to dogs, lesions tend to occur on the face (chin, ears, neck) and can become generalized to include the limbs and trunk. Some cats are pruritic, but this is generally mild. Cats suspected of demodicosis should be tested for retroviruses, diabetes mellitus, hyperadrenocorticism, and systemic lupus erythematosus. Dermatopathies with similar lesions include bacterial pyoderma, atopic skin disease, and seborrhea. Similar to dogs, diagnosis is based on clinical findings and demonstration of the mite from skin scrape, acetate tape impression or biopsy [75]. There are descriptions of *D. cati* mites associated with squamous cell carcinoma *in situ* [76].

Demodex gato is a more recently discovered, contagious mite which lives in the keratin layer of the epidermis, not the hair follicle. Infection with this parasite results in pruritus, alopecia, broken hairs, erythema, crusts and excoriations of the face, neck, hindlimbs, ventrum, and elbows [75]. Superficial skin scraping and/or tape cytology is used for diagnosis. Multiple (>10) samples are sometimes necessary to identify the mites and histopathology is less useful since only mites trapped in keratin will be identified [62].

Treatment for feline demodicosis is achieved by topical lime-sulfur dips, systemic ivermectin and topical amitraz. There is a recent report of successful treatment of *D. gato* using 10% imidicloprid/1% moxidectin weekly for 10 weeks [77].

Scabies is a relatively uncommon, infectious, pruritic dermatopathy of dogs and cats. It commonly affects young dogs, with the majority being less than 1 year of age. The most common clinical sign is pruritus, affecting up to 77% of infected dogs [78]. The severe pruritus leads to excoriations, scabs, and crusts. Alopecia, erythema, and papules may also occur [62]. Distribution of lesions affects areas with less hair such as the ventrum, pinnae, distal limbs, and elbows. This mite is zoonotic and concurrent human infection occurs in 4–20% of canine cases and there is up to 33% contagion from dog to dog.

Diagnosis of scabies is challenging. Mites may be found in only 22–50% of affected dogs by skin scrape [78]. The intense pruritus produces a demonstrable otapedal reflex in a majority of cases [62,78]. Demonstration of the mite is diagnostic and should be performed using

Table 15.10 Treatment options for scabies (sarcoptic mange).

Drug	Dose and route
Metaflumizone plus amitraz (ProMeris)	0.133 mL/kg bimonthly or biweekly topical spot-on (2–4 treatments total)
Milbemycin oxime (<i>non-MDR 1 dogs only</i>)	2 mg/kg orally, 2 doses total 14 days apart
Fipronil spray	0.25% once a week for 4 weeks
Amitraz	250 ppm once a week every 3 weeks
Ivermectin 1% injectable (<i>non-MDR 1 dogs only</i>)	0.2–0.4 mg/kg SQ twice, 14 days apart
Ivermectin topical/pour-on (<i>non-MDR 1 dogs only</i>)	0.5% solution, 0.1 mL/kg topically, 2 doses total 14 days apart

mineral oil on areas with papules and crusts. Preferably, the elbows, hocks, and pinnae are superficially scraped too [62]. Mites are round-bodied with midabdominal triangular spines. They have six legs, with long unsegmented pretarsi of their front legs. Additionally, an ELISA test is available, but seroconversion can take many weeks, causing false-negative results if tested too early [60]. Recently, a real-time PCR has been developed which can identify *Sarcoptes scabiei* [79].

There are many topical treatment options for scabies which include fipronil, amitraz, and metaflumizone plus amitraz [80]. Injectable ivermectin has long been a mainstay of therapy for non-MDR 1 mutation dogs but there have been reports of ivermectin resistance [81]. Table 15.10 lists the various medications and routes of administration to treat scabies.

One of the greatest concerns for emergency veterinarians, staff, and clients once there is diagnosis of sarcoptic mange is the zoonotic potential of this ectoparasite. Dog-to-human transmission is widely reported, especially in less developed regions. Appropriate measures such as the use of protective gowns, gloves, and isolation of the affected animals should be taken. Pet owners should be warned and advised to consult with their local health department or family medical doctor for care.

Atopy

In terms of emergency medicine, atopy is likely an issue which will cause dogs and cats to present for intractable pruritus and lesions associated with self-trauma and secondary infection. Additionally, dogs and cats may present with problems related to atopic management since immunosuppressive agents are widely used for pruritus

and associated dermatopathy. Infection, endocrinopathies, hepatic issues, and gastrointestinal symptoms are just a few of the adverse effects from atopic medical management.

Atopy is defined as a genetic allergic skin disease that causes inflammation and pruritus [82]. The inflammation is mediated by IgE response to environmental or other antigens. The pruritus may be seasonal and affects a large proportion of dogs, with some estimates as high as 10% of all dogs who visit the veterinarian [83]. Up to 20% of cats who present for pruritus will not have flea or food hypersensitivity and are categorized with hypersensitivity dermatitis [84]. Atopy is more prevalent in animals aged 6 months to 3 years with many animals having recurrent dermatitis for over 2 years [82].

The pathophysiology of atopy involves innate and acquired defects of the epidermal barrier. Studies have found ultrastructural and functional changes of the barrier. There is an imbalance of fatty acids and ceramides of the stratum corneum which is either a primary, genetic defect or due to inflammation from commensal bacteria or environmental allergens such as dust mites. It is believed that loss of the normal epidermal barrier allows allergens to interact with Langerhans cells.

Cell-mediated immunity, specifically T-lymphocytes, play an important role in the pathogenesis of atopic dermatitis. T-cell populations differ during the acute phase (Th2 predominance) versus the chronic phase characterized by Th1 predominance. The altered T-cell response results in overexpression of cytokines such as IL-2, interferon (INF)-gamma, TNF-alpha, and IL-4. Overproduction of IL-4 results in production of allergen-specific IgE due to class switching by B-cells. There is also lower than normal TGF-beta which is thought to account for lack of tolerance to environmental allergens [85].

Diagnosis of atopy is one, primarily, of exclusion. Differential diagnoses include flea allergic dermatitis, demodicosis, scabies, chyletiellosis, *Otodectes*, staphylococcal pyoderma, food allergy, *Malassezia* dermatitis, contact dermatitis, and cutaneous lymphoma. All pruritic dogs and cats should be examined for ectoparasites by flea comb, superficial and deep skin scrapes. Acetate tape impressions with routine cytological staining and gram staining should be performed. Similar to scabies and food allergy, the lesion distribution most commonly involves the pinnae, ventrum, axillae, inguinal region, and especially distal extremities. In most cases, there is a lesional pruritus which progresses to erythema and papules. Worsening lesions such as abrasions, excoriations, alopecia, hyperpigmentation, and crusting occur secondarily to self-trauma, infection, and chronic inflammation [82]. Figures 15.7, 15.8 and 15.9 are examples of atopic dermatitis lesions in dogs and cats. Additional diagnostic measures are beyond the scope of emergency practice



Figure 15.7 Fine dander noted in a cat with atopy. Reproduced with permission of Kimberly Coyner.

and include intradermal skin testing and IgE serological testing. Neither has been standardized and false-negative results are common, with 10–30% of atopic dogs having negative intradermal skin tests [87].

Definitive diagnosis and multimodal therapy for atopy are beyond the scope of this chapter. In general, emergency clinicians will need to treat secondary infection (see section on pyoderma) and pain, and provide



Figure 15.8 Alopecia, hyperpigmentation, and erythema affecting the ventrum and inguinal regions of a dog with atopy. Reproduced with permission of Kimberly Coyner.



Figure 15.9 Ventral neck and thorax of the same dog as shown in Figure 15.8. Reproduced with permission of Kimberly Coyner.

medication to try to relieve the pruritus. Short-term glucocorticoids are primarily used in the short term to provide the patient with some relief, using anti-inflammatory doses of prednisone or prednisolone of 1–2 mg/kg. Antihistamines such as hydroxazine, chlorpheniramine, and

amitriptyline can all be considered in conjunction with glucocorticoids. Temaril-P (trimeprazine tartrate and prednisolone) combines antihistamine with low-dose glucocorticoid which is very useful in animals with an atopic “flare-up.” Since there is a good probability that a previously diagnosed atopic animal presents with recurrence or illness related to medication use, emergency clinicians should be familiar with common side-effects of glucocorticoids, maropitant, cyclosporine, antihistamines, and nutritional supplements such as vitamin E and eicosapentaenoic acid.

Conclusion

Dermatopathies are one of the primary reasons pet owners seek veterinary care and because of the convenience of emergency veterinary services, will likely present for assessment of skin problems. While it is not practical for emergency clinicians to perform skin biopsies and extensive work-ups as part of their practice, routine dermatological tests of external examination for ectoparasites, deep and superficial skin scraping along with acetate tape cytology should be part of the work-up. Most skin disorders appear with similar signs and distribution of lesions and eliminating differential diagnoses, especially those which are zoonotic, should be performed. As with other conditions, detailed medical records and properly noting lesion distribution and appearance are very important for follow-up care and maintaining a good working relationship with general practitioners.

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16

Toxin Exposure

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Introduction

In emergency medicine, the “poisoned patient” is not uncommon. Most intoxications are accidental (dropped pill, animal given wrong medication, etc.) with the offending agent being identified. These cases can be easily managed with proper treatment and a predictable outcome. However, many owners will request that the antidote be given. It is important to remember that the vast majority of toxic agents have no specific antidote. Treatment for most toxins is symptomatic and supportive. Even in the few cases where antidotes do exist for the specific toxicant, there are often barriers to their use in veterinary medicine, including high cost and lack of availability. For example, using digoxin immune FAB fragments for a digoxin overdose is cost prohibitive for most clients [1].

Occasionally, the veterinarian may suspect that an unidentified poison has intoxicated the patient. Even though identification of the agent involved is extremely helpful in determining proper treatment and prognosis, it is important to remember that the majority of these types of cases are managed without the offending agent ever being identified. Even if the identity of the toxicant remains a mystery, the veterinarian can still deliver appropriate and effective treatment. Whether the toxic agent is known or not, it should always be remembered that the goal is to “treat the patient, not the poison.”

Whatever the reason for presentation, upon initial examination, the animal should be evaluated for immediate life-threatening problems. Follow the ABCs (airway, breathing, circulation) of emergency medicine and address seizures, hemorrhage, and hyperthermia to ensure patient survival (see Chapter 2) [2]. Stabilization is the number one priority in animals presenting with severe clinical signs. A brief history may be gathered from the client while stabilization is taking place.

If possible, before giving any medications, obtain venous access and draw blood for laboratory and potential diagnostic testing. A 3 cc EDTA tube and two serum tubes are ideal, but this must be tailored for the patient. Pretreatment samples can be important as some common medications can interfere with diagnostic tests; for example, propylene glycol in injectable diazepam or glycerol in activated charcoal can make the cageside ethylene glycol tests false positive [3,4].

When presented with a seizing animal, anticonvulsants, particularly benzodiazepines, should be administered slowly IV, as rapid administration may induce a dysphoric effect with some toxicants and temporarily exacerbate the situation. Monitor patients closely after administration as hypnotics and sedatives can also cause apnea in patients ingesting isoxazole mushrooms [5].

Life-threatening cardiac arrhythmias should be treated as needed [2]. Arrhythmias not deemed immediately life-threatening can be treated after a better history has been obtained (see Chapter 53).

General supportive care is the mainstay of treatment and includes maintaining hydration, ensuring adequate urine output, monitoring of respiratory, cardiac and neurological status, and managing clinical signs as they develop [6]. Start intravenous fluids and blood components as needed. Any electrolyte or acid–base abnormalities should be corrected. Body temperature should be normalized. Once the patient has been fully stabilized, a more comprehensive physical examination and history taking may be performed [7].

If the poisoned patient is asymptomatic, decontamination may be considered. Emesis may be induced, depending on the time frame of ingestion. As a general rule, emesis is most productive if performed within 1–2 hours after ingestion. This can vary with the substance ingested. Acetaminophen and cold medications can have blood levels within 10 min and complete absorption occurs rapidly. In these cases, emesis

is rarely fruitful unless the pill was given in a piece of food (cheese, hot dog) or Pill Pocket. Other items such as grain-based rodenticides will stay in the stomach for up to 4 h. Chocolate actually increases the pyloric sphincter tone and can be recovered with emesis up to 8 h later. Feeding a small meal or slice of bread prior to inducing vomiting can increase the chances of an adequate emesis. Emetics generally empty 40–60% of the stomach contents and are assumed to be more efficacious than gastric lavage [8]. The vomitus should be examined for evidence of the ingested substance.

Contraindications to inducing emesis include cases where the animal has already vomited, is at risk of aspiration (CNS depression, dyspnea, laryngeal paralysis, or other severe clinical signs), or has ingested corrosive agents (acids, alkalis, cationic detergents) or hydrocarbons [8]. Pre-existing conditions of the patient (seizure disorders, megaesophagus) or recent abdominal surgery may also cause the use of an emetic to be contraindicated.

Potential complications from emesis induction include aspiration, persistent gastritis, and transient bradycardia secondary to vagal stimulation. A gastric lavage can be considered in cases where animals are not good candidates for emesis induction.

While administration of activated charcoal is recommended for many cases of ingested poisons, it should not be an automatic response. Activated charcoal adsorbs toxicants and facilitates its excretion via the feces. There is a risk of aspiration or electrolyte abnormalities (hypernatremia secondary to shift of free water into the GI tract) [9]. Unless the toxin undergoes enterohepatic recycling, once it has been absorbed, activated charcoal will not provide any benefit.

There are also contraindications to giving activated charcoal. Activated charcoal should not be given to animals that have ingested caustic materials. There are also situations where activated charcoal does not work. Charcoal does not effectively adsorb ethanol, methanol, fertilizer, fluoride, petroleum distillates, most heavy metals, iodides, nitrates, nitrites, sodium chloride, and chlorate [8].

Cathartics enhance elimination of substances, including activated charcoal, by moving them through the GI tract. They are commonly found in prepared activated charcoal products. Without cathartics, the toxicant which is bound to activated charcoal by weak van der Waals forces can eventually dissociate and be absorbed from the GI tract [8]. Cathartics are not used if the animal has diarrhea or is dehydrated as they increase the risk of electrolyte abnormalities. Osmotic cathartics, like sorbitol, pull electrolyte-free water into the GI tract.

In situations where emesis and/or activated charcoal are not feasible (severe CNS depression, vomiting), enemas may be helpful. Enemas can increase the elimination of toxicants from the lower gastrointestinal tract. The

general technique is to use plain warm water or slightly soapy warm water (10 mL/kg). Plant material, seeds, and bait can be identified in the stool.

While many household products have labels recommending dilution with milk or water, this is not an appropriate treatment for all exposures. Dilution with milk, water, or liquid from water-packed tuna fish is recommended in cases of ingestion of corrosive or irritant products, exposure to toad secretions, or taste reactions due to topically applied products (“foaming kitties” following flea spray application) [2]. Administration of large volumes of oral liquids can increase the risk of aspiration.

When faced with inhaled toxins (smoke, carbon monoxide, etc.), remove the patient from the source of the inhalant and administer oxygen as needed. Monitor for up to 24 h for the development of non-cardiogenic pulmonary edema.

Once the animal is stable, a more in-depth history can be performed in an attempt to narrow down the possible causes for the animal's signs [10]. Important information that should be obtained includes age and prior health status of the animal. What is the duration of signs, and are there any initial signs that are no longer apparent? When was the last time the animal appeared normal? Where was the animal in the last few hours prior to the development of clinical signs? Any history of administration of medications/herbal products/flea or tick control products to this animal or other animals in the household in the past 24 hours? The type of environment in which the animal lives will help to determine other questions to ask.

For indoor animals, the owner should be questioned about areas to which the animal has access (bathroom, kitchen, etc.). What types of human prescription or over-the-counter medications or herbal products are available? Any veterinary prescription or over-the-counter animal medications in the household? Have there been any recent visitors who may have dropped medication (elderly, teenagers)? Are there any houseplants in the home? Have you used any rodenticides or insecticides in the house? Do the other pets in the house appear normal?

In cases where illicit drugs may be involved, or where owners have inappropriately administered medications or other products to their pets, the veterinarian may notice some reluctance to questioning. Tactful questioning and separating family members may aid in obtaining the desired information. In other cases, it may be helpful to mention that without knowledge of the agent involved, more intensive (and expensive) diagnostics and treatments may be necessary.

For animals confined outdoors by fences or other means, identification of potentially toxic agents in outbuildings, garages or sheds to which the pet may have access is important. These spaces can contain

rodenticides, insecticides, and automotive products. Other potential outdoor hazards include compost piles, plants, ponds, mushrooms, and yard treatments (especially some systemic insecticides and crabgrass killers).

Free-roaming animals provide much more of a challenge. The number of potentially toxic agents available is almost endless. Determining whether the animal is in an urban, suburban, or rural environment and identifying the animal's immediate surroundings (e.g. wooded areas versus parks and lawns) may help in narrowing down

the potential agents. If livestock are present in the pet's environment, ask about the pet's access to the barns or feed bins. Medicated feeds, fly baits or feeds with growth promotants in them can all cause clinical signs. Have any livestock been recently medicated or dewormed? Have any livestock been recently euthanized and buried on the property?

Armed with as much history as possible and a thorough physical examination, the clinician should then formulate a list of differential diagnoses (Table 16.1). Many

Table 16.1 Potential toxicological rule-outs.

Clinical sign	Potential etiologies	Clinical sign	Potential etiologies
Contact dermatitis	Acids	Cardiovascular dysfunction	Lead
	Alkalis		Methotrexate
	Cationic detergents		Phenylbutazone
	Essential oils		Sulfonamides
	Mineral spirits		Vincristine
	Phenols		Beta-blockers
	Pine oils		Calcium channel blockers
Hemolytic anemia	Turpentine		Cardiac glycosides (digoxin, foxglove, oleander, <i>Bufo</i> toads, etc.)
	<i>Allium</i> spp		Grayanotoxin plants (rhododendron, azalea, etc.)
	Brown recluse spider		Methylxanthines
	Methylene blue		Tricyclic antidepressants
	Naphthalene		Yew (<i>Taxus</i>)
	Phenols	Asphyxiation	Carbon dioxide
	Propylene glycol		Carbon monoxide
Methemoglobinemia	Zinc		Cyanide
	3-Chloro-p-toluidine hydrochloride (Starlicide)		Hydrogen sulfide
	Acetaminophen	CNS depression	Methane
	Benzocaine/lidocaine		Alcohols
	Chlorate		Amitraz
	Onions/garlic (rare)		Barbiturates
	Phenazopyridine	Tremors	Benzodiazepines
Coagulopathy	Phenols		Ethylene glycol
	Anticoagulant rodenticides		Ivermectin
	Aspirin		Marijuana
	Brown recluse spider		Opioids
	Pit vipers		Phenothiazines
Bone marrow suppression	Sulfonamides		Bifenthrin (dogs)
	5-FU		Electrolyte abnormalities (e.g. hypernatremia)
	Chloramphenicol (cats)		
	Estrogen		

Clinical sign	Potential etiologies	Clinical sign	Potential etiologies
Seizures	Metaldehyde	Hepatic injury	Colchicine
	Nicotine		Insoluble calcium oxalate plants (<i>Dieffenbachia</i> , <i>Philodendron</i> , etc.)
	Paintballs		Iron
	Permethrin/phenothrin (cats)		Mushrooms
	Strychnine		NSAIDs
	Tetanus toxin		Acetaminophen
	Tremorgenic mycotoxins		Aflatoxin
	4-Aminopyridine (avicide)		Blue-green algae
	5-FU		Castor bean (<i>Ricinus</i>)
	Bromethalin		Iron
	DEET		Ketoconazole (cats)
	Ethylene glycol		Mushrooms (<i>Amanita</i>)
	Hypoglycemic agents (xylitol, diabetic meds)		NSAIDs (idiosyncratic)
	Methylxanthines		Phenols
	Lead		Sago palm (<i>Cycas</i>)
Gastrointestinal	Organophosphates/carbamates	Kidney injury	Xylitol
	Paintballs		Ethylene glycol
	Stimulant meds (amphetamines, antidepressants, cocaine, etc.)		Grapes/raisins
	Strychnine		Lilies (cats)
	Zinc phosphide		NSAIDs
	Arsenic		Oxalic acid (rust removers)
	Boric acid		Rhubarb, shamrock
	Chinaberry		Vitamin D and analogues

potential items can be removed from the list as they would not cause the type of signs seen in the patient. It is important to remember that the causative agent may not be a poison. Infectious diseases, metabolic disorders, and other processes may present like an acute toxicosis. For example, a variety of toxicants may cause an acute onset of seizures, but other potential etiologies to consider include encephalitis (rabies, distemper), idiopathic epilepsy, hypoglycemia, head trauma, hypoxia, hepatic failure, and acid–base abnormalities.

While the adage “think horses, not zebras” applies to toxicology, with the exponential increase in new pharmaceuticals, nutraceuticals, and household items available for an animal to encounter, sometimes help is needed. The ASPCA Animal Poison Control Center is available for toxicology consultations 24 hours a day, 365 days a year. They can be contacted at 888-426-4435.

Unfortunately, there is no one test that will detect all known toxicants. Testing for multiple agents can become

costly. Generally, one needs to have an idea of the general type of agent that may be involved before analytical testing is attempted [11]. For suspected rodenticide, insecticide, or heavy metal exposure, most veterinary diagnostic laboratories offer basic screens. Some diagnostic laboratories offer specialty panels, such as “convulsant” screens that might detect agents such as bromethalin, tremorgenic mycotoxins, strychnine, etc. For suspected human medication ingestions, human hospitals may be willing to run tests for illicit drugs, antidepressants, cardiac drugs, acetaminophen, or other common methods of suicide, such as ethylene glycol or carboxyhemoglobin levels on a STAT basis. In many situations, analytic testing is only done for confirmation as it can take days to weeks to get results back [11].

There are a few options for cage-side testing. Over-the-counter home drug urine testing kits may be considered. They are not validated for non-humans but are quick, easy, and cost-effective in cases of suspected

exposure to illicit drugs and certain human medications. Unfortunately, many of these tests will give a false negative with THC ingestions.

If the situation could become a legal case, documentation is crucial. Written and photographic records should be maintained. It is important to maintain records of

the chain of custody for samples (vomitus, carcass, etc.). Gastric contents from spontaneous or induced emesis or gastric lavage should be kept in case analytical testing is desired. Contents should be placed in a clean glass jar with a tight lid and kept refrigerated or frozen. Seal with tape and initial/date the sample.

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17

Epistaxis

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Introduction

Epistaxis, or nasal bleeding, is a common presenting complaint [1,2]. Blood loss is often quite dramatic, and it can be easy to overestimate the actual amount. From an emergency perspective, the major goals are to control the hemorrhage and to provide the client with a reasonable plan for diagnostic testing, which may be pursued after stabilization. Most cases of epistaxis can be acutely managed by controlling hemorrhage with either direct or pharmacological therapies.

The patient's signalment, clinical history, and physical examination may be very helpful in determining the underlying cause. The general goals are to determine if the epistaxis is due to local or systemic disease, and to adequately control the hemorrhage. The duration of bleeding and if it is unilateral or bilateral would be suspected to be useful intuitively though one large study did not demonstrate a difference in these parameters and the underlying disease ultimately identified [1].

Overall, systemic disease is significantly less common as a cause of epistaxis than local nasal causes in most of the world although in *Leishmania*-endemic Greece, epistaxis was more common with *Leishmania* infection and *Ehrlichia* than due to local factors [3]. However, in most cases, emergency clinicians should assume a local disease, but exclude systemic disease prior to imaging and biopsy.

The general approach to epistaxis includes first controlling the hemorrhage and secondly, determining the underlying cause of the bleeding. The overall prognosis is dependent on the underlying cause. Some cases have a quick resolution while others are much harder to cure or control. In rare cases, no specific cause can be identified.

Pertinent historical questions should include the onset of signs, potential for trauma, if the bleeding was unilateral or bilateral, and if there were any other premonitory

signs, such as nasal discharge or sneezing. Travel history may be important such as if the patient has been exposed to plant awns or infectious agents. Seizures may reflect spread of a nasal tumor, intracranial hemorrhage, or systemic diseases such as hyperviscosity.

Additionally, other signs of a bleeding tendency, such as the presence of bruising (petechial/ecchymosis) or hematuria, may present important clues that systemic disease (thrombocytopenia) is present. Evidence of GI bleeding, such as hematemesis or melena, may be misleading, as swallowed blood is common in dogs with epistaxis and does not necessarily reflect systemic disease.

Signalment is useful, as older dogs with epistaxis are much more commonly identified with neoplasia, while young dogs are more often identified with coagulopathy and trauma. Cats are far less often affected with epistaxis on an emergency basis, although they often have minor epistaxis associated with infectious, inflammatory, and neoplastic nasal disease. Coagulopathy is less common in cats, but one report highlights a cat with von Willebrand's disease with persistent epistaxis [4].

Physical examination should include careful attention to the head and neck for signs of facial asymmetry, exophthalmos or lymph node enlargement, which may be suggestive of underlying neoplasia. Facial asymmetry may also be seen with aggressive infectious (e.g. *Cryptococcus*) or other inflammatory processes.

Small amounts of serosanguineous nasal hemorrhage may be seen in disseminated intravascular coagulation (DIC), uremia or with severe cardiogenic or non-cardiogenic pulmonary edema. In these cases, epistaxis is rarely considered the major clinical sign, but occasionally an owner will present a pet with severe heart failure, not recognizing respiratory distress. Thus, as with all cases, animals presenting with a complaint of epistaxis should be appropriately evaluated at triage for stability of the major body systems (see Chapter 2).

Pathophysiology

The blood supply to the nasal cavity normally originates from the maxillary and facial arteries that branch from the external carotid artery, as well as the internal and external ethmoidal arteries as a part of the internal carotid artery. All these vessels then branch into a meshwork of capillaries. The normal homeostasis is dependent on normal platelet function to prevent spontaneous bleeding from these capillaries. Due to local exposure of these capillaries, primary hemostatic disorders such as thrombocytopathia, thrombocytopenia or von Willebrand's disease can lead to atraumatic hemorrhage from the nasal cavity, with defects of secondary hemostatic factors (such as anticoagulant rodenticide toxicity) being far less common. Severe hypothyroidism was associated with unmasking von Willebrand's disease in one Shetland sheepdog [5].

Further Laboratory Evaluation

Following a review of history, signalment, and physical examination findings, as well as the control of hemorrhage, the underlying cause of epistaxis can be investigated. If a straightforward cause, such as head trauma, is found, then further testing does not need to be performed for identification of the cause. For animals without a clear-cut cause, further evaluation is recommended.

Baseline laboratory testing includes a complete blood count, chemistry profile, and urinalysis. Cystocentesis should be avoided if there is concern for thrombocytopenia or thrombocytopathia. A prothrombin time and activated partial thromboplastin time may be performed, although epistaxis is far more common with thrombocytopenia. Platelet function may be assessed with a buccal mucosal bleeding time (BMBT) if desired. Blood pressure should be determined as systemic hypertension can also cause epistaxis through increased capillary fragility and rupture. Hyperviscosity caused by polycythemia or hyperglobulinemia can lead to decreased blood flow as well as distension of capillaries and small blood vessels, leading to rupture and epistaxis. Hyperviscosity should be evident on interpretation of laboratory testing.

If *Cryptococcus* is suspected, a antigen latex agglutination test may be performed. Other laboratory tests that may be considered based upon clinical suspicion include PCR for infectious diseases or titers for other infectious diseases. *Bartonella* was supported as a cause in some dogs [6]. If regional lymph nodes are enlarged, fine needle aspirate may be diagnostic for infectious or neoplastic disease.

Nasal Imaging

Skull radiographs are uncommonly performed for evaluation of non-traumatic nasal disease as superimposition of structures makes it difficult to fully evaluate the nasal cavity. Advanced cross-sectional imaging (CT/MRI) is preferred, but will usually require general anesthesia. Advances in CT scanning speed will often permit a scan to be performed without general anesthesia, but nasal biopsy or rhinoscopy requires general anesthesia so often it is more expedient to perform imaging and sampling under general anesthesia. Additionally, anesthesia permits a complete oral examination. Due to wider availability, CT scanning is more commonly performed but MRI is also very useful for identifying nasal tumors (Figures 17.1 and 17.2).

Nasal Biopsy

If imaging identifies a mass lesion or other destructive lesions, a biopsy is advised for a tissue diagnosis. Histopathological diagnosis will provide the best information for the owner as to prognosis and treatment options. Rhinoscopy permits direct visualization of a mass for more accurate biopsy. In smaller dogs and cats, epistaxis can result with insertion of the scope, which will make visualization challenging. Therapeutically, nasal retro-pulsion can be used to debulk nasal tumors and has been associated with improved survival [7].

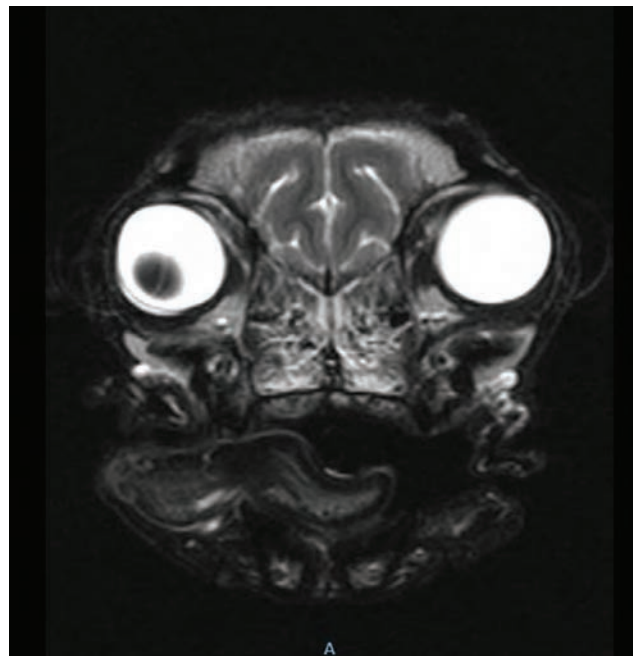


Figure 17.1 An example of an MRI showing a normal nasal anatomy.

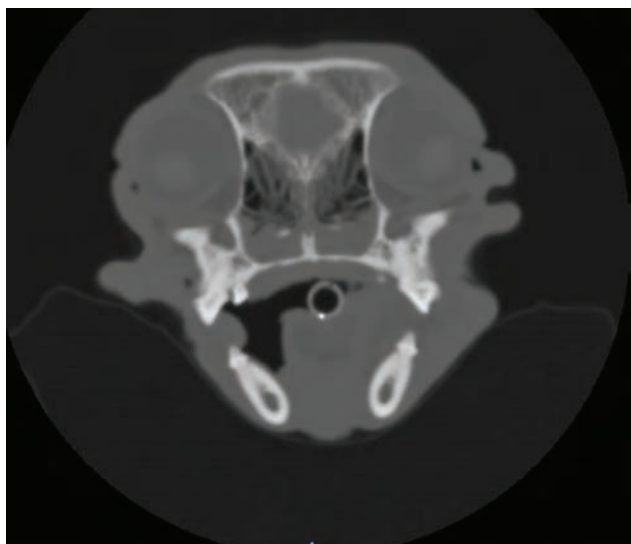


Figure 17.2 An example of a CT from the same dog showing normal nasal anatomy. Note the difference in resolution between an MRI and a CT image.

Emergency Management

Emergency management may be divided into treatment of hypovolemia and control of hemorrhage (see Chapters 153, 189, 176, 177). Severe hemorrhage may require blood transfusion for replacement of lost red cells. IV fluid resuscitation should be provided if there are signs of hypovolemia, such as tachycardia (>150 bpm) or elevated blood lactate (>2.0 mm/L). In acute hemorrhage in dogs, the hematocrit may be deceptively normal due to loss of whole blood and concurrent splenic contraction. Blood may be transfused to restore adequate blood volume. Concurrent crystalloids or colloids may be used as well at the discretion of the clinician. Colloids should be avoided if there is coagulopathy and potentially if there is concern for a potential deleterious effect on renal function. However, most hemorrhage resulting from epistaxis is more visually dramatic than life-threatening.

Control of hemorrhage can be achieved through several approaches. Mild hemorrhage will typically stop spontaneously. If hemorrhage is ongoing, local therapy with ice packs may help promote vasoconstriction. Mild sedation (e.g. acepromazine) can help promote clotting; acepromazine has the added benefit of producing a slight decrease in blood pressure. Sedation may also be useful in preventing the “crime scene” that may be associated with clean-up associated with severe hemorrhage by limiting activity.

More severe hemorrhage can be treated with phenylephrine (diluted to 1 mg/mL with saline or lidocaine)

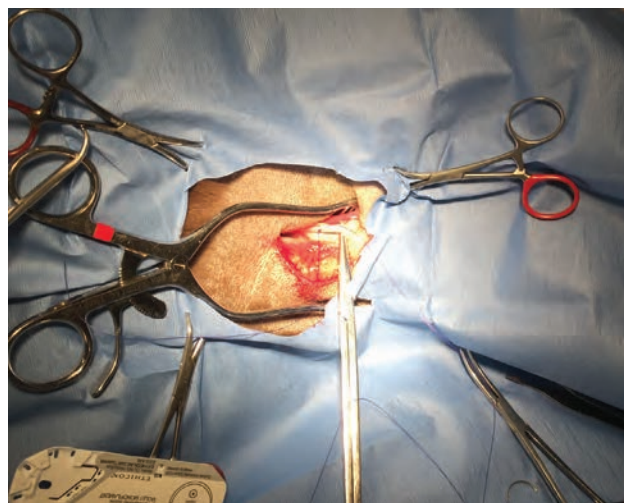


Figure 17.3 Carotid ligation is performed under general anesthesia. The area is clipped and surgically prepped on the side of the hemorrhage. The carotid artery is identified through palpation and gentle dissection. Recall that it runs in close proximity to the vagosymphatic trunk. The artery is isolated and two circumferential ligatures are tied using 3-0 monofilament non-absorbable suture. The artery is **not** divided.

infused into the nasal cavity or soaked in nasal packing material (cotton rolls, tampons, or roll gauze in larger dogs). Nasal packing should be placed with caution as, rarely, penetration into the cranial vault can occur, especially in animals with facial fractures. Anecdotal, Yunnan Baiyao given orally or applied intranasally has been reported to decrease hemorrhage. Similarly, aminocaproic acid has been advocated to treat epistaxis [8]. Diode laser has been reported to control hemorrhage in a animal. In massive uncontrollable local hemorrhage, a Foley catheter may be placed into the nasal cavity and carefully inflated.

Finally, carotid artery ligation may be necessary with persistent and severe cases of epistaxis that is not responding to the above therapy (Figure 17.3). Unilateral ligation is well tolerated in both dogs and cats. Bilateral ligation is not well tolerated in cats, and some dogs.

Conclusion

Epistaxis is a common presenting complaint in the emergency room. Urgent therapy consists of controlling hemorrhage and supporting intravascular volume if needed. Cases without a straightforward etiology, such as trauma, should have further evaluation to assess for local or systemic disease, with local disease being the most common. Unilateral carotid ligation may be useful in severe hemorrhage.

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18

Fever

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Physiology of Normal Thermoregulation

Core body temperature in normal dogs and cats is tightly controlled within a few tenths of a degree (Table 18.1). Thermal sensors located peripherally and centrally feed into the thermoregulatory region of the central nervous system, located primarily in the preoptic area of the anterior hypothalamus, in a region known as the organum vasculosum of the laminae terminalis [1]. This region acts as a thermostat, integrating the afferent input and triggering both unconscious and conscious reactions to increase heat loss or gain to maintain a normal core temperature [2].

What is Fever?

A fever is a controlled rise in body temperature that is generated when the hypothalamic thermostat is reset to a higher core temperature. The main trigger for thermostat adjustment is the presence of either exogenous pyrogens or pyrogenic cytokines. These are substances introduced during infectious and inflammatory conditions that

activate cyclo-oxygenase-2 to induce the generation of prostaglandin E_2 in the hypothalamus. Prostaglandin E_2 resets the hypothalamic thermostat to a higher core temperature. Efferent neurons then trigger changes in vascular tone, muscle activity, and conscious behaviors to increase the animal's generation and retention of heat to increase the core body temperature to the new set point. Excessive elevations in core temperature are prevented with simultaneously activated negative feedback systems which decrease concentrations of pyrogenic cytokines and increase antipyretic cytokines [1,2].

Is Fever Helpful or Harmful?

Generation of fever is an adaptive response, conserved across the entire animal kingdom, which improves animals' abilities to defend against infectious organisms. Elevations in core body temperature have been shown to have a variety of protective effects, including increased leukocyte migration, enhanced lymphocyte and macrophage function, reduced microbial growth, and production of molecular chaperones known as heat shock proteins [3–5]. Because fever arises in a physiologically regulated manner with both positive and negative feedback systems employed, there is little to no danger of a fever getting dangerously high to the point where it will lead to cellular dysfunction and death [6]. For these reasons, fever can generally be seen as helpful in most circumstances.

However, in some specific situations, there is evidence that the presence of fever can be detrimental. Fever increases the overall metabolic rate which increases oxygen consumption and cardiac output. These effects have been shown to contribute to increased mortality in febrile patients with brain injury and with severe non-septic systemic inflammation compared to normothermic patients with these conditions [1,7].

Table 18.1 Normal temperatures for dogs and cats. Reproduced with permission of the Canadian Veterinary Medical Association.

	Celsius	Fahrenheit
Dogs*	38.3–39.1	100.9–102.4
Cats†	36.7–38.9	98.1–102.1

*Sousa MG, et al. Comparison between auricular and standard rectal thermometers for the measurement of body temperatures in dogs. *Can Vet J* 2011;52:403–406.

†Levy JK, et al. Reference interval for rectal temperature in healthy confined adult cats. *J Feline Med Surg* 2015;17:950–952.

How to Differentiate Fever from Hyperthermia

When a patient has an elevated body temperature, the clinician will need to determine if the patient has excessive thermogenesis or inadequate heat loss leading to hyperthermia, or if the patient is physiologically appropriately generating and retaining heat to maintain a fever. This determination is usually derived from the overall picture of patient history and clinical signs. It is important to distinguish between hyperthermia and fever, as diagnostic and treatment plans differ significantly between the two.

History

Patients with hyperthermia often have histories supportive of excessive thermogenesis and/or inability to lose heat to the environment. Excessive thermogenesis results from marked involuntary muscle activity, like that occurring with seizure activity and generalized muscle tremors. It can also result from overexertion during exercise. Inability to lose heat to the environment occurs when an animal is enclosed in a very hot environment, or when an animal has an impaired ability to lose heat by normal mechanisms, such as brachycephalic dogs that are unable to pant effectively due to upper airway obstruction.

Patients with fever typically lack events like those listed above in their histories. Instead, they often are presented to the clinic for lethargy, obtundation, and anorexia. Their owners may also note that they have been demonstrating heat-seeking behavior or shivering at home.

Clinical Signs

Conscious patients with hyperthermia will demonstrate behaviors consistent with those used to lose heat to the environment. Dogs pant, sprawl out, and seek cool surfaces to lie on. Cats sprawl out on cool surfaces, groom themselves, and occasionally pant. Physical examination signs can also implicate hyperthermia over fever, including panting with audible stertor or stridor or exhibiting generalized muscle tremors or seizures.

Conversely, conscious patients with fever may demonstrate behaviors consistent with those used to retain or generate heat. Both dogs and cats will choose to curl up and seek warm surfaces to lie on. On physical examination, they may be shivering and there may be an absence of heat loss behaviors, including panting.

Primary Differentials for Cause of Fever

Fever can be caused by viral, bacterial, fungal, and protozoal infections as well as a variety of non-infectious inflammatory diseases including sterile tissue inflammation, tissue necrosis, immune-mediated diseases, and neoplasia. Additionally, transfusion of blood products and administration of some drugs have been reported to cause fever in animals. Some of the more common causes of fever in dogs and cats are included in Table 18.2. A full physical examination in conjunction with the patient's history and signalment will often provide important clues to help prioritize the list of differentials and guide diagnostic testing.

Table 18.2 Common differential diagnoses for fever in dogs and cats.

	Dogs	Cats
Infectious diseases		
Upper respiratory	Unusual to see fever	Calicivirus Herpesvirus
Pulmonary/thoracic	Aspiration pneumonia Pyothorax Fungal pneumonia (endemic areas) Canine influenza	Pyothorax Fungal pneumonia (endemic areas)
Cardiovascular/hematological	Valvular endocarditis Blood-borne pathogens (e.g. <i>Rickettsia</i> , <i>Anaplasma</i> , <i>Ehrlichia</i> , <i>Babesia</i>)	<i>Mycoplasma hemofelis</i> Feline leukemia Feline immunodeficiency virus Feline infectious peritonitis (causing vasculitis)
Genitourinary	Pyelonephritis Prostatitis Pyometra Lower urinary tract infection	Pyelonephritis Lower urinary tract infection

	Dogs	Cats
Hepatobiliary/gastrointestinal/abdominal	Parvoviral enteritis	Septic peritonitis
	Cholangiohepatitis/cholangitis	Panleukopenia
	Septic peritonitis	
Central nervous system	Infectious meningitis	Infectious meningitis
	Brain abscess	Brain abscess
Musculoskeletal/integumental	Discospondylitis	Septic arthritis
	Septic arthritis	Cellulitis
	Osteomyelitis	Subcutaneous abscess
	Cellulitis	Severe pyoderma/furunculosis/
	Subcutaneous abscess	panniculitis
	Severe pyoderma/furunculosis/	
	panniculitis	
Non-infectious inflammatory diseases		
Pulmonary/thoracic	Pulmonary embolism	Pulmonary embolism
Cardiovascular/hematological	Immune-mediated hemolytic anemia	Immune-mediated hemolytic anemia
	Immune-mediated thrombocytopenia	
Hepatobiliary/gastrointestinal/abdominal	Pancreatitis	Pancreatitis
		Cholangiohepatitis/cholangitis
Central nervous system	Meningitis/meningoencephalitis/ meningoencephalomyelitis	Intracranial haemorrhage
	Intracranial haemorrhage	
Musculoskeletal/integumental	Immune-mediated polyarthritis	Pansteatitis
	Nodular panniculitis	Pemphigus foliaceus
	Juvenile cellulitis	
Other	Transfusion or drug reaction (e.g. albuterol, penicillins, sulfonamides, tetracyclines)	Transfusion or drug reaction (e.g. penicillins, tetracyclines, sulfonamides)
	Trauma/tissue necrosis	Trauma/tissue necrosis
	Neoplasia – solid tumors and infiltrative round cell tumors	Neoplasia – solid tumors and infiltrative round cell tumors

Early Diagnostics to Consider for Febrile Patients

Initial diagnostics are generally focused on ruling out infectious causes for fever. Early tests include complete blood count, biochemistry, cultures of blood and urine, thoracic radiographs, and brief ultrasonographic assessment of body cavities for the presence of effusion (see Chapter 182). Later tests may include advanced diagnostic imaging, evaluation for specific infectious diseases, tissue biopsies, cerebral spinal fluid analysis, and joint fluid analysis.

Diagnostic tests should be chosen based on the patient's signalment, history, physical examination findings, and results of previous tests performed. It is important to note that sepsis is a life-threatening condition, and delay in appropriate antimicrobial therapy has been shown to increase risk of death in septic people (see Chapter 159) [8]. It is therefore warranted to empirically treat for suspected infectious diseases while commencing diagnostic tests to rule out systemic infectious causes for fever.

Upon admission to the emergency department, febrile patients should have initial blood analyses, diagnostic

imaging, and cultures performed. A complete blood count can be used to determine if there are significant aberrations in white blood cell, red blood cell, or platelet counts. A markedly low neutrophil count should prompt commencement of broad-spectrum antimicrobial therapy, regardless of underlying cause for neutropenia. A blood smear can be evaluated for the presence of infectious organisms or cellular changes that can occur with different diseases mentioned in Table 18.2. A biochemistry profile can help determine if there is evidence of organ dysfunction from sepsis or other inflammatory disease.

Chest radiographs are part of the recommended initial diagnostic work-up in people with fever [9]. Likewise, they should be performed early on in the diagnostic work-up in veterinary patients, particularly if physical examination findings, historical information, or patient signalment increase the suspicion for pneumonia as a cause of fever. Point-of-care ultrasound should be performed to evaluate the abdominal and thoracic cavities for the presence of effusion or overt abnormalities that may be causing the fever (see Chapter 182) [10]. Cultures of blood, urine, and other relevant fluids or tissues should ideally be performed prior to the administration of antimicrobial therapy to optimize the chance of microbial growth. However, sample collection should not be allowed to delay the administration of antimicrobials in patients that are exhibiting signs of sepsis [8].

Other initial diagnostics to consider depend on the history, signalment, and physical examination findings. For example, it is warranted to test cats for feline leukemia and feline immunodeficiency virus if they are in contact with untested cats or have never been tested before. Puppies and unvaccinated adult dogs with gastrointestinal signs should be tested for parvovirus to ensure early appropriate handling of patients with this highly contagious infection. Patients with joint effusion should have arthrocentesis performed early to ensure that appropriate care commences as soon as possible. Animals in infectious disease endemic areas exhibiting clinical signs specific to those diseases should be tested for them at admission and should commence empirical treatment where applicable.

Treatments to Consider

It is important to remember that fever is a physiologically appropriate adaptive response, and negative feedback prevents the temperature from increasing to levels high enough to cause cellular dysfunction and death [6]. Actions should not be geared toward dropping the patient's temperature, but rather toward determining

the underlying cause for this clinical sign. Septic patients may require blood volume and blood pressure stabilization, which are discussed elsewhere (see Chapter 159). Although there are no treatments specifically recommended to be used in all febrile patients, antimicrobial drugs, antipyretics, and external cooling will be discussed below.

Broad-spectrum antimicrobial therapy should be started urgently in febrile patients demonstrating clinical signs of sepsis as well as in any febrile patient where infection is highly suspected. Ideally, these drugs are started immediately after cultures are collected and no more than 1 h after hospital admission [8]. The spectrum of antimicrobials chosen should cover all potential suspected infectious organisms. For example, if the febrile patient has evidence of acute kidney injury and is living in an area with leptospirosis, the antimicrobial spectrum should include *Leptospira* species as well as other microbes that commonly cause pyelonephritis. If the febrile patient has clinical signs and thoracic radiographs that may be consistent with fungal pneumonia, and lives in an endemic area, appropriate antifungal drugs should be added to the antimicrobial spectrum.

Antipyretics are drugs that stop the synthesis of prostaglandins and re-establish normothermia at the hypothalamic thermostat. Examples of these drugs include non-steroidal anti-inflammatory drugs and acetaminophen. Studies investigating the use of these medications in most febrile people have not shown any clear benefit in terms of mortality, morbidity, or length of hospitalization [7,11–13]. These medications can have significant side-effects including gastric ulceration, acute kidney injury, hepatic damage, and oxidative injury to red blood cells. Given the lack of overt benefit and the risk of increased morbidity from side-effects, there is no indication to administer these medications to most febrile patients. The exception to this is febrile patients with neurological disease, as fever is independently associated with increased mortality in these patients [14]. Thus, lowering body temperature using antipyretics can be considered in these patients.

While external cooling via convection and evaporation are effective ways to cool hyperthermic patients, these methods are not recommended to cool patients with a fever. Implementing external cooling without concurrent administration of antipyretics has been shown to increase the metabolic rate due to the ongoing physiological responses to maintain the fever. Additionally, external cooling of febrile patients leads to significant patient discomfort [12]. For these reasons, external cooling should not be implemented in patients with fevers.

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Section 3

Emergency Conditions by System

A. Neurological Disorders

19

Traumatic Brain Injury

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Introduction

Traumatic brain injury (TBI) is a cause of significant morbidity and mortality in veterinary patients, occurring in approximately 25% of cases sustaining blunt trauma [1]. The causes of TBI in dogs and cats include motor vehicle trauma, bite wounds, falls, crush injuries, missile injuries, and human-inflicted trauma [2–4]. This chapter will focus on the pathophysiology of TBI, initial triage and stabilization, treatment, and prognosis.

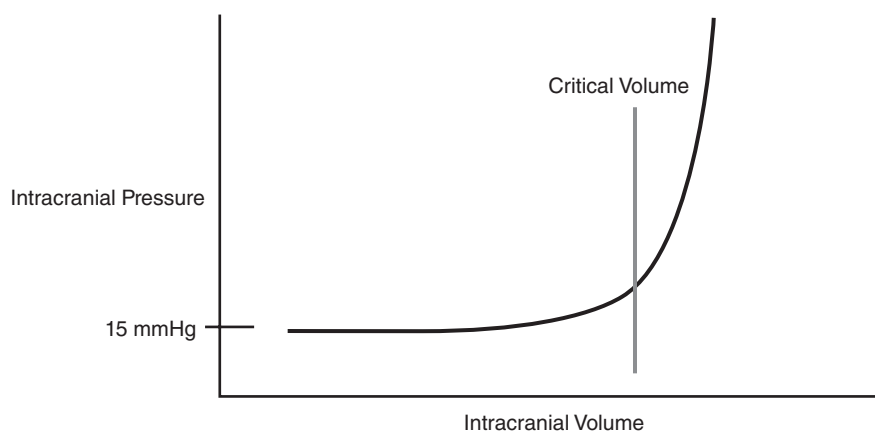
Pathophysiology

Traumatic injury to the brain can be divided into primary and secondary injury. Primary injury occurs immediately after trauma and is the direct result of impact [5]. It is classified based on extent, location, and type of injury [6]. Primary injuries include epidural and subdural hematomas, subarachnoid hemorrhage, cortical contusions/hematomas, and traumatic axonal injury [7,8].

Secondary injury is referred to as delayed injury. Delayed injury begins within minutes of injury and can last for weeks [2,4]. Neuronal cell death is exacerbated by glutamate accumulation, influx of sodium and calcium intracellularly, free radical production, inflammatory mediator release, and loss of autoregulation [2,4,9,10]. Hypoxemia, hypotension, hypercapnia, hypocapnia, hyperglycemia, hypoglycemia, acid–base and electrolyte disturbance, hyperthermia, and systemic inflammation potentiate injury. Intracranial hypertension, edema, compromise of the blood–brain barrier (BBB), vasospasm, hemorrhage, infection, mass effect, and seizure activity further exacerbate injury [7].

The Monroe–Kellie doctrine states that the cranial vault is a rigid, defined space that has a fixed volume composed of the brain, cerebrospinal fluid, blood, and mass lesion (if present). An increase in the volume of any of these will result in a compensatory decrease in one or more of the others (defined as intracranial compliance), without which an increase in intracranial pressure (ICP) will occur (see Figure 19.1 for a graphical representation of the intracranial compliance curve). Intracranial

Figure 19.1 Intracranial compliance curve.



compliance is primarily dependent on reductions in CSF and blood volume. Increases in ICP combined with decreases in mean arterial pressure (MAP), a finding that is common in trauma patients, can result in decreases in cerebral perfusion pressure (CPP) (with $CPP = MAP - ICP$) [2–4].

Severe, acute intracranial hypertension may result in the Cushing reflex or CNS ischemic response. Decreased cerebral blood flow as a result of increased ICP results in elevations in carbon dioxide sensed locally at the vaso-motor center, causing an increase in sympathetic tone, leading to systemic vasoconstriction and increased cardiac output [11]. This increase in pressure stimulates baroreceptors in the aortic and carotid sinuses, resulting in a reflex sinus bradycardia. This response signifies life-threatening intracranial hypertension [2,4,7].

Physical Examination

Systemic Assessment

Initial triage assessment of the patient with TBI should focus on global patient stability with emphasis on the respiratory and cardiovascular systems (see Chapter 2). Minimum database should include standard vital signs, blood pressure, pulse oximetry, PCV/TS, blood glucose, blood gas, and electrolytes.

Neurological Assessment

An initial efficient neurological examination should occur before administration of analgesics to allow adequate assessment of the neurological status of the patient. It is also important that the patient has been adequately resuscitated, as shock can affect neurological status [4].

The Modified Glasgow Coma Scale (MGCS) is useful in the assessment of TBI patients, as it provides a more objective determination of improvement or progression of signs [12]. The MGCS has been demonstrated to sigmoidally correlate with the probability of survival (with a score of 8 associated with a 50% likelihood of survival) in the first 48 hours after TBI in dogs (Figure 19.2). A recent study evaluating trauma in dogs prospectively found that a score of ≤ 17 was predictive of non-survival with 82% sensitivity and 87% specificity [13]. Repeated neurological assessment is recommended every 30–60 minutes after initial presentation and after interventions are made [14].

Diagnostic Imaging

Intracranial imaging for the TBI small animal patient has been previously indicated in patients who fail to

Level of Consciousness

- (6) Occasional periods of alertness and responsive to environment
- (5) Depression or delirium, capable of responding but response may be inappropriate
- (4) Semi-comatose, responsive to visual stimuli
- (3) Semi-comatose, responsive to auditory stimuli
- (2) Semi-comatose, responsive only to repeated noxious stimuli
- (1) Comatose, unresponsive to repeated noxious stimuli

Brainstem Reflexes

- (6) Normal pupillary light reflexes and oculoccephalic reflexes
- (5) Slow pupillary light reflexes and normal to reduced oculoccephalic reflexes
- (4) Bilateral unresponsive miosis with normal to reduced oculoccephalic reflexes
- (3) Pinpoint pupils with reduced to absent oculoccephalic reflexes
- (2) Unilateral, unresponsive mydriasis with reduced to absent oculoccephalic reflexes
- (1) Bilateral, unresponsive mydriasis with reduced to absent oculoccephalic reflexes

Motor Activity

- (6) Normal gait, normal spinal reflexes
- (5) Hemiparesis, tetraparesis, or decerebrate activity
- (4) Recumbent, intermittent extensor rigidity
- (3) Recumbent, constant extensor rigidity
- (2) Recumbent, constant extensor rigidity with opisthotonus
- (1) Recumbent, hypotonia of muscles, depressed or absent spinal reflexes

Figure 19.2 Modified Glasgow Coma Scale [12].

respond to intensive medical management, patients who deteriorate after initial response, and those with focal or asymmetric deficits (as this is suggestive of extra-axial hemorrhage that may be amenable to surgical correction). Computed tomography (CT) has been the modality of choice for characterization of TBI in the acute setting, as it is quick, relatively inexpensive, and has excellent ability to identify the majority of lesions [5,6,8]. Beyond the acute setting, magnetic resonance imaging (MRI) has been recommended when patients continue to be non-responsive to treatment or deteriorate despite having normal CT scans [8]. However, this has been changing in recent years. A recent study evaluated the use of MRI in canine patients with TBI and revealed that abnormal findings were detected in 66% of patients that were assessed with MGCS scores correlating with relatively mild TBI. A grading system for MRI abnormalities was generated and grades were negatively correlated with MGCS score. Posttraumatic seizures were documented in patients that had larger intraparenchymal lesions, potentially indicating the significance of these lesions [15]. Another recent study evaluated MRI performed within 48 hours of trauma and found that patients that had injuries affecting both the rostral and caudal fossae typically had poorer outcomes [16].

Therefore, while MRI is clearly useful and likely identifies abnormalities and offers prognostic information beyond the capacity of CT, the length of time of anesthesia, its cost and the clinical utility for the particular patient should be considered [15].

Treatment

Initial Stabilization

Oxygen Therapy

Oxygen should be supplemented to maintain normoxemia, but should be titrated to avoid hyperoxemia, which worsens reperfusion injury (see Chapter 181) [4]. If adequate oxygenation cannot be maintained with high fractional oxygen concentrations (FiO_2) greater than 60%, if hypoventilation exists or if a patient is experiencing respiratory fatigue, mechanical ventilation is indicated [17].

Ventilation

Hypoventilation and hyperventilation should be avoided in TBI patients, and close monitoring of end-tidal CO_2 (ETCO_2) and blood gases is warranted. Normal partial pressure of carbon dioxide (PCO_2) (venous 40–45 mmHg, arterial 35–40 mmHg) should be targeted in all cases [18]. Those patients at risk of cerebral herniation or that have significant neurological decompensation can be hyperventilated for short periods. The targets of hyperventilation should be conservative ($\text{ETCO}_2 = 30\text{--}35$ mmHg) to prevent excessive cerebral vasoconstriction and ischemia. Studies evaluating prophylactic hyperventilation during initial resuscitation have consistently shown poor outcomes [19–21].

Intravenous Fluid Therapy

Controversy exists in veterinary medicine regarding the best fluid for resuscitation in the TBI patient. It is recommended that isotonic fluids containing the least amount of free water (e.g. 0.9% NaCl) be administered, barring significant sodium derangements. Because fluid shifts between the interstitial and intracellular compartments of the brain are predominantly driven by osmolality, colloidal solutions have not demonstrated any benefit in TBI [22]. However, owing to rapid redistribution of crystalloids after administration, a combination of colloidal therapy with crystalloid therapy can be considered to provide longer-lasting volume resuscitation [4].

Hypertonic saline (HTS) has several potential benefits, including rapidly increasing intravascular volume, increasing cardiac output, improving regional cerebral blood flow, increasing vessel diameter, decreasing ICP, and enhancing cerebral oxygen delivery [23–28]. HTS should be used only in euhydrated patients without

significant sodium derangements. In addition, it is imperative that HTS be followed by crystalloid therapy to maintain adequate hydration.

Anemic patients should be treated with packed red blood cells or whole blood transfusions to maintain adequate oxygen delivery to damaged nervous tissue. Fresh frozen plasma should be administered to the coagulopathic patient (see Chapter 176). Those patients that do not respond to fluid resuscitation warrant vasopressor support [4].

Pain Management

Analgesic therapy is essential in the management of the TBI patient. The degree of analgesia and sedation must be balanced with preservation of blood pressure and ventilation and the need for serial neurological reassessments. Adequate analgesia in the TBI patient avoids transient increases in ICP caused by pain and agitation [29].

Opioids are the analgesic drugs of choice in critical patients, because of their ease of reversal and relative safety. Several studies suggest that bolus infusion of opioids should be avoided, and constant rate infusions (CRIs) are preferred [29–33]. Because of the ease of reversal, it is recommended that full agonist opioids be used [34,35].

Treatment Strategies Specific for TBI

Hyperosmolar Therapy

Intracranial hypertension has consistently been associated with poor outcomes in patients with TBI [36]. The brain is composed of approximately 80% water, making its volume very responsive to changes in water content. An osmotic agent is only effective if the BBB is impermeable to it. Sodium and mannitol have near-perfect exclusion by the BBB, making HTS and mannitol extremely effective for addressing intracranial hypertension [37].

Mannitol, a sugar alcohol, is recommended as a first-line treatment for intracranial hypertension in human medicine [18]. Mannitol is not recommended for prophylactic use in patients with TBI unless there is concern for elevations in ICP, because its effectiveness is related to the degree of intracranial hypertension and its effect decreases as the cumulative dose increases [38,39]. Mannitol should always be followed by fluids to avoid hypovolemia, and serum osmolality should ideally be measured when repeated doses are administered due to concern over kidney injury [4].

Hypertonic saline affords similar osmotic benefits as mannitol, but is a less potent diuretic with mechanisms discussed previously. Relative contraindications to HTS include significant sodium derangements and dehydration [40–42].

There is no evidence that mannitol is superior to HTS or vice versa [43–46]. A recent retrospective study evaluating prognostic indicators in dogs with head trauma revealed that HTS was used more frequently in non-survivors. As the discussion states, this is less likely related to a treatment benefit of mannitol over HTS, but rather to the use of HTS in patients that are more severely affected [47]. It is likely that HTS is preferable in hypovolemic patients but in euvoletic patients, either is reasonable. When patients do not respond to treatment with one agent, the alternative should be considered.

Administration of furosemide to treat intracranial hypertension has not been shown to have any benefit and increases the risk of hypovolemia [48]. Therefore, its use is not recommended.

Decreasing Cerebral Blood Volume

Elevation of the head by 15–30° reduces cerebral blood volume, thereby decreasing ICP and increasing CPP without affecting cerebral oxygenation [49]. A stiff slant board should be used for head elevation to avoid bending of the neck and occlusion of the jugular veins [4].

Corticosteroids

Evidence from the CRASH trials showed that high-dose methylprednisolone was associated with an increase in mortality at 2 weeks and 6 months after injury [50,51]. Corticosteroids are therefore not recommended in the treatment of TBI patients.

Anticonvulsant Therapy (see Chapter 21)

Posttraumatic seizures are classified as immediate (within 24 hours of injury), early (24 hours to 7 days after injury), or late (greater than 7 days after injury) [19]. Seizures increase secondary brain injury by increasing cerebral metabolic demand, ICP, and excitatory neurotransmitters. Prophylactic antiepileptic drugs are recommended for 7 days post-TBI in humans; no such recommendations exist in veterinary medicine [52].

Posttraumatic epilepsy has a documented incidence of 6.8–10% with risk increasing with severity in dogs [53–55]. If seizures do develop, antiepileptic drug (AED) therapy is indicated to reduce secondary brain injury. If risk factors for seizures are present (e.g. penetrating head wounds, depressed skull fractures), it is reasonable to consider prophylactic AED therapy for the first 7 days after injury. The duration of therapy is debatable. Should seizures occur, benzodiazepines should be used. A variety of AEDs for continued seizure control are available. At the authors' institutions, levetiracetam is frequently used for its rapid onset, minimal side-effects, and low toxicity.

Barbiturate Therapy

Barbiturates are considered secondary therapy for the treatment of refractory intracranial hypertension in

people, as high-dose therapy can control ICP when other therapies have failed. This does not translate to improved outcome [19]. Barbiturates cause cerebral vasoconstriction, decrease cerebral metabolism, reduce ICP, decrease excitotoxicity, and decrease free radical-mediated injury [56]. They also have anticonvulsant properties. Barbiturate coma has been described in association with therapeutic hypothermia in a dog with TBI and refractory seizure activity [57]. Patients in which barbiturate therapy is instituted must be monitored closely for hypoventilation, and may require mechanical ventilation.

Therapeutic Hypothermia

Many of the processes of secondary injury in TBI are temperature dependent [58]. Therapeutic hypothermia (TH), targeting temperatures of 32–34 °C (89.6–93.2 °F), decreases basal and cerebral metabolism, prevents apoptosis and necrosis and decreases cerebral edema formation and disruption of the BBB by decreasing release of excitotoxic amino acids and production of proinflammatory cytokines. Seizure activity is also reduced [59].

Therapeutic hypothermia is indicated as a second-line treatment in humans for intracranial hypertension and status epilepticus [58–60]. It is challenging to implement and has many potential complications [58–60]. Its successful use in a dog with protracted seizure activity associated with TBI has been described [57]. Current recommendations in human medicine for implementing controlled hypothermia include maintenance of hypothermia for at least 48 h with slow rewarming rates. The recent report involved targeting temperatures of 33–35 °C (91.4–95 °F) with implementation through the use of evaporative and surface cooling. It is very important to avoid shivering through the use of benzodiazepines and general anesthetic medications, as shivering can increase body temperature and increase metabolic demands. Mechanical ventilation is mandatory when implementing therapeutic hypothermia [57].

Decompressive Craniectomy

Early craniotomy is indicated for evacuation of extra-axial hematomas. The role of decompressive craniectomy is more controversial. The DECRA trial was a modest trial in human medicine comparing decompressive craniectomy with standard care in the treatment of intracranial hypertension. It revealed that surgical decompression reduced intracranial pressure and length of ICU stay, but was associated with more unfavorable outcomes, although analysis of the results revealed that patients managed surgically had more significant primary injury and there was a high cross-over rate in case management [61].

Therefore, although decompressive craniectomy should not be employed as primary management for the vast majority of cases, it does have utility for those cases that remain refractory to medical management.

Supportive Care

Supportive care of the patient with TBI should include the provision of dry, clean bedding, frequent turning, range of motion, bladder care, ocular care, and nutrition. Hypermetabolic states have been documented and early feeding is recommended [62]. The method of feeding should be based on the patient's ability to protect the airway. Although hyperglycemia has been associated with worsened mortality rates and neurological outcome scores in humans [63], and degree of hyperglycemia has been associated with severity of TBI in animals [64–67], intensive insulin therapy is not recommended for the control of hyperglycemia.

Prognosis

Prognosis for recovery from traumatic brain injury depends on the severity of injury, its cause, site of the lesion, and timing and efficacy of treatment [14]. Small animals with neurological trauma have the capacity for significant improvement and a tremendous ability to compensate for neurological deficits. The MGCS and advanced imaging have prognostic ability. A recent retrospective study evaluated prognostic factors in canine head trauma and revealed that hypoperfusion and hypoxemia were associated with non-survival. Patients with lower MGCS scores and higher animal trauma triage scores (more severe concurrent injuries) were also noted to have a poorer prognosis for survival. Finally, those patients that required endotracheal intubation and the administration of HTS were less likely to survive [47].

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20

Altered Mentation

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Introduction

Many patients may present for alterations in mental status or behavior in the emergency setting. Hospitalized emergency patients can also be dynamic in nature, and close monitoring of neurological status is imperative as this may change rapidly. It is important to differentiate primary neurological causes from metabolic or toxic contributions as this will significantly change treatment options and prognosis.

Initial Assessment (see Chapter 2)

An initial triage assessment of every patient's airway, breathing, and circulatory system must be performed. Once airway and oxygenation status have been addressed, assessment of perfusion and cardiovascular status may help to determine the presence of hypoperfusion or arrhythmias. Initial neurological assessment occurs during triage, assessing overt mentation and interaction with the environment. Patients that are in severe states of shock secondary to a variety of causes must be resuscitated prior to drawing conclusions of primary neurological disease as metabolic alterations and perfusion status can cause severe changes in mentation.

Neuroanatomy

The cerebral cortex is responsible for control of the level of consciousness, and does so via interpretation of sensory information from the reticular activating system or RAS. The RAS is a group of nuclei located in the brainstem that extends into the diencephalon. The adrenergic or sleep system within the thalamus and RAS are maintained in a tight balance, which when disturbed

may result in either hyperexcitability or coma. Sensory information from the spinal cord and afferent cranial nerves is sent to the RAS, the thalamus, and ultimately the cerebral cortex. The cerebrum is then "activated," as it integrates and responds to this information. Thus, any disease process affecting the medulla, midbrain, or cerebral cortex may result in alterations in mental status. However, the nuclei in the rostral pons, midbrain, and thalamus appear to be the most important in determining level of consciousness [1,2].

Neurological Examination

Neurological localization involves assessment of mental status, neuro-ophthalmological signs, respiratory pattern, and postural signs. The institution of the Modified Glasgow Coma Scale (MGCS) has been recommended for initial assessment and prognostic information, as well as to serially monitor changes in the patient's neurological status. In patients suffering traumatic brain injury, a low MGCS was shown to be the strongest predictor of non-survival (Table 20.1) [3,4].

Mental Status and Neurological States of Consciousness

Classification of the various states of consciousness will aid in determination of disease localization, progression, response to treatment, and prognosis. A normal animal is interactive and aware of its environment. The majority of severely ill animals will be classified as *dull*, but will still respond normally to stimuli. *Confusion* or *disorientation* refers to patients that may be overall aware, but respond inappropriately to their environment which may be displayed as vocalization or head pressing (Figure 20.1). Although this may be seen

Table 20.1 Modified Glasgow Coma Scale [4].

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 opisthotonos	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

**Figure 20.1** Head pressing in an older poodle secondary to a brain tumor.

with systemic disease, it may also occur with forebrain disease. Patients described as *drowsy* or *obtunded* are those with decreased wakefulness without continuous stimuli. Patients within this category may have systemic or neurological illness but drowsy and confused patients will often have forebrain disease. Patients classified as *stuporous* will not respond to most stimuli, but will still react to noxious stimuli. *Comatose* describes severely affected patients that are unconscious and unresponsive to noxious stimuli. Often, these patients have severe neurological disease affecting the brainstem or bilateral cerebral hemispheres [5].

Neuro-ophthalmological Signs

Although pupil size and reactivity may remain unaltered with both primary neurological and metabolic diseases, abnormalities may help to localize central lesions and provide prognostic information. The optic chiasm, optic nerves, and retina must all be functional for appropriate pupillary symmetry and light response. Additionally, injury and certain drugs will also alter pupil size and reactivity. Overall pupil size is a consequence of a balance between the parasympathetic and sympathetic nervous systems. Signaling from the sympathetic nervous system or loss of signaling from the parasympathetic nervous system results in mydriasis [5]. As parasympathetic signaling involves cranial nerve (CN) III and the midbrain, lesions in either of these areas will result in pupillary dilation whereas lesions in the brainstem (pons) [6], thalamus or cerebrum may result in pupillary constriction. Fixed and dilated pupils are typically associated with a guarded prognosis as this may indicate severe midbrain disease or herniation. The oculocephalic reflex is typically maintained in all patients except those with severe brainstem disease.

The nerves and tracts responsible for physiological nystagmus include CN VIII, the brainstem, cerebellum, and CN nuclei of III, IV, and VI [6]. These pathways are adjacent to areas of the brainstem required for arousal, so lack of a physiological nystagmus in a comatose patient indicates severe brainstem involvement with a guarded prognosis [2,6].

Postural Response

Patients with brain disease of various etiologies may present with abnormalities ranging from ataxia to tetraparesis. In patients that are not comatose, voluntary motor activity should be maintained. Increases in muscle tone and reflexes of all four limbs may be seen in animals with cerebral or cervical disease; however, comatose animals may lose all muscle tone and reflexes. Decerebrate or decerebellate postures are characteristic of specific

lesion locations. Decerebrate posture describes opisthotonus with spastic rigidity of all four limbs and altered mentation. It is typically associated with severe disease of the midbrain or pons due to firing of the alpha and gamma motor neurons in the vestibulospinal system and RAS. Decerebellate rigidity is associated with cerebellar lesions or herniation, and may appear similarly. However, these animals are often mentally aware and demonstrate extension of the forelimbs and flexion of the pelvic limbs [7–9].

Respiratory Patterns

Specific respiratory patterns may be appreciated in patients with severe brainstem lesions or herniation. Patients with bilateral lesions of the cerebral cortex or diencephalon may demonstrate *Cheyne–Stokes* respiration. This breathing pattern involves alternating periods of apnea and hyperpnea. Apneustic and ataxic breathing may be seen with pons or medullary lesions whereas neurogenic hyperventilation is characteristic of lesions within the midbrain pneumotaxic center [2,6]. Respiratory patterns should always be assessed with ventilation and oxygenation status and history.

Differential Diagnoses and Diagnostic Approach

Altered mentation may be seen in patients with severe metabolic or primary neurological disease. A thorough physical examination, history, and comprehensive diagnostic plan can help to differentiate the underlying cause. Physical examination may help to rule out underlying trauma or shock. Manipulation of the neck and spine should only be performed with caution until trauma has been ruled out. Discussion about historical diseases, as well as what medications or toxins are available, may also help to identify etiology.

Diagnostic Approach

Laboratory Testing

Patients with altered mentation should have a full biochemical profile, complete blood count, urinalysis, and blood gas analysis. Patients with primarily neurological disease may have relatively normal lab work. Severe alterations in organ function can result in a toxic metabolic encephalopathy as in the case of hepatic or uremic encephalopathies, prompting more advanced organ function testing such as ammonia or bile acids. Severely anemic patients may demonstrate dull behavior

secondary to decreased oxygen delivery [10,11]. Monitoring of markers of perfusion such as lactate can indicate ongoing or progressive hypoperfusion, but they may also be elevated due to severe acute renal or hepatic failure [12].

Initial and repeated monitoring of blood glucose measurement is important in the critical patient. As the brain exclusively utilizes glucose for energy, neuroglycopenia is a common cause of neurological dysfunction secondary to decreases in ATP. Acute hypoglycemia will result in dysfunction of the Na-K-ATPase pumps, leading to cerebral cellular swelling, astrocyte glutamate uptake, and rapid cellular influxes of calcium, potassium, and chloride. Even after normalization, hypoglycemia will trigger cellular apoptosis and necrosis potentiating signs [13]. Alternatively, patients presenting with hyperosmolar syndrome may demonstrate disorientation, ataxia, or seizures. Similar to hypernatremic patients, these patients also develop idiogenic osmoles and rapid drops in glucose are not recommended [14].

Initial and repeat electrolyte monitoring should be performed, particularly in patients with known alterations of osmolality (hypernatremia, hyperglycemia, or severe azotemia) or receiving hyperosmotic therapy. Other electrolyte alterations that may result in neurological sequelae include seizures or tremors in severely hypocalcemic patients, profound weakness in hypokalemic patients, or dull mentation and head pressing in hyperammonemic patients. Specific guidelines for treatment of electrolyte abnormalities can be found in Section 3F. If an intoxication is suspected, there may be laboratory tests that will aid in confirming the diagnosis. More information can be found on this topic in Section H.

Advanced Neurological Testing

In patients with primary neurological disease, laboratory testing may not be significantly altered or suggestive of an underlying disease process. Neuroimaging and cerebrospinal fluid analysis may be indicated to determine underlying etiology and provide prognostic information. Computed tomography (CT) scans are often helpful in trauma patients for identification of hemorrhage and calvarial fractures. Although other changes such as edema and hydrocephalus may be apparent, lack of detail makes etiological diagnosis more difficult [15,16]. Magnetic resonance imaging (MRI) provides superior detail of cortical and subcortical structures not apparent on CT, and has been shown to provide significant prognostic information in dogs with head trauma [17,18]. However, it also has several drawbacks including availability, cost, and necessity of a lengthy anesthesia time.

Brainstem auditory evoked response (BAER) can be used to assess prognosis in comatose animals providing

that peripheral hair cells are still functional. This diagnostic procedure assesses central auditory pathways and can be used indirectly to assess brainstem function. Loss of BAER is an overall poor prognostic indicator. Similarly, electroencephalography may be considered to assess cortical function or for non-convulsive status epilepticus [19]. A flat tracing during auditory or noxious stimuli in the comatose patients is suggestive of poor prognosis.

Treatment and Monitoring

Treatment should be geared towards the underlying disease process wherever possible while maintaining patient stability and continued supportive care. Initial blood pressure assessment to assess for decompensated shock or a Cushing reflex, along with electrocardiography, is imperative. Cerebral ischemia can result in mental dullness so an accurate full neurological assessment can be made only after appropriate resuscitation. Serial neurological monitoring is essential as neurological status can change rapidly.

Those patients identified with or at risk for increases in intracranial pressure should be placed on a slant board at 15–30° to enhance venous drainage from the head, with continuous blood pressure, heart rate, and pulse oximeter monitoring. Previous studies in people have monitored changes in intracranial pressure, cerebral perfusion pressure, and various measures of hemodynamics including cardiac index in patients with intracranial hypertension at various angles of elevation and while flat. Maintaining head elevation between 15 and 30° will optimize venous drainage without jeopardizing cerebral perfusion pressure and cardiac output.

Monitoring with targeted therapy to maintain normoxia and normotension is critical in patients with intracranial hypertension, with arterial catheterization for continuous blood pressure monitoring being ideal where possible. Patients with even brief periods of hypoxia and hypotension have increased mortality and worse neurological outcomes compared to those without. Hypoventilating patients may require mechanical ventilation as tight ventilatory control is recommended in patients with suspected cerebral edema. Hypercapnia will result in cerebral vasodilation secondary to cerebral acidosis and exacerbate edema and intracranial hypertension. Hypocapnia will result in vasoconstriction, and although mild hypocapnia may help to decrease the severity of cerebral edema, moderate or prolonged decreases in carbon dioxide may result in ischemia and poorer outcomes [20].

Seizures (see Chapter 21) should be treated promptly with the administration of a benzodiazepine. Some

patients may require continuous infusions to prevent further seizure activity along with additional antiepileptic medications such as levetiracetam (30–60 mg/kg) [21], ketamine (2–8 mg/kg) [22] or phenobarbital. In patients with refractory status epilepticus, infusions of propofol, pentobarbital or inhalant anesthetics may be required for seizure control. Alternative medications such as fosphenytoin may prove useful in the future [23].

Hyperglycemia has been associated with poorer outcomes in people with head trauma [24]. However, although hyperglycemia has been associated with the severity of head trauma, it has not been shown to be associated with outcome. Thus patients with severe hyperglycemia (>250 mg/dL) [25] may benefit from judicious insulin therapy targeting normoglycemia or mild hyperglycemia targeting blood glucose levels of <200 mg/dL (see Chapter 19) [26].

Patients demonstrating a Cushing reflex or rapid decline in mental status indicating possible increases in intracranial pressure may benefit from the administration of hyperosmotic agents such as hypertonic saline (HTS) or mannitol. Both mannitol and HTS act similarly to decrease intracranial pressure by creating an osmotic gradient between the plasma and intracranial compartment and drawing fluid out of the brain. Mannitol (0.5–2 g/kg) has been shown to increase blood rheology, cerebral blood flow, and tissue oxygenation [27].

Both mannitol and HTS will result in an acute increase in intravascular volume, and should be used cautiously in animals with cardiac or renal disease. However, mannitol may result in significant osmotic diuresis and potential volume depletion, electrolyte shifts, and hypotension which should all be avoided in patients with increased intracranial pressure. HTS has been shown to result in decreased intracranial pressures, increased cerebral perfusion pressure, and tissue oxygenation along with improved overall hemodynamic effects [28,29]. HTS also may be beneficial in patients with suspected intracranial hemorrhage, as it has a higher reflection coefficient and thus less risk of extravasation. HTS will result in typically transient increases in blood sodium and chloride concentrations and should be used with caution in patients with severe sodium derangements.

The superiority of mannitol or hypertonic saline has not been demonstrated in patients with intracranial hypertension and the decision for one over the other, or in conjunction, should be made on a case-by-case basis [30,31]. For instance, the use of HTS may be preferred in traumatic brain injury as it may both decrease intracranial hypertension and aid in overall fluid resuscitation and hemodynamic support. The use of corticosteroids has been shown to be detrimental in patients suffering head trauma and is not recommended [32]. Overall,

corticosteroids have not been shown to decrease either cytotoxic or interstitial edema, but may be beneficial in reduction of vasogenic edema in patients with brain tumors [33].

Conclusion

Patients presenting with altered mentation may have a variety of metabolic or primary neurological diseases.

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21

Seizures

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Introduction

Seizure is defined as the clinical manifestation of an abnormal and excessive excitation and synchronization of a population of cortical neurons. Within this broad definition are various types, classifications, and associated vocabulary. For the purpose of this chapter we will use the following.

- Epilepsy is the term used for patients with recurrent seizures.
- Status epilepticus (SE) is by clinical definition a seizure that lasts longer than 5 minutes, inducing permanent brain damage if the duration is longer than 30 minutes. SE also describes the patient who does not regain consciousness between seizure events.
- Cluster seizure describes two or more seizures within 24 hours.
- Focal seizures occur with or without loss of consciousness and can lead to secondary generalization. In focal or partial seizures, the animal is generally conscious but the mentation can be altered. Common manifestations of partial seizures include hypersalivation, jaw champing, fly biting, symmetrical or asymmetrical facial twitches, and rhythmic contractions of a limb.
- Generalized seizures can appear as convulsive or non-convulsive ("sensory" seizure, difficult to characterize and demonstrate in dogs). Generalized or tonic-clonic motor seizures are characterized by violent, bilateral, and symmetrical muscle contractions, loss of consciousness and autonomic phenomena such as hypersalivation, urination, and defecation. Once the gross motor activity has subsided, one can still observe rhythmic twitches of the eyelids or of a limb. That activity should be still considered seizure activity and should be treated. Some animals can continue to slowly paddle at the end of the convulsions; this stage is usually the beginning of the recovery and should not be treated.

History

The signalment of the animal and pertinent history provide important clues in determining the most likely etiology for seizure activity. The following questions should always be part of the history when approaching a seizing animal.

- Is this the first time that seizures have occurred or is there a pre-existing seizure disorder?
- When did the first seizure occur and what was the animal doing at the time (sleeping, playing, occurred after a meal)?
- Has the patient maintained consciousness during the seizure (sometimes owners are unsure; ask if they tried to call the animal's name, offer a treat, etc.)?
- Has the patient been systemically healthy in the past 4 months (inquire about changes in behavior or personality)?
- Inquire about travel history, vaccination status, recent trauma or toxin exposure.
- Is the patient on any medication? If so, inquire about doses and frequency, especially if antiseizure medications have already been administered.
- In cats, ask if the animal is indoor only or if it has unsupervised access to outdoor areas.

Initial Patient Assessment (see Chapter 2)

Provide basic medical emergency care (insure the presence of open airways, intact breathing, and circulation) before examining the patient's neurological condition. A large-bore intravenous catheter should be placed as soon as possible.

As part of the initial systemic stabilization, 100% oxygen should be administered immediately, either as

flow-by via face mask or after intubation if necessary. Seizures increase the cerebral metabolic demands and insuring oxygen supply reduces the chance of lactate formation in the brain which has been shown to increase twofold in hypoxic animals during seizure [1].

Rectal temperature should also be monitored and the patient should be cooled as needed; hyperthermia occurs frequently and can often lead to systemic complications, such as renal failure or rhabdomyolysis.

Neurological Examination

When possible, the neurological exam should be performed before sedatives, pain medications or anticonvulsants are given. However, if the patient is actively seizing, this is not always possible. Patients presenting during a preictal phase, which occurs hours to minutes prior to ictus (seizure), may have the following signs:

- agitation
- clinging
- hiding.

Those in the postictal phase, which can last up to 72 hours, may show:

- impaired vision, lack of menace
- disorientation/confusion
- hyperactivity
- need to go outdoors
- increased hunger/thirst
- aggressiveness
- exhaustion.

In general, animals with seizures are given an anatomic localization of prosencephalon (forebrain).

Differential Diagnoses

Differential diagnoses for seizure-like events must be ruled out. Box 21.1 is a summary of events that can be confused with seizure.

Causes of true seizures can be broken into three simple categories: metabolic, structural, and idiopathic. Metabolic, also called reactive epilepsy, occurs in response to metabolic disease or toxin exposure. Structural disease or symptomatic epilepsy occurs in response to an anatomic or pathological abnormality of the brain. Idiopathic epilepsy is diagnosed when there are no anatomic or pathological abnormalities to explain seizures. Finally, idiopathic epilepsy describes seizures with no obvious underlying cause but where symptomatic epilepsy is presumed. Further breakdown of differential diagnoses is provided in Table 21.1.

Box 21.1 Differentials for seizure-like events.

Syncope
Pain episode
Movement disorder
Idiopathic head bobbing
Behavior
Vestibular disease
REM sleep disorder
Narcolepsy/cataplexy
Episodic weakness
Severe pruritus

Table 21.1 Common causes of seizure activity.

	Examples
Degenerative	Lysosomal storage diseases
Anomaly	Hydrocephalus, lissencephaly, arachnoid cyst
Metabolic	Hepatic or renal encephalopathy, hypoglycemia, hypocalcemia, hypertriglyceridemia, hyperosmolarity, hyper/hyponatremia
Nutritional	Thiamine deficiency
Neoplasia	Primary or secondary brain tumor
Inflammatory	Granulomatous meningoencephalitis, necrotizing meningoencephalitis, necrotizing leukoencephalitis, meningoencephalitis of unknown etiology, eosinophilic meningitis
Infectious	Canine distemper virus, feline infectious peritonitis, rabies, <i>Cryptococcus</i> or other fungal, <i>Toxoplasma</i> , cuterebra migration, Rocky Mountain spotted fever or other rickettsial
Idiopathic	Idiopathic epilepsy
Toxic	Lead, strychnine, metaldehyde, bromethalin, organophosphates, pyrethrin, illicit drugs
Traumatic	Head trauma (can be years prior)
Vascular	Ischemic or hemorrhagic infarct

Quick Assessment Tests

Quick assessment tests should be performed as soon as possible to assess the patient's general health status.

- Packed cell volume (PCV) and total protein (TP) can be increased if the patient is dehydrated or due to pathology.
- Blood glucose should be measured. This can be the cause for seizure activity in puppies and kittens or in older animals if an insulin-secreting or insulin-like growth factor-secreting tumor is present.
- Blood urea nitrogen (BUN) sticks can help rule out the presence of renal disease.
- If available, an arterial blood gas will add useful information as well as evaluation of electrolyte status (sodium, potassium, chloride), lactate concentration (lactate levels might be increased due to abnormal muscle activity) and ionized calcium concentration. Hypocalcemia is a life-threatening condition usually seen at 2–3 weeks postpartum in small-breed bitches that gave birth to a large litter or in animals with hypoparathyroidism, phosphate enema toxicity, or administration of chelating agents.
- ECG monitoring should also be performed to identify the presence of cardiac arrhythmias. Myocardial injury can happen as a consequence of prolonged seizure activity.

Extended Laboratory Tests and Diagnostic Images

Comprehensive laboratory tests and advanced imaging techniques are the next step to reach a definitive diagnosis. Complete blood cell count (CBC) and biochemical profile abnormalities have to be carefully reviewed in light of the history, physical, and neurological examinations. In most cases, CBC changes are non-specific but they can be supportive of some differential diagnoses. Neutropenia can be supportive of an infectious disease process such as canine distemper virus, a peripheral eosinophilia can be present in cases of eosinophilic meningitis or parasitic/fungal encephalitis and the presence of thrombocytopenia can be indicative of Rocky Mountain spotted fever or other tick-borne diseases associated with seizures [2–4] or be a cause for hemorrhage into the brain.

The biochemical profile identifies potential systemic abnormalities causing symptomatic seizures but postictal changes must be considered. These include elevated creatinine kinase and AST, mild electrolyte abnormalities, mild liver enzyme elevations, and mild hypoglycemia.

Increased liver enzymes may also be present in animals that are on maintenance treatment with drugs, such as phenobarbital, that induce these enzymes. Fasting ammonia level or pre- and postprandial bile acid levels are helpful adjunctive tests to evaluate liver function.

Urine should be collected for urinalysis, ideally before administering intravenous fluids, as part of the renal assessment. Toxicological tests can also be performed on urine, if appropriate, with commercial drug screening tests which have been shown to identify barbiturates, opiates, benzodiazepines and amphetamines/methamphetamines. The on-site tests may sometimes not be successful in identifying marijuana or methadone [5].

Samples for tick-borne disease titers, protozoal titers, common infectious viral diseases (FIV and FELV in cats), lead poisoning, and cholinesterase levels can be acquired after patient stabilization, along with serum for antiepileptic drug levels.

Thoracic radiographs should be performed if non-cardiogenic pulmonary edema or secondary aspiration pneumonia is suspected and to rule out metastatic disease. Advanced imaging techniques include computed tomography (CT) scan, especially in cases of head trauma or the unstable patient, or magnetic resonance imaging (MRI). MRI has increased sensitivity and specificity in detecting intracranial disease compared to CT, but it requires longer acquisition time. For this reason, CT is still the preferred imaging modality for unstable patients. MRI in the postictal period can have temporary hyperintense lesions on T2-weighted images in the temporal cortex, piriform lobes, and cingulate gyrus. These correspond to areas of edema, neovascularization, astrogliosis, and neuronal necrosis on biopsy evaluation [6].

Cerebrospinal fluid collection and analysis is a fundamental part of the neurological work-up, providing useful information when infectious or inflammatory diseases are suspected. CSF evaluation was found to be a good predictor of MRI abnormality in dogs having seizures, with sensitivity and specificity of 79% and 69% [7].

Emergency Management

The goal of emergency management is to control immediate or ongoing seizure activity to avoid sequelae of prolonged ictus which include increased intracranial pressure, irreversible neuronal injury, non-cardiogenic pulmonary edema, acidemia, tissue hypoxia, disseminated intravascular coagulation, and death. After oxygen administration and placement of an intravenous catheter as outlined above, the next step is to control obvious generalized or partial activity.

If hypoglycemia is present (blood glucose < 65 mg/dL, 3.5 mmol/L), a bolus of 50% dextrose can be administered at a dose of 0.5 mL/kg, diluted 1:4 with normal saline. A glucose solution can also be administered orally, since it is well absorbed by the oral mucosa. Blood glucose should be re-evaluated after initial therapy, keeping in mind that, in many instances, hypoglycemia is a consequence of prolonged seizure activity and not the cause (see Chapter 111).

Hypocalcemia (serum total calcium < 8 mg/dL or 2 mmol/L, ionized calcium < 0.6 – 0.7 mmol/L) should be treated if clinical signs are present. A 10% calcium gluconate solution is the preferred treatment at a dose of 0.5 – 1.5 mL/kg IV, administered slowly over 10–30 minutes. Continuous ECG monitoring is mandatory and if bradycardia, shortened QT interval or vomiting are noted, the infusion must be slowed or suspended (see Chapter 110).

Benzodiazepines

Benzodiazepines are fast-acting anticonvulsant drugs and they can be administered not only IV (diazepam 0.5 – 1 mg/kg, midazolam 0.07 – 0.22 mg/kg), but also via rectal administration (diazepam 0.5 – 2 mg/kg), IM injection (midazolam 0.07 – 0.22 mg/kg) or intranasal administration (diazepam 0.5 mg/kg). Although often recommended, a recent study showed that compounded diazepam suppositories should not be used as an emergency treatment for seizures or status epilepticus because therapeutic plasma concentration is not achieved after rectal administration in an effective timeframe [8]. A midazolam gel formulation (50 mg/mL) has been shown to have superior bioavailability and peak plasma concentration, which may prove helpful in seizure management [9].

If the seizure activity initially presents as cluster seizures, the approach should be to administer single boluses of benzodiazepine during or after each seizure to a maximum of three boluses. If seizures keep reoccurring more frequently than 20–30 min apart, if they are not controlled after the administration of the three boluses and/or if the animal doesn't regain consciousness in between them, a continuous-rate infusion (CRI) of diazepam (0.5 – 2 mg/kg/h diluted in 5% dextrose or 0.9% saline) or midazolam (0.2 mg/kg/h) should be started. Before preparing the diazepam CRI, one should remember that diazepam is incompatible with other medications, is light sensitive and binds to plastic tubing.

Phenobarbital

For cluster seizures, status epilepticus or if treatment with a long-acting antiepileptic drug is planned, phenobarbital should be considered. Phenobarbital is a safe and

inexpensive barbiturate and can be administered orally, IV, and IM. The loading dose of phenobarbital is 4 – 6 mg/kg q6h, to a maximum of 24 mg/kg total over 24 hours. If the dog is receiving phenobarbital as maintenance therapy, a 2 – 5 mg/kg IV bolus can be administered after blood collection for phenobarbital serum levels.

If the patient does not respond to phenobarbital or benzodiazepines to the above-mentioned doses after a 12-hour period, disease should be considered refractory. Investigating for a structural lesion (neoplasia, encephalitis, metabolic derangements) responsible for the clinical signs is recommended [10]. More aggressive treatment should be considered at this point and several options are available.

Levetiracetam

Levetiracetam is an antiepileptic drug available in oral and injectable forms. Although the mechanism of action is not completely understood, it has been shown to modulate neurotransmitter release by binding the SV2A glycoprotein, reducing neurotransmitter release. It is minimally metabolized and primarily eliminated by renal excretion, has no known drug interactions, readily crosses the blood–brain barrier and has a very short half-life (3–4 h in dogs). If available, levetiracetam can be administered IV at the dose of 20 mg/kg q8h. The drug has been demonstrated to have minimal side-effects (sedation and mild ataxia) up to a dose of 60 mg/kg IV q8h (also used as loading dose) [11]. In a study conducted in cats, plasma concentration of levetiracetam was within the human therapeutic range 10 minutes after administration IV and remained in the range for 9 hours [12]. Given its safety margin and minimal side-effects, levetiracetam can be used in combination with other antiepileptic drugs on an emergency basis and as an oral maintenance anticonvulsant for long-term treatment.

Propofol

Propofol is a hypnotic/amnestic agent used for induction of general anesthesia. It has barbiturate and benzodiazepine-like effects and can be administered as a bolus (1 – 4 mg/kg slowly to effect) or CRI (0.1 – 0.6 mg/kg/min). Apnea, vasodilation, and myocardial depression are the most common side-effects experienced with propofol, and can happen after a bolus or at any point during the CRI. Suppression of the gag reflex and aspiration pneumonia can occur, so close monitoring and preparation of equipment to perform endotracheal intubation and mechanical ventilation are recommended.

The efficacy of propofol in controlling seizure activity is still controversial; the drug seems to have both, anti- and proconvulsant properties and its antiepileptogenic effect might be dose dependent, since at higher doses it might raise the neuronal excitatory threshold. Yet, idiopathic epileptic dogs under propofol anesthesia were shown to have continued epileptiform activity on electroencephalogram recordings [13]. A report on the use of propofol in combination with phenobarbital to control status epilepticus in dogs suffering from hepatic encephalopathy after portosystemic shunt surgery showed promising results in controlling refractory seizure activity [14].

Ketamine

Ketamine is a NMDA receptor antagonist, used mainly as an anesthetic, analgesic or sedative agent in veterinary medicine. Experimental evidence exists for the NMDA receptor antagonist's role in the management of refractory seizures in people and rodents. NMDA receptor activation has been shown to be associated with loss of GABAergic inhibition. Therefore, the use of ketamine may be beneficial in controlling prolonged activity [15]. There is one report of ketamine use in a dog for the management of refractory status epilepticus. The dose of ketamine used was 5 mg/kg as a bolus, followed by a CRI at 5 mg/kg/h [16].

Dexmedetomidine

Dexmedetomidine is a highly specific alpha-2 adrenoceptor agonist. It is commonly used as a sedative, anxiolytic, and anesthetic adjunct in dogs and cats. Dexmedetomidine is considered contraindicated in hypovolemic and/or hypotensive patients and in dogs with mitral insufficiency and dilated cardiomyopathy. Dexmedetomidine has been recently investigated as treatment for SE in rats. In the study, the rats were injected intraperitoneally with two different dosages (50/100 µg/kg) and the results showed that dexmedetomidine effectively decreases the number and cumulative time of repeated seizures. The level of glutamate in the hippocampus of the treated rats was decreased, therefore the mechanism of action is suspected to be related to antioxidant effects and inhibition of glutamate release [17]. There is currently one retrospective study evaluating dexmedetomidine for seizure control in dogs and cats. A single IM (rarely IV) dose of 375 µg/m² was given as either a first- or second-line medication with success and all 26 cases survived to discharge [18].

Acepromazine

Acepromazine is a phenothiazine derivative whose mechanism of action is to inhibit dopaminergic-2 receptors in the brain. Phenothiazines, such as chlorpromazine, have

been shown to lower seizure threshold and have been avoided in dogs with epilepsy. However, in one report 36 dogs with seizure history were treated with acepromazine with no seizure after administration. It was specifically used to decrease seizure activity in 11 dogs and was successful in 8/10 dogs actively seizing [19]. Therefore, a dose of 0.005–0.01 mg/kg IV, IM or SC with a maximum total of 3 mg IV can be considered in the refractory patient. Due to its relevant vasodilatory effects, caution should be exercised in patients with cardiovascular derangements and blood pressure should be monitored closely.

Intracranial Pressure

If rapid deterioration of mental status along with pupil changes (anisocoria → mydriasis → miosis), decreasing heart rate (<60 beats per minute) and increasing blood pressure (systolic >180 mmHg) is observed in a patient experiencing cluster seizures or status epilepticus, a Cushing's reflex must be considered. This reflex is evidence of increased intracranial pressure (ICP). To maintain cerebral perfusion pressure (CPP), the mean arterial pressure (MAP) is increased and a reflex bradycardia occurs. In that case, immediate treatment is required and administration of mannitol 0.25–2 g/kg of 15–25% solution given IV over 20 minutes is indicated. Mannitol can be repeated every 4–5 hours for a maximum of 3–4 times in a 24-hour period. Since mannitol is an osmotic diuretic, its administration may intensify inadequate hydration or hypovolemia by sustaining diuresis. Shifting of sodium-free intracellular fluid into the extracellular compartment following mannitol infusion may lower serum sodium concentration and aggravate pre-existing hyponatremia.

Alternatively, hypertonic saline 5% or 7% bolus (6–10 mL/kg max.) at the rate of 1 mL/kg/min can also be considered with the same indications of mannitol. Administration of hypertonic saline can also be responsible for severe electrolyte imbalances (hypernatremia). For these reasons, administration of multiple doses within 24 hours has to be limited.

The current literature on hyperosmolar therapy for treatment of elevated intracranial pressure has suggested relative superiority of hypertonic saline over mannitol. The majority of the experts in neurocritical care prefer HTS over mannitol, reporting that the most common side-effects of mannitol administration (osmotic diuresis and acute kidney injury) are much less common in patients treated with HTS.

A simple elevation of the head 30°, taking care not to occlude jugular veins, can be therapeutic while more complex treatments include intubation and hyperventilation. ICP, CPP, cerebral blood flow (CBF), mean carotid pressure and other cerebral and systemic physiological parameters have been measured in head-injured patients

in human medicine. The mean carotid pressure was significantly lower when the patient's head was elevated at 30° than at 0°, as was the mean ICP. There was no statistically significant change in CPP, CBF, cerebral metabolic rate of oxygen, arteriovenous difference of lactate, or cerebrovascular resistance associated with the change in head position. The data indicate that head elevation to 30° significantly reduced ICP in the majority of the 22 patients without reducing CPP or CBF [20].

Long-term Management of Seizures

The initiation of long-term treatment of seizures, especially in the case of idiopathic epilepsy, should start with a discussion regarding the goal of treatment. The goal in treating epilepsy is to reduce the frequency and severity of seizure events, taking care to note that it may not be possible to stop seizures completely. Table 21.2 is list of medications in order of use by the authors.

Table 21.2 Maintenance antiepileptic drugs.

Drug and mechanism of action	Dose	Side-effects	Recommended follow-up
Phenobarbital			
<ul style="list-style-type: none"> Enhances GABA-activated Cl⁻ conductance 	2–5 mg/kg PO BID	<ul style="list-style-type: none"> PU/PD/PP Hindlimb weakness Induces hepatic enzymes Interferes with thyroid testing Blood dyscrasia 	<ul style="list-style-type: none"> CBC, chemistry, serum drug level in 2 weeks then q6 months Liver function tests PRN
Potassium bromide			
<ul style="list-style-type: none"> Enhances GABA-activated Cl⁻ conductance 	20–40 mg/kg PO q24h	<ul style="list-style-type: none"> PU/PD/PP Hindlimb weakness Associated with pancreatitis 	<ul style="list-style-type: none"> CBC, chemistry, UA and drug level q6 months
Levetiracetam (Keppra)			
<ul style="list-style-type: none"> SV2A receptor 	20–60 mg/kg PO TID Higher dose necessary when used in conjunction with phenobarbital	<ul style="list-style-type: none"> Ataxia Mild sedation 	<ul style="list-style-type: none"> Routine bloodwork q6–12 months
Gabapentin (Neurontin)			
<ul style="list-style-type: none"> Blocks Na⁺ channel Enhanced GABA-activated Cl⁻ conductance Reduced Ca²⁺ channel current 	10 mg/kg PO TID	<ul style="list-style-type: none"> Mild sedation Ataxia 	<ul style="list-style-type: none"> Routine bloodwork q6–12 months
Zonisamide			
<ul style="list-style-type: none"> Blocks Na⁺ channel Reduced Ca²⁺ channel current 	5–10 mg/kg PO BID Higher dose necessary when used in conjunction with phenobarbital	<ul style="list-style-type: none"> Keratoconjunctivitis sicca Blood dyscrasia Necrotizing skin lesions 	<ul style="list-style-type: none"> Routine bloodwork q6 months
Topiramate			
<ul style="list-style-type: none"> Blocks Na⁺ channel Enhanced GABA-activated Cl⁻ conduction Reduced glutamate excitation 	2–5 mg/kg PO BID	<ul style="list-style-type: none"> Inappetence Weight loss 	<ul style="list-style-type: none"> Routine bloodwork q6–12 months
Clorazepate			
<ul style="list-style-type: none"> Enhanced GABA-activated Cl⁻ conductance 	1 mg/kg PO TID for 3 days following seizure	<ul style="list-style-type: none"> Sedation Ataxia Polypahgia 	<ul style="list-style-type: none"> Routine bloodwork q6–12 months

BID, twice a day (*bis in die*); CBC, complete blood count; GABA, gamma-aminobutyric acid; PD, polydipsia; PO, by mouth (*per os*); PP, polyphagia; PRN, as required (*pro re nata*); PU, polyuria; TID, three times a day (*ter in die*); UA, urine analysis.

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22

Intracranial Disease

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Clinical Signs

A full physical examination should be performed prior to or concurrent with the neurological examination. Life-threatening non-neurological abnormalities should be addressed as indicated (see Chapter 2). Abnormalities noted on the neurological examination directly correlate to the portion of the central nervous system (CNS) affected. Localization of the lesion, along with history and signalment, can help to narrow the list of differential diagnoses. This chapter focuses on intracranial abnormalities (affecting the cerebrum, brainstem, and cerebellum).

The cerebrum is divided into two parts: the telencephalon and diencephalon. Lesions affecting the telencephalon are characterized by seizures and/or movement disorders, changes in behavior, compulsive activity, contralateral vision deficits, and contralateral proprioceptive deficits. Lesions within the diencephalon are characterized by a normal gait but slow proprioceptive responses contralateral to the lesion. Contralateral menace deficits with dilated, unresponsive pupils may be associated with lesions to the optic chiasm or tracts. Level of consciousness (obtunded, stupor or coma) may be affected. Pituitary lesions may result in Cushing's disease, diabetes insipidus or other regulatory dysfunctions. Circling, seizures, and abnormal behavior may also be noted. Occasionally, acute thalamic lesions may result in vestibular signs [1].

The hindbrain is divided into four parts: the medulla, pons, cerebellum, and mesencephalon. Lesions within the pons or medulla result in disruption of upper motor neuron tracts, and spastic tetraparesis or tetraplegia which is ipsilateral to the lesion. Lesions affecting respiration centers can result in hypoventilation or irregular breathing patterns. Cranial nerve (CN) deficits can be noted depending on the location of the lesion, including

paresis/atrophy of the tongue (CN XII), dysphagia (CN IX, X, XI), medial strabismus (CN VI), central vestibular signs (CN VIII), facial paralysis (CN VII), atrophy of the masticatory muscles or facial analgesia (CN V). A cerebellar lesion may result in hypermetria and ataxia, central vestibular signs, menace deficits, and intention tremor. Severe rostral cerebellar lesions may cause opisthotonus and decerebellate rigidity (increased extensor tone to all four legs with flexion at the hips). Lesions within the mesencephalon may cause opisthotonus and decerebrate rigidity (increased extensor tone to all four legs). Ipsilateral or contralateral tetraparesis are possible depending on the location of the lesion. Damage to the reticular activating system may result in changes to the level of consciousness (depression to coma). Mesencephalic lesions can also cause CN abnormalities such as extorsion strabismus (CN IV), ventrolateral strabismus and ptosis (CN III), or mydriasis (CN III) [1].

Diagnostic Tests

A minimum database (complete blood count, chemistry, urinalysis, thoracic radiographs, and blood pressure) are recommended. Depending on relevance, there may be benefit in evaluating abdominal radiographs, abdominal ultrasound, prothrombin time/partial thromboplastin time (PT/PTT), platelet count, lactate, serum osmolality, blood typing, bile acids, or ammonia level. Ultimately, magnetic resonance imaging (MRI) (or if contraindicated due to anesthetic concerns or availability, a CT scan) and cerebrospinal fluid (CSF) analysis are needed to obtain a diagnosis and prognosis, and formulate a directed treatment plan. Specific tests for infectious diseases (PCR, titers, culture and sensitivity, etc.) may also be beneficial depending on test results and differential diagnoses.

Differential Diagnoses and Prognosis

This will primarily focus on the more common diseases that would present in an emergency setting (Table 22.1).

Neoplasia

Intracranial neoplasia may be primary or secondary. The most common primary intracranial neoplasm is meningioma, followed by glial tumors, then choroid plexus tumors [2]. The most common secondary intracranial tumors are hemangiosarcoma, pituitary tumors, lymphoma, metastatic carcinoma, extension of nasal neoplasms, and histiocytic sarcoma [2,3]. The majority of dogs with intracranial neoplasms are middle aged or older, with a mean of 9 years [4]. Dogs with secondary neoplasms may have other body systems affected as well, such as lungs, kidneys, or heart [3]. In cats, the most common intracranial neoplasms are meningiomas, followed by lymphoma, glial tumors, and pituitary tumors. Other tumor types are less common in cats [2,5].

The majority of brain tumors in both dogs and cats are located within the cerebrum. The most common presenting clinical signs are seizures, followed by changes in mentation, vestibular signs, circling, ataxia, blindness, and anisocoria [4–6]. Minimum database is recommended to rule out other underlying conditions, but ultimately MRI or CT (and possibly spinal fluid analysis) are needed for a diagnosis. In the emergent setting, treatment of seizures (see Chapter 21) and supportive care are indicated. Mannitol may be used if increased intracranial pressure is suspected. Corticosteroids should be avoided prior to advanced imaging if possible as they could interfere with obtaining a final diagnosis, but are helpful in the long-term management of brain tumors.

Treatment options include surgery, radiation therapy, chemotherapy, and newer treatment options such as stereotactic radiosurgery, immunotherapy, and

convection-enhanced delivery of chemotherapeutics [7]. Conservative therapy (corticosteroids +/- antiseizure medications) has a median survival time of 1–10 weeks, regardless of tumor type (although outliers are possible) [2]. Surgical debulking of meningiomas has a median survival of 4.5–7 months, and debulking with radiation therapy increases median survival to 16.5–30 months [2]. In cats, surgical removal alone of meningiomas has a median survival of 23–28 months [2]. Gliomas tend to have shorter survival times. Newer treatment options are showing promising results, but large studies are lacking and centers performing these techniques are limited [7].

Immune Mediated

Immune-mediated encephalitis encompasses a large number of diseases, including granulomatous meningoencephalitis, necrotizing meningoencephalitis, necrotizing leukoencephalitis, eosinophilic encephalitis, and steroid-responsive meningitis-arteritis. Many group granulomatous meningoencephalitis, necrotizing leukoencephalitis and necrotizing meningoencephalitis into one category of meningoencephalitis of unknown etiology, given the similarities in prognosis and treatment.

Meningoencephalitis of unknown etiology (MUO) is typically acute in onset and progressive in nature, with a focal, multifocal, or diffuse neurolocalization. Dogs are typically young to middle aged, and often (but not always) small-breed dogs. Diagnosis is a combination of MRI findings, CSF analysis, and ruling out infectious etiologies. Treatment is a combination of corticosteroids and immunosuppressive or chemotherapy medications (cyclosporine, cytosine arabinoside, procarbazine, lomustine, etc.). If possible, initiation of corticosteroids should wait until after performing MRI and collecting CSF. Prognosis with prednisone alone has a median survival of 1.3–2 months [8,9]. Immunosuppressive medications and chemotherapeutics have an overall similar

Table 22.1 A summary of common signalments and localizations for disease classifications of intracranial diseases.

Disease classification	Typical age of onset	Onset and progression	Distribution
Neoplasia	Older	Chronic or acute, progressive	Focal, often asymmetric
Immune mediated	Young to middle-aged	Chronic, subacute or acute, progressive	Multifocal (or focal)
Infectious	Any	Insidious or acute, progressive	Multifocal (or focal)
Vascular	Older	Peracute, improving or static	Focal, asymmetric
Metabolic	Any	Insidious, waxing/waning or progressive	Multifocal or diffuse and symmetric
Congenital malformation	Young	Insidious, progressive or static	Diffuse and symmetric
Trauma	Any	Peracute, improving	Focal and asymmetric

long-term prognosis, with a median survival of 10.1–17.7 months [9–12].

Eosinophilic encephalitis is an uncommon cause of meningoencephalitis in dogs, and is thought to be immune mediated in etiology. There is no breed predilections, and median age is 3.5 years. Multifocal or diffuse neurolocalization is common. MRI, CSF analysis, and infectious disease tests are needed to obtain a diagnosis. Prognosis is fair, with death or euthanasia in only 25% of dogs in one study [13].

Steroid-responsive meningitis-arteritis (SRMA) is an immune-mediated disease found in medium to large-breed, young adult dogs. Predispositions exist in Bernese mountain dogs, Nova Scotia duck tolling retrievers, boxers, and beagles [14]. Clinical signs include severe cervical pain and neck guarding, reluctance to move, and pyrexia. Diagnosis is obtained with CSF analysis, which most often shows a marked neutrophilic pleocytosis and elevated globulins [14]. IgA (serum and CSF) and C-reactive proteins (CSF) are also elevated [14]. Treatment is immune suppression with corticosteroids (prednisone 2–4 mg/kg/day) [14–16]. Azathioprine (1.5–2 mg/kg q48h) or mycophenolate mofetil (20 mg/kg/day) can be used to decrease corticosteroid dose and side-effects. Clinical resolution of signs can be obtained in 80–100% of dogs with long-term (4–12 months) treatment [15,16].

Infectious

Intracranial infectious diseases can be caused by bacterial, viral, rickettsial, protozoal, and fungal organisms. Diagnostic tests for infectious intracranial diseases include MRI and CSF analysis. Blood, urine, and CSF culture and sensitivity may be beneficial. Infectious disease titers and PCR can also be utilized.

Bacterial meningitis is rare in dogs, and the most common presenting complaints are cranial nerve deficits, altered mentation, paresis, pyrexia, and neck pain [17]. Prognosis is overall guarded, with a reported 43% mortality rate [17]. Emergent treatment is composed of supportive care (intravenous fluids, anticonvulsants, mannitol if indicated), and broad-spectrum antibiotics. Consideration should be given to antibiotics that cross the blood–brain barrier (BBB). Trimethoprim-sulfonamide, metronidazole, fluoroquinolones, and vancomycin are bactericidal and have good penetration of the BBB. Chloramphenicol, minocycline, doxycycline, and pyrazinamide are bacteriostatic and have good penetration of the BBB. Aminoglycosides and beta-lactams typically have poor CNS penetration. Clindamycin has poor penetration, but can be useful in treatment of protozoal organisms.

The most common viral diseases within the CNS are canine distemper virus (CDV) in dogs and feline infectious peritonitis (FIP) in cats. Viral infections are most common in younger animals. Systemic signs of illness (fever, weight loss, vomiting, diarrhea, lethargy) may be noted prior to neurological signs for viral diseases [18]. FIP encompasses approximately half of infectious or inflammatory neurological disorders in cats [19]. In FIP, routine lab work may show an increase in total protein due to increased gamma-globulins [20]. In CDV, CBC may show intracytoplasmic eosinophilic inclusion bodies. On examination, dogs with CDV may have hyperkeratosis of the pads or enamel hypoplasia of the teeth [21]. Definitive diagnosis for either CDV or FIP can be difficult. Titers indicate either exposure (CDV or FIP) or vaccination (CDV), and do not guarantee causality [20]. Prognosis for CDV and FIP is overall poor. Supportive care is recommended, and directed treatments are lacking [20,21].

Rickettsial infections (ehrlichiosis, anaplasmosis, and Rocky Mountain spotted fever) are uncommon causes of CNS signs in dogs. Treatment is doxycycline, tetracycline, or chloramphenicol.

Toxoplasma (cats and sometimes dogs) and *Neospora* (dogs) are both protozoal infections which occasionally cause myositis and/or meningoencephalitis. Studies on prognosis are lacking, but clinical experience indicates an overall guarded prognosis. Treatments used most often are a combination of clindamycin (12.5–20 mg/kg orally every 12 hours) and trimethoprim-sulfonamide (15 mg/kg orally every 12 hours) for a minimum of 4 weeks (often longer). *Toxoplasma* (but not *Neospora*) has the potential for zoonotic transmission [22].

The most common CNS fungal infections in dogs are cryptococcosis, coccidioidomycosis, and rarely blastomycosis and histoplasmosis. *Cryptococcus* is the most common CNS fungal infection in cats. Occasionally, the fungal organism can be identified outside the CNS (lungs, nasal passages, eyes). Clearing a fungal infection can be difficult, and life-long treatment may be indicated. Prognosis is overall guarded. Fluconazole is the treatment of choice, as it crosses the BBB [23].

Vascular

Vascular events often present acutely or peracutely. Worsening of signs can occur for up to 24 hours due to edema. Clinical signs are dependent on the location of the vascular event. The most common clinical signs include seizures, disorientation, menace deficits, circling/head turn, proprioceptive deficits, central vestibular dysfunction, hypermetria, and death [24,25]. They can be divided into two main categories: ischemic or hemorrhagic infarction. Ischemic strokes are predominantly

due to a thrombus or embolism, while hemorrhagic infarcts result from disruption of the blood vessel wall [24,25].

There is no specific treatment for vascular events in dogs; treatment focuses on general nursing care and maintaining adequate brain perfusion and oxygenation. Directed treatment of clinical signs, such as seizures, is also indicated. Severe (>180 mmHg systolic) hypertension should be treated, but moderate hypertension should be ignored during the acute stages [25]. Mannitol may be utilized if increased intracranial pressure is suspected. A complete work-up for underlying predisposing causes for strokes is indicated, as is subsequent treatment of the underlying disease conditions [24,25]. While largely untested in animals, in the case of an ischemic infarct, unfractionated heparin, aspirin (0.5 mg/kg orally once daily), or clopidogrel (1 mg/kg orally once daily) may be useful to prevent future infarcts [26].

The outcome depends on the size and location of the lesion, and the severity of the clinical signs. In one study of 33 dogs, 10 were euthanized due to neurological deficits or severity of concurrent medical conditions [27]. Having a concurrent medical condition was also associated with shorter survival times [27].

Metabolic

Metabolic diseases are discussed predominantly in other chapters. Sodium disturbances (see Chapter 108), calcium abnormalities (see Chapter 110), hypoglycemia (see Chapters 111 and 112), and hypothyroidism (see Chapter 116).

Hepatic encephalopathy (HE) is another metabolic condition that can cause brain dysfunction. Clinical signs of HE include confusion, ataxia, seizures, ptialism, stupor, coma, and death. Signs often wax and wane [28]. Signs are typically symmetrical, and may be worse after feeding [29]. Most dogs with HE have a portosystemic shunt (PSS), although acute (see Chapter 90) or end-stage liver failure can also result in HE. Typically with PSS, the onset of clinical signs is within the first year of life, and acquired liver failure occurs in older animals [28]. Blood work may reveal hypoproteinemia, hypoalbuminemia, hypoglycemia, hypocholesterolemia, and prolonged clotting times. Liver values (ALT, ALP, AST, and GGT) may be normal or mildly elevated with PSS or end-stage liver failure. Increased ammonia or pre/postprandial bile acids are useful in diagnosis of HE or PSS [29]. Abdominal ultrasound or, if non-diagnostic, CT angiography or magnetic resonance angiography are often needed for diagnosis of PSS or underlying causes for HE [29]. Liver biopsy may be useful to determine causes of liver failure or end-stage liver disease.

Emergent treatment of HE focuses on decreasing blood ammonia. Lactulose is a non-absorbable disaccharide that can be administered orally (1–3 mL/10 kg) or rectally (5–10 mL/kg) in the case of severe, life-threatening signs. Lactulose provides an acidic environment to promote conversion of ammonia to ammonium, which is excreted in the feces. Antibiotics can be administered to decrease the number of ammonia-producing bacteria in the flora of the colon [29]. Options include neomycin (20 mg/kg PO q12h), metronidazole (7.5 mg/kg PO q12h), and amoxicillin/clavulanate potassium (13.75 mg/kg PO q12h). Restricted protein diets are a mainstay of treatment [29]. Seizures should be controlled with an anticonvulsant that is not hepatically metabolized (levetiracetam or potassium bromide). Levetiracetam has been shown to decrease the frequency of severe seizure activity postoperatively in PSS ligation [30]. Diazepam is contraindicated due to liver metabolism, and its use may result in excessive sedation [29].

Congenital Malformation

Malformations of the brain include hydrocephalus, hydranencephaly/porencephaly, holoprosencephaly, corpus callosum agenesis/dysgenesis, lissencephaly, polymicrogyria, meningoencephalocele, intracranial cysts, cerebellar malformations (such as cerebellar agenesis or dysgenesis), and hamartomas [31]. Most dogs and cats with a congenital malformation present with signs at a young age, although sometimes onset of signs will occur in a mature animal [31].

The most common congenital brain malformation is hydrocephalus. This is most common in toy-breed dogs (Maltese, Yorkshire terrier, Chihuahua, Pomeranian, and toy poodle). English bulldog, Lhasa apso, cairn terrier, Boston terrier, pug, and Pekingese also have increased risks [32]. Often, but not always, the patient will have a dome-shaped head and persistent fontanelle. Ventrolateral strabismus is commonly noted. Neurological deficits include predominantly forebrain signs such as abnormal behavior, cognitive dysfunction, ataxia, circling, blindness, and seizures [32]. Decreased appetite is also a common presenting or historic complaint. Occasionally, vestibular dysfunction may also be noted either from increased intracranial pressure or concurrent malformations of the cerebellum. The disease course is variable, but patients may present for acute worsening after relatively minor head trauma [32]. Medical treatment includes mannitol (for acute decompensation: 1 g/kg intravenously over 20 minutes), loop diuretics (such as furosemide: 1 mg/kg orally once daily), carbonic anhydrase inhibitors (acetazolamide: 10 mg/kg orally q8h), omeprazole (1 mg/kg orally once daily), and corticosteroids

(prednisone: 1 mg/kg/day starting dose, weaning to lowest effective dose) [32–34].

Polymicrogyria and lissencephaly would predominantly present on an emergent basis with seizures, although cognitive dysfunction and/or behavior changes are also possible [35]. Blindness, and sometimes hypermetria, are noted in polymicrogyria [35]. Polymicrogyria is a disorder characterized by an excessive number of small, disorganized gyri, and is thought to be hereditary in standard poodles [35]. Lissencephaly is characterized

by a lack of or reduction in the normal gyri in the brain, and is hereditary in Lhasa apsos [1]. Treatment for both predominantly focuses on controlling clinical signs such as seizures (see Chapter 21), and prognosis is variable depending on response to treatment.

Trauma

Please see Chapter 19 for further discussion on traumatic brain injuries.

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23

Vestibular Disease

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Introduction

The vestibular system is responsible for maintaining balance, body posture, and eye position [1,2]. It is composed of two main components – the peripheral vestibular system and the central vestibular system.

The peripheral vestibular system contains the vestibular organs (the utricle, saccule, and three semi-circular canals) within the bony and membranous labyrinths of the inner ear. Endolymph movement within these organs causes deflection of specialized hair cells, leading to activation of the vestibular component of the vestibulocholear nerve (cranial nerve (CN) VIII). The vestibular ganglion, containing the cell bodies of the bipolar vestibular nerve, is located within the petrous temporal bone [3].

The central vestibular system begins with the vestibular axons. The majority of these axons terminate in the medulla at the vestibular nuclei, with some axons projecting directly to the cerebellum via the caudal cerebellar peduncles [1,3]. The vestibular nuclei send projections to the spinal cord, brainstem, and cerebellum. The spinal cord projections modulate extensor and flexor tone and allow for co-ordination of the limbs, neck, and trunk. The brainstem projections of the vestibular system regulate and co-ordinate eye movements, provide input to the vomiting center, and allow for conscious perception of balance. The cerebellar projections of the vestibular system co-ordinate the eyes, neck, trunk, and limbs [1].

Clinical Signs (Table 23.1)

Vestibular dysfunction can result in a range of clinical signs, including changes in mentation, head tilt, ataxia, circling or rolling, paresis, pathological nystagmus, cranial nerve deficits, and proprioceptive deficits. A thorough neurological examination can help differentiate

between peripheral and central vestibular disease; this differentiation will dictate diagnostics, treatment, and prognosis.

Peripheral Vestibular Disease

Mentation

Patients with peripheral vestibular disease should have normal mentation. Patients may seem disoriented or anxious after a peracute onset of clinical signs.

Gait/Posture

Evaluation of the patient's posture can occur with the patient at rest as well as during ambulation. It is best to evaluate gait on a non-slip surface, such as carpet or rubber mat. Patients with vestibular disease may need assistance to rise and stand, and may require sling assistance to walk.

A head tilt is a common finding with vestibular disease. With peripheral disease, the head will be tilted towards the lesion. The degree of head tilt can vary, and may worsen after manipulation.

Patients with peripheral vestibular disease typically exhibit ataxia. Vestibular ataxia is characterized by listing, leaning, and falling towards the lesion. The patient should have normal strength.

Circling and alligator rolling towards the side of the lesion may be noted with peripheral vestibular disease. Patients may be most comfortable when they are positioned with the affected side down.

Cranial Nerves

Pathological nystagmus, or spontaneous nystagmus, is an abnormal oscillation of the eyes with distinct fast and slow phases of eye movement. It is a hallmark of vestibular disease. In peripheral vestibular disease, the two most common nystagmus patterns are horizontal

and rotary. Rarely, a patient with peripheral vestibular disease can exhibit vertical nystagmus, although this is classically associated with central vestibular disease. The fast phase of the nystagmus will be directed away from the lesion. In a study that evaluated the clinical signs of peripheral and central vestibular disease, it was found that peripheral vestibular disease was associated with a faster rate of spontaneous nystagmus than central vestibular disease [4].

Patients with peripheral vestibular disease may exhibit ipsilateral CN VII (facial nerve) deficits and/or ipsilateral Horner's syndrome due to the close anatomical relationship of these nerves with CN VIII in the inner ear.

Postural Reactions

The patient should have normal strength and postural reactions (knuckling and hopping responses).

Central Vestibular Disease

Mentation

Patients with central vestibular disease often have concurrent damage to the ascending reticular activating system (ARAS), which can lead to decreased levels of consciousness. They may appear dull, obtunded, stuporous, or comatose.

Gait/Posture

Patients with central vestibular disease may exhibit a head tilt towards the lesion.

Vestibular ataxia, with the patient listing, leaning, and falling towards the side of the lesion, is often seen with central vestibular disease. If the patient has a lesion that is also impacting the cerebellum, cerebellar ataxia may also be noted. Cerebellar ataxia is characterized by hypermetria and exaggerated stepping movements. The patient may also exhibit truncal sway (titubation), and intentional tremor. Ipsilateral hemiparesis may also be present.

Circling or rolling will occur towards the lesion in central vestibular disease.

Cranial Nerves

Patients with central vestibular disease can exhibit pathological nystagmus that is horizontal, rotary or vertical in nature. The fast phase of the nystagmus should be away from the lesion. The nystagmus may also be positional, changing in character or appearing only after a change in head and/or body position (i.e. rolling the patient onto his or her back or elevating the head).

Central vestibular disease may be accompanied by ipsilateral deficits in CN V–XII. Horner's syndrome, due to disruption of the preganglionic segments, is possible but uncommon with central vestibular disease.

Postural Reactions

Patients with central vestibular disease often exhibit postural reaction deficits ipsilateral to the lesion. These deficits are typically accompanied by ipsilateral hemiparesis. The presence of postural reaction deficits and paresis helps localize a patient to the central vestibular system, but their absence does not rule out central vestibular disease.

Paradoxical Vestibular Disease

Paradoxical vestibular disease, caused by a lesion impacting on the cerebellopontine angle, is a subset of central vestibular disease. Because the cerebellum's influence on the vestibular system is largely inhibitory, lesions in this location cause vestibular release that is interpreted as a contralateral deficit. This results in clinical signs that are consistent with a lesion on the opposite side (i.e. a right-sided paradoxical vestibular lesions will result in clinical signs consistent with a lesion on the left). This can be misleading, however additional cranial nerve deficits, and postural reaction deficits will remain ipsilateral to the lesion.

Mentation

Because this is a central disease, patients with paradoxical vestibular disease may have an altered level of consciousness due to disruption of the ARAS.

Gait/Posture

Patients with paradoxical vestibular disease will exhibit a head tilt *away* from the lesion.

Vestibular ataxia, with the patient listing, leaning, and falling *away* from the lesion, can be seen with paradoxical vestibular disease. It is common to see an associated cerebellar ataxia with lesions of the pontomedullary angle.

Circling will occur *away* from the lesion in paradoxical vestibular disease.

Cranial Nerves

Patients with paradoxical vestibular disease will exhibit pathological nystagmus with the fast phase directed *towards* the lesion. The nystagmus can be horizontal, rotary, or vertical, and it may have a positional component.

Paradoxical vestibular disease may be accompanied by ipsilateral deficits in CN V–XII. Horner's syndrome, due to disruption of the preganglionic segments, is possible but uncommon.

Postural Reactions

Patients with paradoxical vestibular disease exhibit postural reaction deficits ipsilateral to the lesion. These deficits are typically accompanied by ipsilateral paresis. The postural reaction deficits will be opposite the head tilt and nystagmus.

Bilateral Peripheral Vestibular Disease

Bilateral peripheral vestibular disease is an uncommon presentation, but is seen more frequently in cats than in dogs.

Mentation

Mentation should be normal; disorientation can occur with an acute onset of clinical signs.

Gait/Posture

Patients with bilateral peripheral vestibular disease typically appear crouched and remain close to the ground. The ataxia is more symmetrical and patients may fall and list to either side. Patients often exhibit characteristic wide head excursions from side to side.

Cranial Nerves

Bilateral peripheral vestibular disease results in complete loss of vestibular function, so a head tilt and pathological nystagmus are absent. Physiological nystagmus, or the oculocephalic reflex, allows for tracking of objects in the visual field when the head is moved. The head is rotated in a horizontal plane and the eyes are evaluated for a series of fast and slow eye movements – saccades. The fast saccade will be in the direction of the head movement. With bilateral peripheral vestibular disease, this reflex will be absent. Patients with bilateral peripheral vestibular disease may exhibit concurrent CN VII deficits and/or Horner's syndrome.

Postural Reactions

Postural reactions and strength should be normal.

Common Causes of Vestibular Disease

(Table 23.2)

Peripheral Vestibular Disease

Otitis Media/Interna

Otitis media/interna is the most common cause of peripheral vestibular disease in dogs [5]. Patients may present with concurrent CN VII deficits and/or Horner's syndrome due to the close anatomical relationship of these structures [1]. Common pathogens include *Staphylococcus* spp, *Pseudomonas aeruginosa*, beta-hemolytic streptococcus, *Proteus* spp, and *Escherichia coli* [6]. *Cryptococcus neoformans* has been isolated from the tympanic bulla in cats with otitis media/interna [7].

Otitis media/interna can often be diagnosed via otoscopic examination. An intact tympanic membrane does not rule out otitis media/interna [8,9]. Advanced imaging such as CT or MRI may be indicated to evaluate the inner ear, and rule out intracranial extension, neoplasia, nasopharyngeal polyps, or foreign bodies [10]. A myringotomy can be performed to obtain samples for cytology, as well as culture and sensitivity.

Table 23.1 Clinical signs associated with peripheral and central vestibular disease.

Clinical sign	Peripheral vestibular disease	Central vestibular disease	Paradoxical vestibular disease
Mentation	Normal, may appear disoriented	Normal to comatose	Normal to comatose
Gait/posture			
Head tilt	Towards lesion	Towards lesion	Away from lesion
Ataxia	Vestibular ataxia	Vestibular ataxia +/- cerebellar ataxia	Vestibular ataxia +/- cerebellar ataxia
Circling	Towards lesion	Towards lesion	Away from lesion
Weakness	Absent	Ipsilateral to lesion	Ipsilateral to lesion
Cranial nerves			
Nystagmus direction	FP away from lesion	FP away from lesion	FP towards lesion
Nystagmus character	Horizontal, rotary, rarely vertical	Horizontal, rotary, or vertical; may see positional changes	Horizontal, rotary, or vertical; may see positional changes
Concurrent CN deficits	Ipsilateral CN VII, Horner's syndrome	Ipsilateral CN V–XII	Ipsilateral CN V–XII
Postural reactions	Normal	Deficits ipsilateral to lesion	Deficits ipsilateral to lesion
Spinal reflexes	Normal	Normal	Normal
Palpation	Ear/facial pain	Possible neck pain	Possible neck pain

CN, cranial nerve; FP, fast phase.

Therapy consists of a combination of cleansing and flushing the ear, topical medications, and systemic antibiotics for at least 6–8 weeks [11]. Ideally, antibiotic therapy should be based on culture and sensitivity results, as antibiotic resistance is common [12]. Empirical antibiotics may include amoxicillin/clavulanic acid, cephalosporins, or fluoroquinolones. Chronic relapsing otitis media/interna, or cases with suspected intracranial extension, may require a bulla osteotomy and possibly a total ear canal ablation [13,14].

Nasopharyngeal Polyps, Inflammatory Polyps

Nasopharyngeal polyps are the most common benign pharyngeal and external ear canal masses diagnosed in cats [15,16]. Patients are typically young cats presenting with vestibular signs as well as chronic upper respiratory, pharyngeal, or ear infections [17]. Nasopharyngeal polyps can be diagnosed via otoscopic or oropharyngeal examination, but advanced imaging may be required. Traction can be used to remove most polyps, with a recurrence rate of approximately 30% [15]. In cases with significant middle ear involvement, or recurrent polyps, a ventral bulla osteotomy can be performed. This surgery is associated with a lower recurrence rate, less than 10%, but a higher rate of complications [17,18].

Nasopharyngeal polyps have also been reported in dogs [19,20].

Toxins

Peripheral vestibular disease and hearing loss can be associated with the use of ototoxic drugs including aminoglycosides, cisplatin, loop diuretics, chlorhexidine, erythromycin, chloramphenicol, and minocycline. Patients can compensate for vestibular dysfunction over time but hearing loss is often permanent if it occurs [21–23].

Vestibular signs have been reported in cats after ingestion of five-lined skinks in the south-eastern US [24].

Hypothyroidism

Hypothyroidism can present with clinical signs of peripheral or central vestibular disease. Peripheral vestibular disease can be accompanied by CN VII dysfunction. This syndrome is poorly understood, but clinical signs may be secondary to myxomatous compression of the nerves. The diagnosis is based on low total thyroxine (TT4), low free thyroxine (FT4), and high thyroid-stimulating hormone (TSH) levels. Improvement can occur with thyroid hormone supplementation [2,25–27].

Idiopathic Vestibular Disease

Idiopathic vestibular disease is the second most common cause of peripheral vestibular disease [5]. In dogs, it is also called “old dog vestibular disease” or “geriatric vestibular disease.” Patients demonstrate an acute onset

of peripheral vestibular signs without additional neurological deficits. The median age of canine patients with idiopathic vestibular disease is 12.5 years [5,28].

Idiopathic vestibular disease in cats, by contrast, is seen most frequently in outdoor cats, and is not restricted to geriatric animals. There is a higher incidence of feline idiopathic vestibular disease in the late summer and early fall. This disease can present as unilateral or bilateral peripheral disease without additional neurological deficits [29,30].

The diagnosis of idiopathic vestibular disease is one of exclusion. There is no specific therapy for this disease. After 3–5 days, most patients will begin to show signs of improvement, with resolution occurring over 2–4 weeks. It is common for patients to have a residual head tilt and/or mild ataxia. Idiopathic vestibular disease can relapse.

Polyneuropathy

An idiopathic polyneuropathy impacting CN VIII and VII has also been reported in cats and dogs [31–34]. In a case series of 16 dogs with idiopathic facial and vestibular neuropathy, only 31% had a complete recovery and 15% relapsed [34].

Neoplasia

Neoplasia can arise from, or secondarily invade, the tympanic bulla, leading to peripheral vestibular disease. Common primary aural neoplasias include squamous cell carcinoma, sebaceous gland adenocarcinoma, and ceruminous gland adenocarcinoma [17,35,36]. Middle ear angiocentric/angioinvasive T-cell lymphoma has been described in a cat [37].

Cholesteatomas are benign masses arising in the middle ear [17,38,39]. Early surgical treatment of cholesteatomas can be curative. Patients with more advanced disease and those presenting with vestibular signs or pain with opening of the mouth may have a more guarded prognosis [38].

Central Vestibular Disease

Strokes and Vascular Events

Vascular events, including transient ischemic attacks (TIAs) and ischemic or hemorrhagic strokes, are a common cause of central vestibular signs. TIAs are caused by a temporary vascular disruption and result in short-term neurological signs (less than 24 hours). TIAs can be recurring [40,41].

Strokes within the rostral cerebellar artery or the thalamus can result in central vestibular signs [42,43]. Typically, patients will present with a peracute non-progressive onset of central (or paradoxical) vestibular signs. The diagnosis can be made based on typical MRI findings of ischemia or hemorrhage restricted to a vascular territory [44,45]. Patients should be screened for hypertension, underlying cardiac or renal disease, coagulopathies, hypothyroidism, hyperadrenocorticism, and underlying

Table 23.2 Differentials for peripheral and central vestibular disease.

Etiology	Peripheral vestibular	Central vestibular
Vascular		Stroke (ischemic or hemorrhagic) TIA Feline ischemic encephalopathy
Infectious	Otitis media/interna	Viral Bacterial Rickettsial Protozoal Fungal
Inflammatory	Nasopharyngeal polyp	MUE
Trauma	Iatrogenic: ear flush, bulla surgery Bulla fracture	Head trauma
Toxin	Aminoglycosides Cisplatin Loop diuretics Chlorhexidine Erythromycin Chloramphenicol Minocycline Five-lined skink exposure	Metronidazole Lead Ivermectin
Anomalous	Congenital vestibular disease Congenital pendular nystagmus	Hydrocephalus Intracranial intra-arachnoid cysts
Metabolic	Hypothyroidism	Hypothyroidism Thiamine deficiency
Idiopathic	Idiopathic vestibular disease Polyneuropathy	
Neoplasia	Primary aural neoplasia: squamous cell carcinoma, ceruminous gland adenocarcinoma, sebaceous gland adenocarcinoma Neurofibrosarcoma Cholesteatoma	Primary intracranial neoplasia: meningioma, gliomas, lymphoma, choroid plexus tumors Metastatic neoplasia: hemangiosarcoma, lymphoma, metastatic carcinoma
Degenerative		Lysosomal storage diseases Cerebellar cortical abiotrophy

MUE, meningoencephalitis of unknown etiology; TIA, transient ischemic attack.

neoplasia [45]. Greyhounds and spaniels may be predisposed to strokes [42,44]. Many patients with strokes can make a functional recovery with adequate supportive care and time. In one study, patients with concurrent medical conditions had shorter survival times and a higher rate of subsequent strokes [45].

Meningoencephalitis

Meningoencephalitis frequently causes central vestibular signs. These diseases are diagnosed using a combination of MRI, CSF analysis, and appropriate infectious disease testing based on geographic region and travel history.

Infectious diseases that can cause central vestibular signs include the following.

- Viral meningoencephalitis: canine distemper virus [46,47], feline infectious peritonitis [48,49], rabies [50].
- Bacterial meningoencephalitis: otogenic infections [13,14], septic meningitis, penetrating trauma [51].
- Rickettsial meningoencephalitis: Rocky Mountain spotted fever [52], ehrlichiosis [53].
- Protozoal meningoencephalitis: neosporosis [54,55], toxoplasmosis [29].
- Fungal meningoencephalitis: cryptococcosis [56], blastomycosis [57,58], aspergillosis [59], coccidioidomycosis [60], pheohyphomycosis [61–65], fusariosis [66], histoplasmosis [67].

Treatment should consist of long-term antibiotics or antifungals based on the suspected or confirmed organisms.

Meningoencephalitis of unknown etiology (MUE) is a clinical diagnosis that encompasses granulomatous meningoencephalitis (GME), necrotizing leukoencephalitis (NLE), and necrotizing meningoencephalitis (NME). A definitive differentiation of these diseases requires histopathology. Eosinophilic meningitis can also cause vestibular disease, but it has distinct CSF findings that differentiate it from MUE. Diagnosis of MUE requires compatible MRI and CSF analysis results with negative infectious disease testing. Treatment consists of long-term immunosuppression using a combination of corticosteroids and immunomodulators. A more thorough discussion of pathophysiology and treatment options can be found elsewhere [68–70].

Toxins

Metronidazole toxicity is typically noted at doses higher than 60 mg/kg/day, but individual sensitivity, hepatic insufficiency, and chronic administration may contribute to toxicity at lower doses. Neurological signs of metronidazole toxicity in dogs include head tilt, nystagmus (typically vertical), ataxia, paresis, and tremors [71,72]. Cats tend to present with disorientation, seizures, and blindness [73,74]. Treatment of metronidazole toxicity primarily consists of supportive care and drug withdrawal. Administration of diazepam (0.5 mg/kg IV, then 0.5 mg/kg orally every 8 hours for 3 days) has been associated with a more rapid recovery [75].

Hypothyroidism

Central vestibular signs have been associated with concurrent hypothyroidism in several studies [26,45,76]. The pathogenesis is not well understood, but hyperlipidemia and associated atherosclerosis, increased blood viscosity, and thromboembolic events have been postulated

[26,76,77]. The diagnosis is based on low TT4, low FT4, and high TSH levels. Improvement has been reported after thyroid hormone supplementation.

Thiamine Deficiency

Central vestibular signs have been reported in dogs and cats with thiamine (vitamin B1) deficiencies [78–81]. Vestibular signs are followed by bilateral mydriasis, blindness, and seizures. Thiamine deficiency has been associated with fish diets high in thiaminase, prolonged anorexia, and incorrectly formulated diets. It has also been reported in cats fed commercial diets that were adequately formulated [79]. MRI evaluation will reveal characteristic lesions within the midbrain and brainstem, which have been demonstrated to resolve with thiamine supplementation [80,81]. The prognosis for recovery can be good with early treatment and supportive care.

Neoplasia

Central vestibular disease can be caused by primary or metastatic neoplasia. Common primary intracranial neoplasias include meningiomas, astrocytomas, oligodendrogliomas, choroid plexus tumors, and primary central nervous system lymphosarcoma [82,83]. The most common metastatic neoplasia in the brain is hemangiosarcoma, followed by lymphosarcoma, and metastatic carcinomas [84]. In one study, boxers, Boston terriers, golden retrievers, French bulldogs, and rat terriers had a significantly increased risk of primary intracranial neoplasia, while cocker spaniels and Doberman pinschers had a significantly decreased risk [85].

Diagnostics

For all patients with vestibular disease, a thorough history is imperative, with particular attention to toxin exposure, diet history, medications, and concurrent medical conditions. A minimum database should be performed, consisting of a complete blood count (CBC), serum chemistry, thyroid panel, and a urinalysis. The results of the neurological examination will help guide additional diagnostics.

Patients with peripheral disease should be screened for otitis media/interna via otoscopic examination. The presence of an intact tympanic membrane does not rule out otitis media/interna. Bulla radiographs can be performed, but CT and MRI are more sensitive and specific for bulla changes and soft tissue changes [86]. Patients presenting with concurrent facial weakness (CN VII) should have a Schirmer tear test performed to screen for neurogenic keratoconjunctivitis sicca.

Patients presenting with central vestibular disease will require advanced imaging (CT or MRI) for a definitive

diagnosis. MRI is the preferred imaging modality for the caudal fossa as it will provide superior soft tissue detail compared to CT. Thoracic radiographs and an abdominal ultrasound can be performed prior to advanced imaging to screen for concurrent diseases and/or metas-

tasis. In one study of patients with primary intracranial neoplasia, 23% of the patients had unrelated neoplasia in the thorax and/or abdomen [82]. In cases of suspected meningoencephalitis, neoplasia, or vascular events, CSF analysis and infectious disease testing can be performed.

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24

Spinal Trauma

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Causes

Spinal cord injury (SCI) is commonly encountered in small animal veterinary practice; it may be caused by external trauma – road traffic accidents, falls, dogfight injuries, gunshot injuries, etc. [1–3] – or by “internal trauma” such as intervertebral disc herniation (IVDH), acute non-compressive nucleus pulposus extrusion (ANNPE), and fibrocartilagenous embolism (FCE). Vertebral fracture/luxations (VFL) may be caused by substantial external trauma or minor traumas in animals with pre-existing vertebral pathology (such as pathological fracture secondary to osteopenia [4], neoplasia [5], or infection [6]). Certain vertebral malformations [7] (e.g. atlantoaxial malformations) may also predispose to SCI.

This chapter will predominantly cover SCI due to external trauma, though the pathophysiology and principles of management of SCI by all causes are, with few exceptions, very similar.

Pathophysiology

Spinal cord injury occurs by two mechanisms. *Primary injury* results from the initial traumatic compressive force exerted on the spinal cord, causing contusion, hematoma formation, compression and/or laceration of spinal cord parenchyma, and, at the cellular level, mechanical disruption of cell membranes, axons, and blood vessels [8]. Clinicians have no influence over the initial primary injury – it has already happened. They may, however, have some control over the potential for further primary injury, if ongoing compression or instability of the vertebral column is present [9].

The primary injury initiates mechanisms of *secondary injury*, a deleterious cascade of vascular, biochemical, and inflammatory events that perpetuate and expand

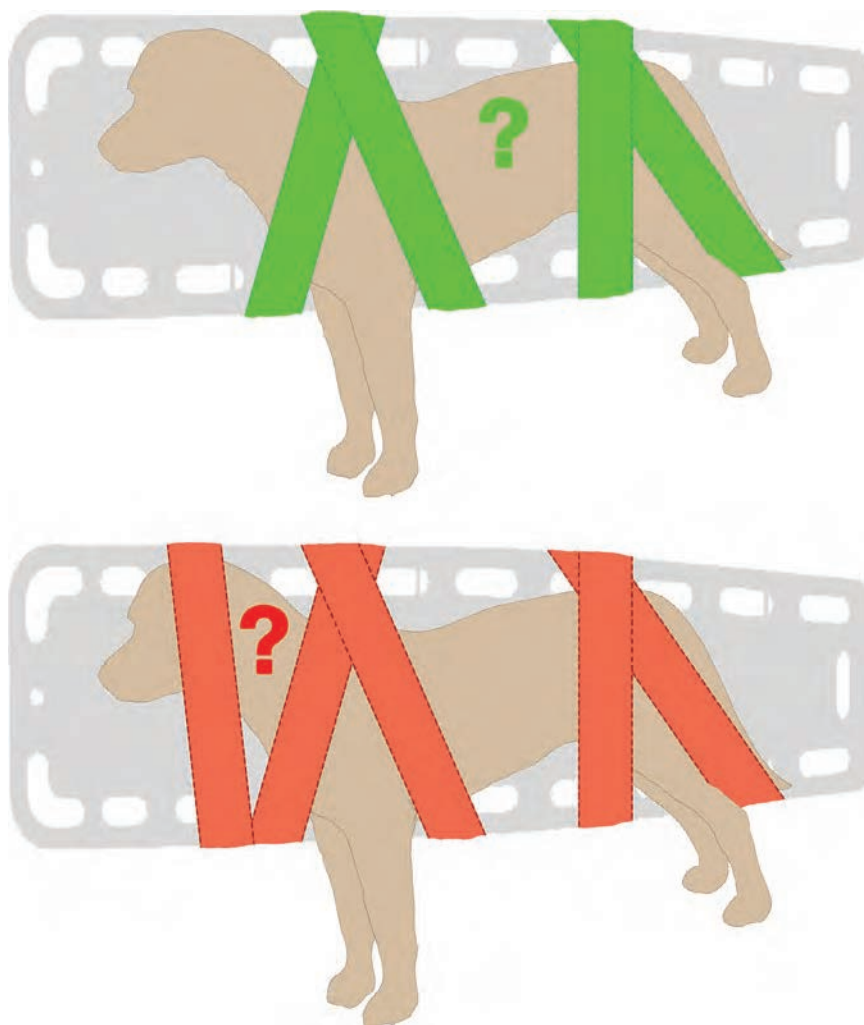
the zone of tissue destruction [10]. Important factors in the progression of secondary injury include tissue hypoperfusion [11], ionic disturbances and excitotoxicity [12], free radical-induced membrane damage [13], and inflammation [14]. Perfusion of the normal spinal cord is tightly regulated; this autoregulation is lost after injury [15]. Secondary mechanisms damage endothelial membranes, induce vasospasm, and through increased interstitial pressure (caused by vasogenic and cytotoxic edema) further limit spinal cord perfusion [11]. Perfusion of the injured spinal cord is closely linked with outcome [11]. Systemic hypoperfusion coupled with loss of autoregulation can worsen spinal cord perfusion, and therefore outcome [10].

Initial Approach

Animals that have suffered trauma sufficient to cause SCI often have injuries to other body systems, which may be more immediately threatening to life. As with any trauma patient, a primary survey assessing airway, breathing, and circulatory status should be rapidly performed on arrival and stabilizing interventions made as necessary [16] (see Chapter 2).

A brief history of what happened should be obtained. The possibility of spinal instability should be recognized early, so that patient handling can be appropriate. Movement of an unstable spine may cause further, potentially irreversible spinal cord injury. *If the history or patient examination leads to any suspicion of spinal instability, the animal should be immobilized in lateral recumbency.* Figure 24.1 demonstrates how such a patient should be secured (usually with tape or straps) to a rigid board. Radiolucent spinal boards are commercially available, though any rigid board of reasonable size and material can be used. Exceptions should only be made for animals

Figure 24.1 How to immobilize a patient with suspected spinal instability. The animal should be strapped down in lateral recumbency to a rigid board. If instability of the thoracolumbar spine is suspected, the animal should be strapped cranial and caudal to the shoulder and the hip (green). If instability of the cervical spine is suspected, the head should also be strapped down (red).



that will not tolerate restraint without the likelihood of further harm by struggling against restraint (e.g. many cats); in these cases, a box or carrier may suffice.

Hypoxemia and hypotension/hypoperfusion should be recognized and corrected immediately; supplemental oxygen should be administered in all cases, and hypovolemic patients should receive appropriate fluid resuscitation (see Chapter 153).

Analgesia should not be given before assessing deep pain perception (DPP) of the limbs and tail. Testing DPP is quick to perform (see below). The presence or absence of DPP is the main prognostic indicator for recovery. An animal with this function intact may not behaviorally respond to stimulation if they have been given analgesic drugs, in which case they may be given a falsely poor prognosis (which is often a trigger for euthanasia). (Note: Additionally, animals in hypovolemic shock may not respond to pain stimuli until the shock is corrected.)

Once the patient is stable, a secondary survey consisting of thorough physical and neurological examinations and a minimum laboratory database should be performed, including packed cell volume (PCV), total protein (TP), blood glucose (BG), and ideally electrolytes and blood gases. Blood should also be collected for a complete blood count (CBC) and serum biochemistry as blunt forces sufficient to cause spinal injury often cause trauma to other body systems.

A more thorough history of the trauma itself and the general health of the patient should also be obtained. If the traumatic incident and/or immediate aftermath was observed, questioning any witnesses as to the level of function after injury can be particularly useful as the neurological examination may need to be limited while the patient is immobilized. For example: Was the animal able to walk? Was there an immediate or progressive loss of function? What limbs appeared to be affected?

Neurological Assessment

Despite the imperative to examine these patients while immobilized in lateral recumbency, a comprehensive neurological examination can still be performed. The following should be assessed in all patients.

- Mentation
- Cranial nerve function
- Voluntary motor function
- Spinal reflexes
- Nociception

Obviously, gait and postural reactions cannot be assessed in the recumbent patient. Voluntary limb and tail movement may be observed as good, diminished (paresis; an incomplete loss of voluntary motor function) or absent (plegia; a complete loss of voluntary motor function [17]). While the vertebral column should not be moved or manipulated, it may be *gently palpated* and the alignment of spinous processes assessed, misalignment being suggestive of VFL. Focal regions of apparent pain may be useful in identifying sites of injury, though firm or deep palpation should be avoided as it may move a VFL site. For a description of the neurological examination in full, the reader is referred to other texts [18,19].

Localizing spinal cord lesions

Anatomically, the spinal cord consists of gray matter centrally (containing the lower motor neuron (LMN) cell bodies) and white matter superficially (containing the axons of the upper motor neurons (UMN)). Reflexes test the LMNs directly; a lesion in this reflex arc will cause decreased reflexes and decreased muscle tone ("LMN signs"). The UMNs are both facilitatory and inhibitory to this arc, the net effect being an inhibition of reflexive and muscle tone. UMN function is not tested directly; it is implied by the presence of paresis and an intact reflex arc (normal to increased reflexes and normal to increased tone – "UMN signs").

Spinal cord lesions are classically localized as follows.

- Tetraparesis with normal to increased reflexes and tone (UMN signs) in all limbs suggest a *C1–C5 myelopathy*.
- Tetraparesis with decreased to absent reflexes and tone (LMN signs) in the thoracic limbs, and normal to increased reflexes and tone (UMN signs) in the pelvic limbs suggest a *C6–T2 myelopathy*.
- Paraparesis with normal to increased reflexes and tone (UMN signs) in the pelvic limbs suggest a *T3–L3 myelopathy*.
- Paraparesis with decreased to absent reflexes and tone (LMN signs) in the pelvic limbs suggest an *L4–S3 myelopathy*.

Peracute SCI (as results from trauma) will often produce findings that confound the classic model.

The first potentially confounding finding is the *Schiff–Sherrington posture*. This occurs with damage to "border cells" in the thoracolumbar spinal cord segments that normally ascend to inhibit thoracic limb extensor tone [20]. The result is rigid extension of the thoracic limbs. This may be misinterpreted as indicating a C1–C5 lesion, but proprioception and nociception of the thoracic limbs will be intact, and movement attenuated only by the increased extensor tone. Animals with this posture are usually paraplegic. The presence or absence of this finding does not affect prognosis [21].

The second potentially confounding finding is *spinal shock*. Spinal shock is the loss of muscle tone and spinal reflexes caudal to the site of peracute SCI, even though the reflex arcs are physically intact [22]. In dogs and cats, this phenomenon is much shorter lived than in humans, with reflexes returning within hours (up to 2 h for patellar reflexes and 12 h for flexor reflexes) as opposed to days to weeks [23]. The initial hyporeflexia may be interpreted as a LMN sign, when the lesion is in fact of the UMNs innervating that limb.

If the spinal cord has been injured at multiple locations, LMN signs will mask the presence of an UMN lesion, as UMN function is evaluated using the LMN reflex arc. As such, imaging the entire vertebral column is advisable in all cases. Neuroanatomically unconnected reflex deficits may be detected (such as pelvic limb reflex deficits and a cranial cutaneous trunci reflex cut-off), signaling distinct lesions.

Damage to sacral or caudal nerves after injury to the sacrum or tail may cause perineal, bladder, rectal and/or tail dysfunction [24].

Severity and Prognostication

Prognosis for recovery from SCI depends on both the diagnosis (the inciting cause) and the severity of dysfunction.

Function is lost after SCI in the following order [25] (and generally regained in reverse order).

1. Proprioception: loss is seen clinically as postural reaction deficits and ataxia.
2. Motor function: loss is seen clinically as paresis or paralysis.
3. Autonomic function: loss is seen clinically as urinary and fecal incontinence (loss generally occurs at a similar time as loss of motor function).
4. Nociception (pain sensation): loss is seen clinically as an absent behavioral response to noxious/painful stimuli.

Nociception has classically been categorized into superficial and deep pain [18]. Superficial pain (likely

analogous to fast or pinprick pain) is sharp, well localized and originates in the skin. Deep pain (slow or true pain) is a duller aching pain that is poorly localized and originates from deeper structures. Deep pain perception is most reliably tested in animals using hemostats or pliers on the periosteum of the nail bed or digit/tail. It is likely transmitted in the ascending reticular formation of the spinal cord [26]; the diffuse nature of this network of neurons makes it resilient in the face of damage, and therefore the last function to be apparently lost (i.e. the last testable function).

It is important to note that limb withdrawal does not mean intact nociception. If the reflex arc is intact, the limb will withdraw, even in the case of complete spinal cord transection. The animal *must* show a behavioral response (whine, growl, turn head, turn to bite, vocalize, etc.). A behavioral response demonstrates that the impulse has traversed the site of spinal cord injury to reach the brain, where it is perceived as a noxious stimulus. Tail sensation should be tested as well as limbs.

Several grading schemes for the clinical severity of SCI are available [25]; an example of a commonly used grading system is given in Table 24.1. It may be difficult to distinguish between grades if the patient is immobilized, but nociception is readily testable and the most important distinction to make.

The presence or absence of DPP is the most important prognostic indicator for neurological recovery; hence analgesia (which may confound this assessment) should not be administered prior to testing. The majority of patients with SCI (due to IVDH [30], FCE [31,32], ANNPE [33], and VFL [1,34]) with intact DPP that are treated appropriately will return to ambulation. If DPP is lost, then the prognosis for return of function is worse, and particularly poor in cases of trauma [35,36]. In one study, 58% of DPP-negative dogs with IVDH treated surgically regained DPP and returned to ambulation, whereas none of the DPP-negative dogs with spinal trauma regained DPP or full urinary and fecal continence, and only 12% returned to ambulation [37]. The nature and severity of other injuries may also affect overall prognosis.

Table 24.1 A grading scheme for severity of spinal cord injury [27–29].

Grade	Severity of dysfunction
1	No deficits/pain only
2	Paresis and ataxia (ambulatory)
3	Paresis and ataxia (non-ambulatory)
4	Plegia
5	Plegia with loss of deep pain perception

Diagnosis

History, signalment, and physical examination can be greatly informative and useful in ranking a list of the most likely causes of SCI [38]. Diagnosis requires spinal imaging of some form; the patient should remain immobilized on the spinal board throughout.

Radiography

Survey spinal radiographs will identify the majority of VFLs, but are insufficiently sensitive to rule one out [39], so further imaging should be considered in all cases where there is a high index of suspicion for VFL. The whole vertebral column should be imaged, as multiple vertebral fractures are common [40,41].

While orthogonal radiographic views of the spine may be diagnostically useful, the patient *should not* be turned into dorsal recumbency to obtain ventrodorsal views, as this may cause further injury to the spinal cord. A ventrodorsal projection may be safely obtained in lateral recumbency using a horizontal beam.

Survey radiographs should ideally be performed with the patient conscious, as heavy sedation or anesthesia will reduce paraspinal muscle tone, increasing spinal mobility (and possibly instability).

It is important to note that radiographs do not prognosticate; prognosis should be based on the neurological examination, specifically the presence or absence of DPP. If referral to a center better equipped to diagnose and manage VFLs is a feasible and desired option, and radiographic findings are unlikely to change that plan, then early referral without survey radiographs should be considered as a better use of time and owner finances.

Myelography

Myelography may show spinal cord swelling or compression, but will provide limited additional information regarding fractures or luxations over survey radiography [42]. Myelography requires general anesthesia, and performing a myelogram may involve some manipulation of the patient. Epidural contrast may also make interpretation difficult.

Computed Tomography

Computed tomography (CT) is the gold standard imaging modality used in screening for spinal trauma in humans [43]. Excellent bone detail makes it highly sensitive for detecting fractures. The thorax, abdomen or other body parts can also be assessed rapidly for evidence of trauma. Relatively quick acquisition times for modern CT scanners enable these studies to be performed under

sedation. As cross-sectional images are acquired, no turning of the patient is necessary to obtain other projections. Multiplanar and three-dimensional reconstructions may be diagnostically useful and are often invaluable for surgical planning.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) offers excellent contrast resolution of the soft tissues, which may yield useful information on the location and extent of damage to supportive soft tissue structures of the vertebral column, as well as direct visualization of the spinal cord itself [44]. Other causes of acute myelopathy such as IVDH, FCE, ANNPE, meningomyelitis, and spinal neoplasia are all readily identified using MRI. Imaging of bone is relatively poor compared to CT, as is spatial resolution if thick slices are used. Scan times are relatively long, necessitating general anesthesia. For these reasons, a CT scan would be the preferred option in most cases of suspected or confirmed spinal trauma.

Treatment of Spinal Cord Injury

Treatment of SCI should initially be directed at both preventing ongoing primary injury and minimizing the development and progression of secondary mechanisms of injury. Good nursing care and a rehabilitation plan are crucial over the medium to longer term.

Management of Secondary Spinal Cord Injury

Management of secondary injury is mentioned here first, as it is appropriate in all cases of SCI (regardless of cause) and can be started before treatments that address the ongoing primary injury. The principal aim of therapy is to maintain spinal cord perfusion by avoiding hypoxemia and hypotension, which are strongly correlated with poor neurological outcomes [11].

While many medical therapies for the acute phase of SCI have been [45] and continue to be investigated [46], none has proven more consistently beneficial than avoiding hypotension. Maintaining blood pressure targets (mean BP > 90 mmHg) during the acute phase of injury reduces mortality and improves neurological recovery in human SCI patients [47].

Cervical SCI may cause paresis of the thoracic wall muscles and diaphragm, and lead to hypoventilation. Mechanical ventilation should be considered if the PaCO₂ is ≥ 60 mmHg [48].

Glucocorticoids should not be administered to patients with SCI. Methylprednisolone sodium succinate (MPSS) is no longer recommended for human

SCI as there is poor evidence for a clinical benefit and good evidence of association with harmful side-effects (including death) [49]. Methylprednisolone sodium succinate has not been shown to improve outcome in dogs with SCI due to IVDH [50]. Similarly, no difference in neurological outcome has been seen in dogs given dexamethasone after SCI due to IVDH, while dexamethasone administration greatly increases the likelihood of adverse events, such as urinary tract infections and diarrhea [51].

Management of Primary Spinal Cord Injury

Although the initial primary injury is beyond the control of the clinician, ongoing instability and spinal cord compression may be addressed. Appropriate treatment options (surgical or non-surgical) depend on anatomical factors such as which structures have failed, the level of the spine affected, and the size of the patient [36,52].

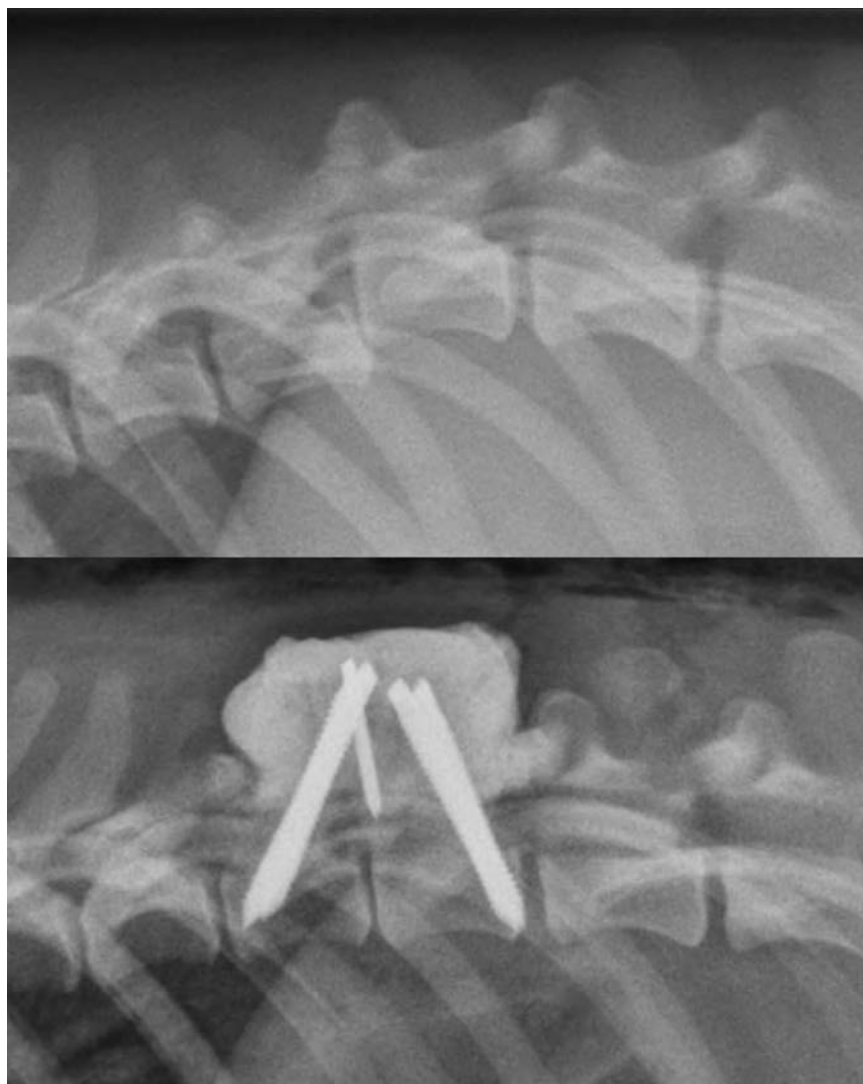
Surgical Management (Figure 24.2)

The primary aims of surgical management of VFL are to stabilize the vertebral column and decompress the spinal cord [52]. The vertebral column should be realigned as best as possible without further trauma to the cord. As all forces acting at the site of the VFL should be neutralized, unstable segments are generally best treated by surgical fixation. The ideal implant type and arrangement depend on the location and configuration of the VFL, and on patient size. Method of fixation may also depend on surgeon preference [52]. Even though the biological rationale for early decompression must be balanced with the survival of the patient if they have sustained other life-threatening injuries, prompt referral to a spinal surgeon should be considered. Early decompression (<24 h post injury) is increasingly advocated in humans with traumatic SCI [9] as prompt decompression improves neurological outcomes [53,54].

Non-Surgical Management

Certain fractures may be managed non-surgically with either strict cage-rest or external coaptation [36,55,56]. Effective casts, splints or bandages may be difficult to apply, and if bulky are often uncomfortable and not well tolerated by many patients. The ability to perform adequate physiotherapy and rehabilitation is also frequently impaired. Moreover, choosing external coaptation to avoid the cost of surgery can be a false economy, as the costs of bandage/cast changes and frequently encountered cast-associated complications add up over time. Recovery time (to optimum function) is usually longer for non-surgically treated dogs when compared to surgically treated dogs [1].

Figure 24.2 The aims of surgical management of vertebral fracture/luxation are to stabilize the vertebral column and decompress the spinal cord. This dog had intact nociception despite the degree of vertebral displacement seen on survey radiographs.



Nursing, Rehabilitation, and Ongoing Care

The intensity of nursing care and rehabilitation a SCI patient needs is largely dependent on their level of dysfunction. Manual emptying of the bladder is required for incontinent patients, in whom urinary tract infections are common [57–59]. Recumbent animals should be

inspected regularly for early evidence of decubitus ulceration, which is best prevented by well-padded bedding, frequent turning and getting the patient up and moving, using hoists or slings if necessary. A physiotherapy program should be tailored to the individual. Patients with a good prognosis for return of function may take several months to reach optimum recovery.

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25

Intervertebral Disk Disease

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Introduction

Intervertebral disk disease (IVDD) is the term for degeneration and either protrusion or extrusion of the intervertebral disk that causes compression or contusion of the spinal cord or nerve roots. As such, it is the most common small animal spinal column disease seen in emergency rooms.

Several large-scale studies have looked at the epidemiology of disk disease in dogs and found a rate of 23 new cases of IVDD per 1000 dogs per year [1]. Dachshunds accounted for 65% of the cases, peak incidence occurred at 5 years of age, and 73% of the patients presented from 3 to 6 years of age [2]. An evaluation of 536 dachshunds and their pedigrees found a prevalence of 19% but no pattern of inheritance [3]. The most recent large-scale study identified dogs with IVDD from insurance claims and found the prevalence to be 3.5% and mortality rate was 1%. Dachshunds continue to have a lifetime prevalence of 20% [4].

The estimates of prevalence of IVDD in cats vary from 0.02% to 0.12% [5]. Evaluation of antemortem data from 88 cats with clinical signs referable to the spinal column showed 6% (five cats) had a cervical localization, 52% (46 cats) had a thoracolumbar localization, and 42% (37 cats) had a L4–S3 localization [5].

Applied Anatomy

The intervertebral disk functions to provide flexibility to the spine and also shock absorption and is composed of two regions: a collagen-rich outer ring or annulus fibrosus (AF) and a gelatinous inner portion rich in proteoglycans, the nucleus pulposus (NP). In the dog and cat, disks are present between each of the vertebrae except the atlas and axis and the three sacral vertebrae, which are fused.

The NP is composed of about 80% water, allowing it to serve as a hydraulic cushion. Water is attracted to the NP by negatively charged proteoglycans which are composed of glycosaminoglycan (GAG) side chains. Unorganized type II collagen fibers are interspersed within the NP and trap the GAG chains. When compressive forces occur, the nucleus transmits the force to the AF which is composed of type I collagen strands and elastic fibers in bundles called fibrils. The fibrils layer together at varying angles to allow forces to dissipate. The annulus is thickest ventrally, about 2–3 times the dorsal thickness. Collagen fibers insert on the cartilaginous endplates of the surrounding vertebra. This cartilage helps to contain the NP and itself is partially deformable.

The disks are bound dorsally by the dorsal longitudinal ligament and ventrally by the ventral longitudinal ligament. Between T2 and T10, the intercapital ligaments connect rib heads and provide additional support. This has been theorized to reduce the rate of disk herniations in these disk spaces [6].

Nerve endings are found only in the outer layers of the AF and are plentiful in the dorsal longitudinal ligament [7]. Most of the intervertebral disk is avascular but the outer AF is supplied by vessels; the remainder receives its nutrient supply from capillary loops that extend from the bone marrow of the surrounding vertebrae [8].

Pathogenesis

Disks degenerate as part of a normal aging process. The NP loses its ability to attract and hold water when the components of NP change with age. Since the NP does not dissipate forces as before, there is an increase in forces transmitted to the AF. The increased load on the AF causes stiffening and bulging which leads to increase in fiber defects and tears.

Chondrodystrophic disks have an accelerated degeneration through a process known as chondroid metaplasia, summed up as a loss of hydroelastic properties of the disk. This occurs in most to all of the disks in chondrodystrophic animals and can begin as early as 2 months with one study showing 75–90% of the NP transformed to more hyaline and cartilaginous tissue by 1 year of age [9]. Non-chondrodystrophic disks show fibrous metaplasia with age, characterized by fibrous collagenization of the nucleus. This leads to bulging of the nucleus and disk protrusion. This usually affects a small number of disks in older animals (over the age of 7) [8].

Disk Protrusion and Extrusion

When disk degeneration occurs, there is an increased likelihood that the disk will have a displacement, including bulging and herniation. Bulging typically describes movement of the annulus alone, while herniation includes movement of the NP as well. Three types of disk herniations are reported in dogs and cats.

- Hansen type I herniations involve a complete rupture of the annulus with displacement of the nucleus into soft tissue structures.

- Hansen type II herniations are ruptures of the inner layers of the annulus and only partial displacement of the nucleus into the annular fibers with annular hypertrophy.
- Non-compressive disk ruptures (also known as high-velocity low-volume, type III, traumatic) are small-volume herniations that result in significant spinal cord injury.

Clinical Signs

Clinical signs are dependent on the location of the disk herniation. However, spinal cord injury can be localized to four basic regions: upper cervical (C1–C5), lower cervical (C6–T2), thoracolumbar (T3–L3), and lumbosacral (L4–S1,3) myelopathy. Table 25.1 is a summary of signs associated with each localization.

Signs can progress from pain to ataxia and loss of proprioception, loss of voluntary movement, and finally to loss of sensation. There are several reasons for this progression of functional loss. The first is the location of the compression or contusion; proprioceptive pathways from the pelvic limbs are located most lateral in the spinal cord and can be damaged first. Thoracic limb pathways

Table 25.1 Clinical signs associated with spinal cord localization.

	C–C5	C6–T2		T3–L3	L4–S1(3)
	All limbs	Thoracic	Pelvic	Pelvic limbs	Pelvic limbs
Gait	UMN-GP	LMN	UMN-GP	UMN-GP	LMN
Postural reactions	Delayed → absent	Normal or delayed → absent	Delayed → absent	Delayed → absent	Normal or delayed → absent
Reflexes	Increased	Decreased → absent	Increased	Increased	Decreased → absent
• Stretch					
• Withdrawal					
Muscle tone	<ul style="list-style-type: none"> • Neck rigidity with spasms • Normal to increased 	Decreased	Increased	Increased	Decreased → absent
Cranial nerve exam	<ul style="list-style-type: none"> • Normal • Horner's syndrome 	<ul style="list-style-type: none"> • Normal • Horner's syndrome 		Normal	Normal
Posture	<ul style="list-style-type: none"> • Low head carriage • Scoliosis, torticollis 	<ul style="list-style-type: none"> • Low head carriage • Scoliosis, torticollis • Root signature 		<ul style="list-style-type: none"> • Kyphosis • Scoliosis • Schiff–Sherrington 	<ul style="list-style-type: none"> • Difficulty supporting weight • Root signature • Schiff–Sherrington
Bladder	<ul style="list-style-type: none"> • Increased tone • Difficult to express 	<ul style="list-style-type: none"> • Increased tone • Difficult to express 		<ul style="list-style-type: none"> • Increased tone • Difficult to express 	<ul style="list-style-type: none"> • Flaccid tone • Easy to express
Anal tone	Normal	Normal		Normal	Decreased

GP, general proprioception; LMN, lower motor neuron; UMN, upper motor neuron.

are medial to these but located superficially as well. Second, the ascending axons carrying proprioceptive information and descending motor pathways are myelinated fibers. Mild compression can disrupt the myelin, sparing the axon and causing delay of information. More severe compression can cause axonal transection and neuronal loss. Finally, pain pathways are composed of small-diameter, minimally to unmyelinated fibers that course bilaterally in the spinal cord. Compression or contusion must be severe to affect these pathways.

A neurological examination should be performed before sedative or pain medications are administered, when possible. Cranial nerve exam findings should be normal. However, a Horner's syndrome may be observed due to compromise of the sympathetic nerve pathway to the eye, which takes a circuitous route through the cervical spinal cord: After leaving the hypothalamus, the axons of the upper motor neuron travel down the spinal cord in the lateral funiculus to the level of T1–T3. Here they synapse on the preganglionic neuron (or general visceral efferent neuron) whose axons leave the spinal cord with spinal nerves, then travel via the ramus communicans to join the sympathetic trunk. After ascending the cervical spine, the axons synapse in the cranial cervical ganglion on the postganglionic neuron which then travels to innervate the eye.

The cutaneous trunci reflex, pinching of the skin bilaterally from the level of the ilial wing to the shoulder blade and eliciting a twitch, can be particularly helpful in localizing a lesion in the T3–L3 region. The pathway responsible for this reflex begins when the pinch stimulates the dorsal branches of spinal nerves in the area. The impulse generated courses to the dorsal gray column via the neuron and synapses on interneurons. The axons of the interneuron travel cranially (and bilaterally) in the fasciculus proprius of the spinal cord to the level of the C8–T1 spinal cord segments. Here they synapse in the ventral gray column on the general somatic efferent neuron. These neurons leave the spinal cord in the brachial plexus and form the lateral thoracic nerve which innervates the cutaneous trunci muscles. When a cut-off is observed in the reflex, this can help to localize the lesion to 0–4 spinal cord segments cranial to the cut-off. The presence of a cut-off was recently shown to be associated with increasing severity of clinical grade in ambulatory but paretic dogs with IVDH and previously it was shown that dogs that were non-ambulatory all had a cutaneous trunci cut-off [10].

Another key to assessment of spinal cord injury is understanding the difference between withdrawal, voluntary motor, and nociception. The withdrawal reflex begins when a noxious stimulus is applied to the distal limb. The impulse travels along the sensory nerve to an interneuron. The axons from this interneuron then synapse on the motor neuron which causes a contraction.

No response is needed from the animal cranial to this local reflex arc. Therefore, an intact withdrawal reflex does not indicate that an animal has voluntary motor ability directed from the motor cortex nor does it indicate intact nociception.

Several observations after spinal cord injury can confound examination findings and cause a mislocalization. Schiff–Sherrington posture can occur in an animal with spinal cord injury in the T3–L5 region. When placed in lateral recumbency, the animal will have increased tone in the thoracic limbs, but may have increased or decreased tone in the pelvic limbs (depending on the lesion localization). The increased tone in the thoracic limbs occurs when either the cell bodies of the border cells in L1–L5 spinal cord segments or their cranially directed inhibitory axons are affected. The loss of this inhibitory input to the motor neurons of the thoracic limbs causes an increase in tone. This can cause one to diagnose a cervical myelopathy, but standing the animal and assessing for proprioception will help to differentiate a thoracolumbar localization from one affecting the thoracic limbs.

Spinal shock is profound loss of segmental reflexes and muscle tone caudal to a lesion in the spinal cord. In humans, this occurs in up to 50% of patients with spinal cord injury. The pathophysiology is not clearly understood but in people is thought to occur due to interruption of pathways from the brain, loss of inhibitory neuronal input, increased concentrations of inhibitory neurotransmitters (glycine) or hyperpolarization of alpha motor neurons [11]. In small animals, the time course for return of reflexes and even turning to hypertonia and hyperreflexia is short, within minutes to days.

In some patients with a midline disk herniation in the cervical spine, we can observe clinical signs that appear to be worse in the thoracic limbs than in the pelvic limbs. This pattern occurs with other disease processes that affect the gray matter of the spinal cord more than or before affecting the white matter. Midline disk herniation in the cervical intumescence can cause compression of the gray matter and lower motor neuron while sparing proprioceptive tracts to the pelvic limbs. In the more cranial cervical spinal cord, a midline disk herniation can cause compression of the more medial proprioceptive tracts associated with the thoracic limbs before compressing the most lateral belonging to the pelvic limbs. This is also known as central cord syndrome.

Lastly, when animals become unable to feel their limbs, it is important to note that <10% will develop progressive myelomalacia or ascending descending myelomalacia [12]. Myelomalacia itself means gross softening of the spinal cord. There can be focal myelomalacia or spreading of the lesion due to unknown changes, likely including primary damage and secondary to vascular, ischemia or free radical production. When present,

this syndrome will cause progressive changes from cranial migration of the cutaneous trunci, loss of tone and reflexes in the pelvic limbs to loss of anal tone and thoracic limb signs. Respiratory failure can occur within days of the development of ascending myelomalacia. It is important to alert owners to the possibility of this development prior to advanced imaging and surgery.

Diagnostics

Performing radiographs of the animal with signs referable to the spine is a good first step to exclude diseases such as osseous neoplasia, diskospondylitis or fracture/luxation. Radiographs can show evidence of disk disease: narrowing of disk spaces, collapse of the intervertebral joint space, bridging spondylosis, and mineralization of the disks. However, compression of the spinal cord and spinal nerves cannot be assessed via radiographs. Therefore, radiographs alone have a 51–61% accuracy for identifying the site of thoracolumbar disk herniation and as such are not reliable for surgical planning [13].

Myelography is the use of iodinated contrast agents in the subarachnoid space to identify compressive lesions. Complications of the procedure include seizures, worsening of clinical signs, meningitis, cardiac arrhythmias, and apnea. Myelography alone has been reported to have 40–97% accuracy [14]. A large study of 116 dogs found a relative sensitivity of 83.6% and the myelogram was more sensitive than CT scan for dogs <5 kg [15]. Computed tomography (CT) is often recommended for chondrodystrophic dogs, where the extruded disk material is likely mineralized. CT scan was used in 66 dogs in the above study and had a relative sensitivity of 81.8%. The CT scan was more sensitive in larger dogs and those more chronically affected. CT can also more accurately determine the side of disk compression. If the CT scan is non-diagnostic, it can be followed by myelogram.

Magnetic resonance imaging (MRI) is now widely available and has greatly improved the diagnostic investigation of spinal cord disease. When compared with CT, MRI has a greater sensitivity (98.5% over 88.6%) [16]. MRI allows visualization of the spinal cord, subarachnoid space, epidural space, disks, vertebrae, and paraspinal tissues. As the only imaging technique that can identify spinal cord contusion from high-velocity disk herniation, spinal cord infarction, and spinal cord neoplasia, it must be considered the gold standard and preferentially utilized.

Cerebrospinal fluid (CSF) analysis can be performed in animals suspected of IVDH and may provide information regarding prognosis. In dogs with IVDH, CSF samples were abnormal in 26–82% and the most common abnormality is albuminocytological dissociation or a higher than expected increase of protein with a mild increase to

normal cell count. Pleocytosis is less common, but may occur (mixed cell, neutrophilic, lymphocytic and even eosinophilic pleocytosis have been reported) [17].

More recently, CSF samples have been evaluated not only for abnormalities but for substances that may relate to prognosis. For example, higher detectable levels of matrix metalloproteinase 9 (MMP9) were found in plegic dogs than in paretic dogs and higher levels of MMP9 were correlated with poor long-term outcome [18,19]. Myelin basic protein (MBP) was found to be in higher concentration in dogs that were non-ambulatory after 6 weeks than control dogs [20]. A concentration greater than 3 ng/mL of MBP was found to be a predictor of poor outcome with a sensitivity of 78% and specificity of 76%.

Treatment

Medical Management

Medical management of confirmed or suspected IVDH is a reasonable first choice for any patient displaying signs of only pain with no neurological deficits, mild non-progressive deficits or if referral for surgical intervention has been declined by the owner. The pillars of medical management of IVDH are cage rest, analgesics, and anti-inflammatory medications.

Cage Rest

Post disk herniation there is concern that excessive or even normal activity may exacerbate inflammation occurring in and around the spine. Further disk extrusion through a tear in the AF may also occur with continued activity. The goal of rest is a total reduction in the patient's movements. The patient is confined to a small cage or room for the majority of the day. Running, jumping, playing, and off-leash activity are strictly eliminated from the patient's daily routine. Avoidance of stairs is recommended. A typical period of restriction is 4–8 weeks to allow the AF to repair [21].

Anti-Inflammatory Medications

There is much written about the use and relative efficacy of the two major classes of anti-inflammatory medications: glucocorticoids (GC) and non-steroidal anti-inflammatory drugs (NSAIDs). Anti-inflammatory prednisone dose is used in a 3-, 5- or 7-day taper (e.g. 0.5 mg/kg PO q12h × 5 days, q24h × 5 days, q48h × 5 doses). There is growing support for the use of NSAIDs rather than steroids, but blinded comparison studies have not yet demonstrated clear evidence of a benefit of GCs versus NSAIDs. One study indicated a decreased rate of relapse with NSAIDs over steroids [22], another study indicated better owner-reported quality of life assessment in their pets with NSAIDs instead of steroids [21].

In light of this ambiguity, patient co-morbidities (kidney disease, endocrinopathies, other locations of osteoarthritis, etc.) may help to guide a rational choice between the two options. Gastroprotection in the form of omeprazole, famotidine or pantoprazole is often recommended when GCs are used, although the efficacy of these medications for prevention of ulceration is unclear [23,24]. Clear information on side-effects and complications of both GCs and NSAIDs should be provided to the owner when prescribing these drugs [25].

Analgesics

Pain associated with IVDH is a frequent finding on neurological exam. Tramadol is often used for pain relief in veterinary patients (2–5 mg/kg PO BID-TID). Gabapentin can be a useful adjunctive pain medication (5–10 mg/kg PO BID-TID). Methocarbamol may be used to alleviate muscle spasm which can be profound in some cases of cervical IVDH (45 mg/kg PO TID). Sedation is a frequent side-effect of these medications, which may help with the patient exercise restriction. For pain uncontrolled on these medications, amantadine or a sustained-release fentanyl patch may be used if surgical referral is declined [26].

Adjunctive Therapy

There are adjunctive therapies available for veterinary patients, not limited to acupuncture, chiropractic therapy, physical therapy, and the use of cold laser [27,28]. The rationale behind many of these therapies is based on human medicine, with few reports in the veterinary literature. One report indicated that electroacupuncture combined with traditional medical therapy showed an improvement compared to traditional therapy [29]. Some owners have an interest in the use of botanicals or botanical extracts (e.g. curcumin, *Boswellia serrata*). Evidence currently exists for reduction of clinical signs of chronic joint and spinal disease with the use of *Boswellia* with minimal gastrointestinal side-effects [30].

Non-Ambulatory Patient Care

For moderately or severely affected IVDH patients, a large portion of their at-home care requires clear and concise owner instructions. Owners of paraplegic dog need to become comfortable with bladder assessment and expression if necessary to prevent bladder damage causing long-term incontinence. Deep, soft, clean bedding, turning frequently, and fastidious urine and fecal hygiene are needed to prevent bedsores, fecal or urine scald and secondary skin infections. Urinary tract infections are frequent and owners should be informed about signs associated with them [31]. Passive range-of-motion exercises and sling walking may help maintain muscle mass during recovery. Exercises can include 10-minute

massage of the affected limbs twice daily, bicycling of the affected limbs by moving the limbs through an exaggerated motion similar to pedaling a bicycle (10 repetitions, 2–3 times per day), assisted or sling standing and walking (3–4 times per day, 3–5 min). Neurological recovery may take weeks to months before patient improvement plateaus. Fitting patients with a sturdy well-padded and machine-washable body harness may enable owners to care for their pet more easily.

Surgical Management of IVDH

In general, surgical intervention is recommended for patients with disk herniation and the following:

- loss of voluntary motor ability in limbs
- loss of nociception in limbs
- intractable pain
- severe or progressive deficits, especially when rapid decline is reported
- failure of medical management.

Surgical approach varies depending on the location of the disk herniation. However, complications are similar for both ventral slot and laminectomy (hemi and dorsal). These include immediate complications (iatrogenic injury, bleeding, inadequate decompression) and postoperative complications (continued pain, instability of the surgery site, hematoma, infection, seroma, aspiration pneumonia, and urinary tract infection). Prognosis is largely based on history, clinical signs, signalment and status prior to surgery and is broadly summarized in Table 25.2. Dogs with cervical disk disease that are ambulatory before surgery tend to have better prognosis than those that are non-ambulatory. Patients with thoracolumbar disk herniation that retain nociception have a good prognosis, while those that lose nociception have much lower rate of recovery.

Table 25.2 Prognosis of patients with IVDH treated medically or surgically (% improved).

	Medical management [32,34,36]	Surgical management [33,35,36]
Cervical	50% However, 30% relapse	58–100%
Thoracolumbar	50–100%	95–97%
• (+) nociception	<5–7%	25–75% with large dogs lower in range
• (–) nociception		
Lumbosacral	50% Relapse is common	73–93%

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26

Diskospondylitis

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Introduction

Diskospondylitis is defined as inflammation or infection of the vertebral endplates and the intervertebral disk (IVD). Infection of a vertebral body is called vertebral osteomyelitis or spondylitis. Infection of just the IVD is called infectious diskitis. Vertebral physisitis is an inflammation or infection affecting the caudal physal zone of a vertebra but sparing the vertebral endplate [1,2]. Physisitis typically occurs in young (<2 years), skeletally immature dogs and can result in vertebral body collapse. Diskospondylitis is uncommon in cats [1].

Pathophysiology

Each vertebra is supplied by the vertebral, intercostal or lumbar artery which ends in a capillary bed in the vertebral endplate. The IVD itself is avascular, receiving nutrition from tissue fluids that diffuse into it from adjacent tissues. The capillary bed drains into a subchondral venous network or into the veins of the marrow spaces. The veins of each vertebra are connected by an internal vertebral venous plexus lying on the floor of the vertebral canal. This plexus does not have valves, so blood may flow cranially or caudally depending on pressure relationships.

The most common route of spinal infection is by arterial spread from a distant source in the body. Sources include the urogenital system, oral cavity, heart valves, and skin [3]. It is suspected that the infection first sets up in the vertebral endplate where blood flow is slow. The adjacent disk is infected from flow through holes present in the endplates. It is also thought that the valveless venous plexus may be the route for infection of other sites along the spine.

Direct inoculation of the organism into the affected site is uncommon, but can happen after spinal surgery, penetrating trauma, abscessation or migration of foreign

material. This is the only scenario where the disk itself could be the start of an infection.

The L2 through L4 vertebrae are most often affected with migrating foreign bodies like plant awns. This is because as the plant awn is inhaled, it migrates through the lungs or mediastinum to the origin of the diaphragm at the ventral margin of these vertebrae.

Causative Agents

The most common causative agents of diskospondylitis include *Staphylococcus* spp, *Brucella* spp, *Streptococcus* spp, and *Escherichia coli*. Less common causative agents include *Bordetella* spp, *Enterococcus faecalis* and *Pseudomonas aeruginosa*. Many fungal infections such as *Paecilomyces* spp and *Coccidioides immitis* have also been reported, though these are also uncommon.

Aspergillus spp are ubiquitous saprophytic organisms that are opportunistic pathogens. Many species of *Aspergillus* have been reported to cause disease in dogs, but *A. terreus* is most frequently associated with systemic aspergillosis and diskospondylitis [4]. There are multiple reports of multifocal *Aspergillus* diskospondylitis in German shepherd dogs (GSDs) [5–8]. GSDs appear predisposed to systemic aspergillosis, accounting for up to 67% of cases, and a hereditary immune defect is suspected. Of 30 dogs affected with systemic aspergillosis, 16 had diskospondylitis with an average of two lesions (range 1–9) [8].

Brucella canis is responsible for approximately 10% of diskospondylitis cases in dogs. It is an important cause of diskospondylitis as it is a zoonotic pathogen and care must be taken to prevent infection of clinicians, animal care staff, and clients. Although it is not a regional disease, dogs in the south-eastern United States are at higher risk of *Brucella canis* as a cause of diskospondylitis [9,10].

Signalment

Male dogs are twice as likely to be affected as female dogs. Patients are an average of 6–9 years of age and large-breed dogs are more frequently affected, especially Great Danes and Labradors. Small and chondrodystrophic breeds are uncommonly affected. Though not a regional disease, there is a higher incidence of diskospondylitis in the American Gulf coast states [10]. However, two-thirds of dogs with systemic aspergillosis and diskospondylitis are young, female German shepherd dogs.

Clinical Signs

The main clinical sign of diskospondylitis is paraspinal hyperesthesia, often with no neurological deficits. Other differential diagnoses for painful spinal lesions include IVD disease, meningitis/meningomyelitis, neoplasia, and trauma. Dogs may show clinical signs for weeks prior to diagnosis, though acute presentations also occur. Occasionally, there is a recent history of infection or immunosuppressive therapy.

Dogs with diskospondylitis are often normal on physical examination. Fever and weight loss are only noted in one-third of cases. A thorough physical examination is important to identify any potential sources of infection.

Neurological deficits may range from non-existent to paralysis with loss of pain perception. The deficits associated with diskospondylitis are due to compressive lesions, which are mostly soft tissue in nature [11], though vertebral subluxation should always be considered. Any intervertebral space can be affected, though the lumbosacral junction is the most frequently affected site. Typically, the junctional areas of the spine are most often affected.

Diagnosis

The diagnosis of diskospondylitis is based on imaging findings and supportive laboratory testing. A diagnosis is often made with radiographs, though advanced imaging may be necessary. Radionuclide bone imaging has been performed in the past, but it has been replaced by higher resolution imaging procedures such as computed tomography and magnetic resonance imaging.

Diskospondylitis lesions appear as symmetrical lytic lesions of the adjacent vertebral endplates with reactive sclerosis and symmetric spondylosis. Collapse of the caudoventral vertebral body and reactive spondylosis only at the caudal vertebral margin are suggestive of phsitis [3]. Diskospondylitis lesions are distinguished from neoplasia primarily based on location.

Most primary vertebral tumors involve one vertebral body and do not affect the IVD or cross the IVD space. Another disease process to distinguish from diskospondylitis is osteochondrosis dissecans (OCD). In young, large-breed dogs, OCD can affect the dorsal aspect of the cranial sacral endplate and a separate OCD fragment may be visible. The changes associated with OCD lesions are smoothly margined, in contrast to the ragged edges seen with diskospondylitis.

Radiography

Spinal radiography is the diagnostic modality for diskospondylitis. Classic radiographic changes include collapse of the IVD space, bone lysis centered at the vertebral endplates, sclerosis, and spondylosis (Figure 26.1). Progressive bony lysis can lead to shortening of the vertebral body, fracture, luxation, and instability.

If a single diskospondylitis lesion is identified on radiographs, the entire spine should be evaluated as diskospondylitis can be a multifocal process in approximately one-third of cases. Because it can take up to 4 weeks for changes to be radiographically visible [12],



Figure 26.1 Lateral radiograph of the thoracolumbar junction of an 8yo SF Belgian malinois presented for evaluation of waxing and waning fever and intermittent spinal hyperesthesia. No neurological deficits were noted on examination. There is diskospondylitis with moderate subluxation at L1–2 with pathological fracture of L2.

early diskospondylitis lesions may not be obvious. In those cases, advanced cross-sectional imaging is highly recommended.

The limitations of radiographs as a diagnostic tool for this disease are the delay between onset of clinical signs and radiographic findings, and the discrepancy between clinical and radiographic signs during recovery [13]. Radiographs also do not allow for visualization of neural structures, so neither epidural involvement nor spinal cord compression can be evaluated unless myelography is performed.

Cross-Sectional Imaging

Computed tomography (CT) is more sensitive than conventional radiography for detection of bony changes (Figure 26.2). The CT characteristics of diskospondylitis are severe irregular bone lysis of vertebral endplates with multiple hypoattenuating holes in the endplates visible on transverse images. With the advent of rapid, high-resolution CT scanners, it is often more effective to scan the entire spine under sedation than to take several radiographs, in addition to obtaining higher resolution images. If there is concern about spinal cord compres-

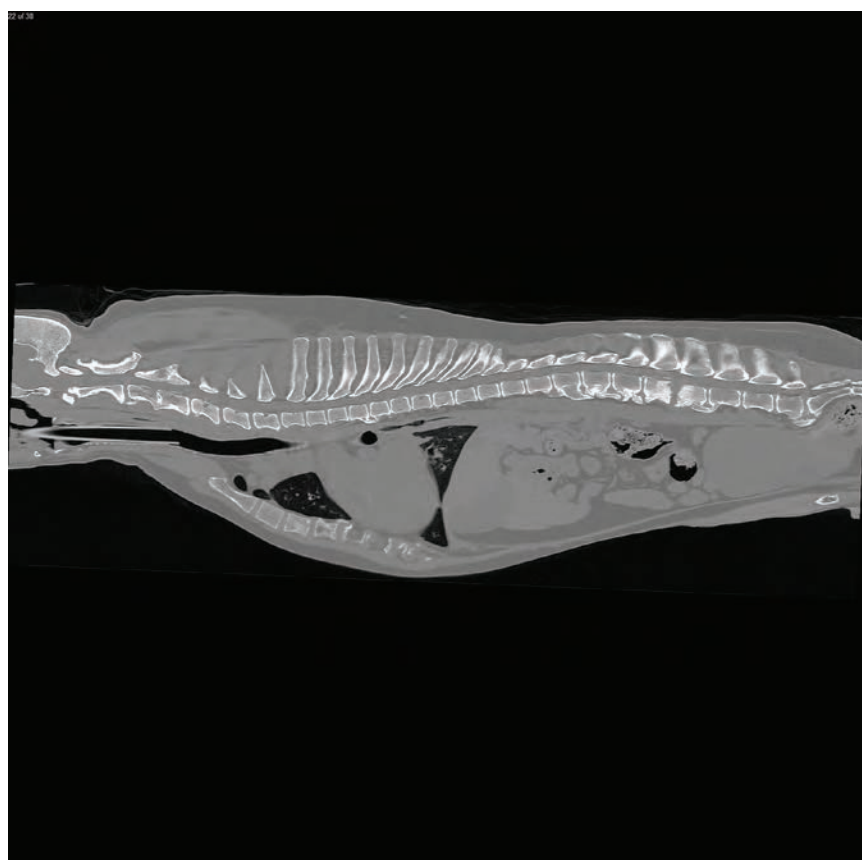
sion, then a CT myelogram can be performed, though magnetic resonance imaging (MRI) is less invasive.

A radiographically unapparent early diskospondylitis lesion will be made obvious by MRI [13]. MRI is more sensitive than plain radiographs or CT as it can detect paravertebral soft tissue changes which are not visible on other modalities [14]. There are multiple causes to consider when endplate changes are noted on MRI, including reactive endplate changes, diskospondylitis, osteochondrosis, intravertebral disk herniation (Schmorl's nodes), and fatty infiltration. Diskospondylitis is diagnosed on MRI with paravertebral signal changes, endplate signal changes, endplate contrast enhancement, enhancement of the IVD space, endplate erosion, and collapse of the IVD space [15]. Diskospondylitis and fatty infiltration are seen most commonly, though the latter occurs with a much higher incidence in small-breed dogs, while diskospondylitis and osteochondrosis (which is rare) occur more often in large-breed dogs.

Laboratory Tests

A minimum database, including complete blood count, serum biochemistry, and urinalysis, should be performed

Figure 26.2 Sagittal postcontrast computed tomographic image from a 5yo CM rottweiler that presented for evaluation of progressive spinal hyperesthesia and non-ambulatory status. The patient was paraplegic with intact pain perception. There is diskospondylitis at L3–4 with mild subluxation and moderate ventral spinal cord compression.



in these cases. Bacterial cultures of urine and blood should be performed as part of the minimum database in all patients with diskospondylitis. The rate of isolation of the causative agent from blood and urine can range from 29% to 78%. Fungal organisms are often more difficult to diagnose without cytology or histopathology. Cerebrospinal fluid analysis is often normal in cases of diskospondylitis as the disease is extradural, though mild, non-specific changes can be present. CSF culture is often negative as the disease does not penetrate the blood–brain barrier (BBB) until late in the course of disease when there is a bacterial meningitis or myelitis.

Many *Brucella* spp are zoonotic, so great care needs to be taken with diskospondylitis patients until this organism has been ruled out. Serological evaluation for *Brucella* spp should be started with a slide agglutination test and, if positive, confirmed with either the tube agglutination test (TAT) or agar gel immunodiffusion (AGID) test. Bacterial culture can also be performed, but the laboratory must be advised about the concern for *Brucella* spp as infection commonly occurs through aerosolization from culture growth.

If there is a suspicion of systemic aspergillosis, fungal culture of urine is most likely to yield positive results. Culture of blood and aspirates of any abnormal-appearing organs is also recommended.

Culture of surgical biopsies of the affected intervertebral site is the most sensitive and reliable way to obtain a definitive diagnosis, but this is invasive and costly. Fluoroscopically guided percutaneous disk aspiration is reported to have a success rate of 75% [16]; this procedure still requires general anesthesia and is not reported to have any adverse effects. Disk aspiration is indicated for patients that do not respond to initial antibiotic therapy. Considering this, surgical biopsy is really only recommended in non-responsive cases with negative disk aspirates or when other surgical intervention is warranted.

Treatment

Treatment for diskospondylitis is multimodal, including cage rest, antimicrobials, and pain control. Treatment has to be long term, at least 2 months, with an average of 1 year [10]. Exercise restriction is crucial to prevent pain, pathological fracture or luxation. Pain control should consist of a combination of a non-steroidal anti-inflammatory drug (NSAID) and other oral pain control drugs such as tramadol and gabapentin. Corticosteroids are contraindicated in cases of diskospondylitis.

Empiric antibiotic therapy should be aimed at the common causative agents (*Staphylococcus*, *Streptococcus*, and *E. coli*). Ideally, the antibiotic regime would

use a bactericidal drug with a spectrum that covers gram-positive and gram-negative bacteria. Treatment with antifungal drugs is not recommended unless there is a definitive diagnosis due to potential side-effects of the medications.

A common initial, empiric protocol consists of cephalexin, an NSAID, tramadol, and strict rest. Dogs appropriately treated for diskospondylitis should show clinical improvement within the first 5 days of treatment. If there is no improvement within the first week, then the patient should be re-evaluated.

Radiographic deterioration can continue despite clinical improvement; radiographic recovery will lag behind clinical recovery but is shorter in young (<1 year) dogs and can last 3–9 weeks in older dogs [12]. In light of this, it is important to remember that radiographic findings do not correlate with clinical signs.

Treatment of *Brucella* diskospondylitis is more difficult. Though dogs with brucellosis will often show a remission of clinical signs, serological testing remains positive and radiographic lesions remain active [9]. Multiple drug protocols have been reported for treatment, including tetracyclines plus aminoglycosides and fluoroquinolones. These dogs should be castrated or spayed, and clients warned of the zoonotic potential. Brucellosis is a reportable disease in many states.

Treatment of systemic aspergillosis is also difficult. Multiple antifungal drugs have been used alone and in combination, including amphotericin B, azole antifungals, terbinafine, and echinocandins. Whichever drug or protocol is chosen, systemic aspergillosis cannot be cured.

Most cases of diskospondylitis respond to medical management, but surgical intervention is sometimes indicated. Cases that are refractory to empirical therapy are candidates for surgical biopsy of the affected tissues as this is most likely to yield a diagnostic sample for culture and organism identification. Cases that have refractory pain, (sub)luxation, and/or instability may also benefit from surgery as stabilization has the potential to rapidly improve pain and instability [17]. There is always significant concern with surgical stabilization of a diskospondylitis lesion as you are placing implants into an already infected site, which could predispose the patient to chronic infection and catastrophic failure.

Prognosis

Long-term prognosis for dogs with diskospondylitis and mild to no neurological deficits is generally good, though prolonged treatment of at least 4–6 months is often required. Early diagnosis and appropriate treatment are central to a good outcome. Interestingly, there is no

significant correlation between degree of compression on imaging, ambulatory status or surgical intervention and outcome [11]. Recurrence is always a potential concern, especially in immunocompromised or immunosuppressed patients. Recurrence is also more common in patients with *Brucella* spp or fungal diskospondylitis.

It is notable that about two-thirds of German shepherd dogs with systemic aspergillosis are euthanized within 1 week of examination, most of them due to severe neurological signs.

Complications

Subluxation is present in about 20% of patients with spinal cord compression [11], though this does not imply instability nor does subluxation require surgical intervention. Catastrophic complications of diskospondylitis would include fracture and/or luxation, epidural empyema, and loss of pain perception. Untreated diskospondylitis can lead to sublumbar and epidural empyema, meningitis or myelitis.

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27

Lower Motor Neuron Disease

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To move is all mankind can do, and for such the sole executant is muscle, whether in whispering a syllable, or in felling a forest.

(Sir Charles Scott Sherrington, 1924)

Introduction

The effector organ of all movement is muscle, and the final common pathway of the motor system is the influence of the lower motor neuron (LMN) on skeletal muscle [1]. The base element of this final common pathway (a LMN, the neuromuscular junctions (NMJ) and the muscle fibers they innervate) is termed a “motor unit” [2].

Lower motor neuron cell bodies are located in cranial nerve nuclei and ventral horn gray matter of the spinal cord. LMN axons project from these into the periphery via the cranial and spinal nerves, respectively. Synaptic transmission from the lower motor neuron to the muscle occurs at the neuromuscular junction. The neurotransmitter acetylcholine (ACh) is released from vesicles within the axon terminal into the synaptic cleft in response to depolarization of the presynaptic membrane and Ca²⁺-influx. ACh binds to nicotinic ACh receptors on the postsynaptic membrane (the motor endplate), leading to depolarization of the sarcolemma and subsequent contraction of the muscle [3]. ACh is then rapidly hydrolyzed by acetylcholinesterase, so as to leave receptors and muscle fibers ready to react the next nervous impulse [4].

Clinical Signs

The terms *lower motor neuron disease* and *neuromuscular disease* are used interchangeably to describe the

syndrome of dysfunction caused by diseases of the LMN itself, the NMJ and the muscle, as disease of any one will lead to similar clinical presentations that are often difficult to distinguish on physical examination [2]. Disease of the motor unit causes a loss of ability to execute movement. Paresis refers to a partial loss of voluntary movement, whereas paralysis or plegia refers to a total loss [5].

The cardinal sign of LMN disease is paresis or paralysis with decreased muscle tone (flaccidity) and decreased segmental spinal reflexes. Manifestations of LMN disease may also include dysphonia, dysphagia, increased fatigability, exercise intolerance, and regurgitation secondary to megaesophagus. Hypoventilation may be seen with severe weakness of the intercostal muscles and diaphragm, and this can sometimes be compounded by laryngeal dysfunction. Ataxia is not seen in purely motor neuropathies and diseases of the NMJ (junctionopathies) or muscle (myopathies). Reflexes are most likely to be preserved in myopathies and certain junctionopathies (e.g. myasthenia gravis). In cases of denervation, atrophy of the muscle may be rapid and profound.

Diagnosis and Initial Approach

A useful diagnostic approach to cases presenting with LMN signs is to determine the onset of clinical signs (acute versus chronic) and their distribution (generalized versus focal versus ascending) (Table 27.1). This requires careful owner questioning and a thorough physical and neurological examination.

Table 27.1 Causes of neuromuscular disease categorized by their onset and distribution.

Acute – generalized	Acute – focal
Neuropathy	Neuropathy
<i>Inflammatory</i>	<i>Trauma</i>
- Polyradiculoneuritis	- Brachial plexus avulsion
Junctionopathy	- Femoral nerve injury
<i>Idiopathic/paraneoplastic</i>	- Sciatic nerve injury
- Myasthenia gravis (fulminant)	- Caudal nerve (tail-pull) injury
<i>Toxic</i>	<i>Vascular</i>
- Botulism	- Ischemic neuromyopathy (aortic thrombus)
- Tick paralysis (Australia; <i>Ixodes</i> spp, US; <i>Dermacentor</i> spp)	Junctionopathy
- Black widow spider (<i>Lactrodectus</i> spp) and red back spider	<i>Idiopathic/paraneoplastic</i>
- Pesticides (organophosphates and carbamates)	- Myasthenia gravis (focal)
- Drugs (aminoglycosides, ampicillin, tetracyclines, ciprofloxacin, imipenem, phenothiazines, antiarrhythmics)	Myopathy
Myopathy	<i>Inflammatory</i>
<i>Metabolic secondary</i>	- Masticatory myositis
- Hypokalemia	- Extraocular myositis
- Hyperkalemic periodic paralysis	<i>Trauma</i>
- Hypoadrenocorticism	- Direct trauma
- Exertional rhabdomyolysis	- Recumbency/compartment syndrome
	<i>Vascular</i>
	- Ischemic neuromyopathy (aortic thrombus)
Chronic – generalized	Chronic – focal
Neuronopathy	Neuropathy
<i>Degenerative</i>	<i>Degenerative</i>
- Inherited and acquired motor neuron disorders	- Degenerative lumbosacral stenosis
Neuropathy	<i>Neoplasia</i>
<i>Degenerative</i>	- Peripheral nerve sheath tumor
- Distal symmetric polyneuropathy	- Lymphoma
- Chronic axonal degeneration	- Meningioma
- Inherited polyneuropathy	<i>Inflammatory</i>
- Lysosomal storage diseases	- Brachial plexus neuritis
<i>Metabolic</i>	Junctionopathy
- Diabetic polyneuropathy	<i>Idiopathic/paraneoplastic</i>
- Hypothyroid neuropathy	- Myasthenia gravis (focal)
- Hyperinsulinism	Myopathy
<i>Inflammatory</i>	<i>Inflammatory</i>
- Chronic inflammatory	- Masticatory myositis
- Demyelinating polyneuropathy	- Extraocular myositis
- Sensory	

(Continued)

Table 27.1 (Continued)

Chronic – generalized	Chronic – focal
- Polyganglioradiculoneuritis	<i>Non-inflammatory</i>
- Paraneoplastic neuropathy	- Fibrotic myopathy (gracilis/semitendinosus myopathy)
<i>Infectious</i>	
Protozoal polyradiculoneuritis (<i>Toxoplasma</i> , <i>Neospora</i> spp)	
<i>Toxic</i>	
- Heavy metals (lead, mercury, thallium)	
- Pesticides (organophosphates)	
- Organic solvents (acrylamide, hexacarbons)	
- Drugs (vincristine, vinblastine, cisplatin)	
Junctionopathy	
<i>Idiopathic/paraneoplastic</i>	
- Myasthenia gravis	
Myopathy	
<i>Metabolic primary</i>	
- Mitochondrial myopathy	
- Glycogen storage disease	
- Malignant hyperthermia	
<i>Metabolic secondary</i>	
- Hypokalemia	
- Hyperkalemic periodic paralysis	
- Hyperadrenocorticism	
- Hypoadrenocorticism	
- Hypothyroidism	
<i>Inflammatory</i>	
- Immune-mediated polymyositis	
- Paraneoplastic polymyositis	
- Dermatomyositis	
<i>Infectious</i>	
- Protozoal (<i>Toxoplasma</i> , <i>Neospora</i> , <i>Babesia</i> , <i>Leishmania</i> , <i>Trypanosoma</i> spp)	
- Bacterial (<i>Clostridium</i> , <i>Leptospira</i> , <i>Rickettsia</i> , <i>Ehrlichia</i> spp)	
<i>Non-inflammatory</i>	
- Centronuclear myopathy	
- Inherited myopathy	
- Fibrotic myopathy (gracilis/semitendinosus myopathy)	
- Muscular dystrophy	
- Myositis ossificans	
- Myotonia congenita	
- Nemaline myopathy	

Table 27.2 Four key causes of acute generalized neuromuscular weakness.

	Polyradiculoneuritis	Tick paralysis	Botulism	Fulminant myasthenia gravis
History	Recent immune trigger (raccoon exposure) in some cases	Paralysis tick endemic area Paralysis tick on animal	Known or suspected scavenging (ingestion of carcass or garbage)	Recent exercise intolerance/episodic fatigue or regurgitation
Clinical progression	Progressive, ascending, Symmetrical	Progressive, ascending, Occasionally focal signs initially	Rapidly progressive, Symmetrical	Progressive, symmetrical Often episodic initially
Motor function	Marked reduction (tetraparesis/tetraplegia)	Marked reduction (tetraparesis/tetraplegia)	Marked reduction (tetraparesis/tetraplegia)	Marked reduction (tetraparesis/tetraplegia)
Sensory function	Normal	Normal	Normal	Normal
Autonomic function	Normal	Megaesophagus, urinary retention/incontinence, cardiovascular and respiratory dysfunction (AUS)	Megaesophagus, urinary retention/incontinence, constipation, cardiovascular (HR) alterations, KCS	Megaesophagus, hypersalivation
Spinal reflexes	Reduced to absent	Reduced to absent	Reduced to absent	Normal to reduced
Muscle tone	Reduced/absent (flaccid)	Reduced/absent (flaccid)	Reduced/absent (flaccid)	Reduced/absent (flaccid)
Cranial nerves	Dysphonia, facial paresis possible	Dysphonia, dysphagia/decreased gag, facial paresis, mydriasis, decreased PLR (AUS)	Dysphonia, dysphagia/decreased gag, facial paresis, mydriasis, decreased PLR	Dysphonia, dysphagia/decreased gag, facial paresis
Hyperesthesia	Possible (spinal palpation)	No	No	No
Electromyography	Spontaneous activity from 4–5 days	Normal	Normal	Normal
Motor nerve conduction	MNCV: normal/reduced CMAP: decreased amplitude (marked)	MNCV: normal CMAP: decreased amplitude	MNCV: normal CMAP: decreased amplitude (mild)	MNCV: normal CMAP: normal
Late (F) waves	Prolonged latency and F-ratios. May be absent	Normal	Normal	Normal
Repetitive nerve stimulation	Normal	Normal	Normal or incremental response	Decremental response
Cerebrospinal fluid findings	Increased protein concentration (albuminocytological dissociation)	Normal	Normal	Normal

AUS, Australian cases; CMAP, compound muscle action potential; HR, heart rate; KCS, keratoconjunctivitis sicca; MNCV, motor nerve conduction velocity; PLR, pupillary light reflex.

Patients with acute, generalized LMN signs are commonly encountered in emergency practice; the majority of this chapter will concern approach to these cases, particularly those diseases that are common or well characterized, namely acute polyradiculoneuritis (AP), “tick paralysis,” botulism, and fulminant myasthenia gravis (MG) (Table 27.2).

Initial approach to a patient with severe generalized LMN paresis should be primarily directed towards evaluation of respiratory function, regardless of the

underlying cause. Patients should be observed for physical evidence of respiratory fatigue, such as labored or poor-quality inspiratory expansion, open-mouth breathing or cyanosis. If hypoventilation is suspected, a PCO_2 should be determined by either capnography or arterial or venous blood gas analysis, and mechanical ventilation considered if the $PaCO_2$ is greater or equal to 60 mmHg (see Chapter 188).

Good nursing care is crucial for patients that are recumbent for prolonged periods, as development of

morbidities such as decubital ulcers and corneal ulceration (from exposure due to a weak blink reflex), aspiration pneumonia (pharyngeal dysfunction combined with a weak cough reflex) and urinary tract infections can be rapid and severe. Soft bedding, frequent examination and turning, while managing the patient in sternal recumbency, when possible, are required to avoid decubitus ulceration, which can be particularly problematic in larger dogs. Artificial tears and/or ointments/gels should be applied liberally in animals with diminished tear production or ability to blink. The bladder may need to be manually emptied by expression or catheterization if voiding is impaired. At all times, the patient should be kept clean and dry. Instituting a physiotherapy plan will help mitigate the effects of prolonged recumbency. A plan for enteral or parenteral feeding will be required for patients with impaired pharyngeal and/or esophageal function. Drugs that may exacerbate neuromuscular weakness should be avoided.

A clinical diagnosis can usually be made on a combination of signalment, history, physical findings, and suggestive or definitive diagnostic test results. For example, snake envenomation is more common in terriers and occurs most frequently during spring and summer. A minimum database of a complete blood count (CBC), serum biochemistry (including measurement of creatine kinase (CK) activity), and urinalysis should be performed in all cases. In Australia and North America, a search for an attached tick, tick crater, or snake bite wound is a critical part of the minimum database. When available, the use of a snake venom detection kit using material from the bite wound or blood or urine (depending on timing of presentation) is also important. Clipping the patient to look for ticks might be prudent in dogs and cats with long coats. Clotting tests are indicated in Australia as some envenomations produce consumptive coagulopathies due to activation of the clotting cascade. Elevations in CK activity may be suggestive of a myopathic cause or snake bite, although mild-to-moderate elevations are possible with recumbency alone.

Thoracic radiographs should be acquired to look for evidence of megaesophagus or a cranial mediastinal mass, and the gag reflex should be tested as a matter of routine to assess pharyngeal function. (Note: Be cautious of rabies.)

Electrodiagnostic studies, such as needle electromyography (EMG), motor nerve conduction studies (MNC) and repetitive nerve stimulation, are important functional diagnostic tests that can be thought of as an extension of the neurological examination. They will not identify the underlying pathology but will reliably differentiate disease of the LMN from the NMJ, from the muscle. When considered in combination with the history, examination and ancillary diagnostic test results,

these studies may be strongly suggestive of a particular diagnosis. General anesthesia is usually required to perform electrodiagnostics, and this is not without risk in a patient with the propensity for aspiration pneumonia.

Sometimes inspection of vomitus or feces, or gastric lavage (under anaesthesia) or rectal examination can be helpful in cases, because of unexpected clues (fish body parts, portions of snake, duck bones can point to etiologies such as puffer fish intoxication, snake bite, botulism, etc.).

Causes of Generalized Lower Motor Neuron Paresis

Acute Polyradiculoneuritis

Acute polyradiculoneuritis (AP) is the most common acute polyneuropathy in the dog [6]. AP is regarded as the canine equivalent of Guillain-Barré syndrome (GBS) in humans [7]. Both AP and GBS appear to be immune-mediated disorders affecting both peripheral myelin and axons. The immune-mediated reaction in AP and GBS appears to be both humoral and cell mediated [6], primarily targeting ventral (motor) nerve roots of spinal nerves, causing leukocytic infiltration, paranodal and segmental demyelination, and axonal degeneration [8]. GBS is commonly a postinfectious aberrant immune response [9] with antiganglioside antibodies playing an important role in mediating the disorder [10]. Anti-GM2 ganglioside antibodies have been demonstrated in a large proportion of dogs with AP [11], which suggests an aberrant immune response similar to GBS. In many cases of AP, contact with raccoon saliva appears to incite the disease; hence the North American colloquial designation “coonhound paralysis.” AP is, however, also frequently encountered in areas where raccoons are not endemic.

Acute polyradiculoneuritis has been reported in a wide range of breeds and ages of dogs. It is typically seen as a flaccid tetraparesis or tetraplegia, with paresis first evident in the pelvic limbs, progressing to involve the thoracic limbs (“ascending” paresis). Maximal dysfunction is reached over a 3–10-day period [12], and may be as severe as tetraplegia with paralysis of respiratory muscles. Segmental spinal reflexes and muscle tone are markedly reduced or absent, excepting the perineal reflex, which is usually preserved. Cranial nerve function is usually unaffected excepting dysphonia, which is common. Facial paresis may occasionally be seen. Though dorsal (sensory) nerve roots may be involved, sensation is usually preserved, as are autonomic functions including bowel and bladder function. Mild hyperalgesia may be noted on spinal palpation in some cases. Interestingly, tail movement often remains good.

Diagnosis of AP is usually made on a combination of consistent history and physical findings, and suggestive electrodiagnostic and laboratory data. Results of electrodiagnostic testing reliably indicate a motor axonopathy most severe in the proximal portion of the nerve. Abnormal findings become pronounced from 4 days after onset of clinical signs [6]. Denervation potentials (fibrillation potentials and positive sharp waves) should be detected on EMG in all dogs 4–5 days after onset of clinical signs. Motor nerve stimulation generates compound muscle action potentials (CMAP) of markedly reduced amplitude with increased temporal dispersion in most cases. Motor nerve conduction velocity (MNCV) remains normal or mildly decreased in most cases. F-wave amplitudes are diminished (or absent), with prolonged latency and increased F ratio [13]. Analysis of lumbar CSF samples usually reveals an elevated protein concentration with normal nucleated cell count (albuminocytological dissociation) [6], though this may not be detected early in the course of the disease or if a cisternal CSF sample is collected.

There is no specific treatment for AP; supportive care is the cornerstone of therapy. Despite an immune-mediated etiology, corticosteroid therapy does not appear to be effective in dogs with AP [6] and may actually slow recovery of humans with GBS [14], presumably due to the catabolic effect of corticosteroids on muscle. Plasmapheresis and/or treatment with intravenous immunoglobulin (IVIg) shortens recovery time and decreases the need for mechanical ventilation in humans with GBS [15]. Treatment with human IVIg may reduce recovery time in dogs, though adverse reactions (anaphylaxis, hematuria) have been reported [16]. Prolonged mechanical ventilation may be required for severely affected patients, who may be best managed by placing a tracheostomy tube. As pharyngeal and esophageal function is usually spared, most animals can eat and drink if supported. Physiotherapy is extremely important in mitigating the effects of prolonged recumbency (joint fibrosis, muscle atrophy contractures, decubitus ulceration).

Provided there is adequate supportive care, most dogs with AP make a full recovery, though the most severely affected may take 4–6 months and may have mild residual neurological deficits [6].

Tick Paralysis

Tick paralysis is caused by envenomation by *Ixodes holocyclus* or *I. cornuatus* (Australia) or *Dermacentor andersoni* or *D. variabilis* (North America) species.

With attachment and feeding, salivary neurotoxin is secreted into the host. The structure of holocyclotoxin has recently been identified [17]. It is thought to impair ACh release at the NMJ by blocking Ca²⁺ influx at the

axon terminal [18]. Holocyclotoxin (Australian ticks) also impairs ACh at autonomic synapses, resulting in autonomic imbalance (predominantly sympathetic overdrive) [19]. Both dogs and cats are susceptible to the Australian form of the disease, whereas cats appear to be resistant to the North American form [20].

Paralysis ticks are endemic in certain geographical locations; most North American cases occur in the Pacific Northwest of the United States/south-western Canada [18]. In Australia, cases are limited to the east coast [20]. Cases of Australian tick paralysis are highly seasonal, with most occurring in the spring and summer months [21].

The North American form is seen as a progressive, ascending, flaccid paresis/paralysis, with signs typically seen first in the pelvic limbs, progressing to tetraplegia over 1–3 days. Muscle tone and segmental spinal reflexes are reduced to absent. Cranial nerves are usually unaffected, with the exception of dysphonia in some cases. Bladder function is usually preserved. Respiratory paralysis may occur if ticks are not removed, though improvement is usually seen within hours of tick removal. Clinical signs are likely to develop more rapidly and be more severe in animals infested with multiple ticks.

Tick paralysis caused by Australian species of hard tick is a more severe disease. The early clinical signs, dysphonia and/or pelvic limb ataxia, can progress to flaccid tetraplegia and respiratory compromise within hours. Muscle tone and segmental spinal reflexes are similarly reduced or absent. Cranial nerves are often affected: pharyngeal and laryngeal dysfunction is common with excessive drooling often seen in animals that cannot swallow. Signs of autonomic dysfunction include cardiac diastolic dysfunction and left-sided congestive heart failure, bladder dysfunction, and pupillary dilation. Animals may vomit or regurgitate secondary to megaesophagus. Signs may be focal or localized in onset [22]. If neurological signs are present, clinical deterioration will often continue for 12–14 hours despite removal or detachment of the tick.

Diagnosis is usually made upon finding an engorged female paralysis tick on an animal exhibiting consistent clinical signs. The tick may not be visible without clipping the entire animal (and checking ears, mouth, genitalia, and anus). Absence of a tick does not exclude tick paralysis as ticks may have detached prior to presentation, so treatment of Australian tick paralysis may be started if the index of clinical suspicion is high. Nerve conduction studies demonstrate decreased CMAP amplitudes without any or significant evidence of slowed MNCV, sensory impairment or denervation potentials on EMG [23].

In North American cases, removal of the tick/s will result in recovery over several hours to days. In Australian cases, progression is likely to occur in spite of

tick removal and treatment with commercially available tick antitoxin serum (TAS) is generally required. Respiratory failure is the main cause of death in both forms of tick paralysis. Australian cases may require ventilation despite treatment with TAS [24]. Supportive care is directed at prolonged recumbency, bladder dysfunction, and treatment of co-morbidities such as aspiration pneumonia. Reported survival probabilities for mechanical ventilation in Australia are 75% (removing the euthanasia decisions based upon cost) which is significantly higher than in other reported studies on mechanical ventilation [25]. Although direct comparison with a previously reported study can be tenuous, those dogs and cats which were being ventilated for tick paralysis and were hypoxemic survived to discharge in 52.6% of cases, compared to 22% in a previous study, and those being ventilated for tick paralysis that were hypoventilating survived to discharge in 90.5% of cases, compared to 39% in the same previous study [25,26]. Although mechanical ventilation is not a benign therapy (and beyond the scope of this chapter; see Chapter 188), requirement for it should not be the basis on which the practitioner makes a terminal decision.

The prognosis for the North American form of tick paralysis is good with removal of the offending tick. Australian tick paralysis has an estimated mortality rate of 5% in spite of treatment [27]. Prevention involves the use of acaricidal products and regular tick searches of pets in endemic areas.

Botulism

Botulism is a rapidly progressive, flaccid paralytic disease caused by intoxication with botulinum neurotoxin (BoNT). BoNT is produced by the gram-positive, anaerobic, spore-forming, saprophytic bacterium *Clostridium botulinum*, which is found in soil worldwide [28]. BoNT is formed under anaerobic conditions and released upon lysis of the vegetative cell or spore. Botulism in dogs and cats is caused by ingestion of preformed BoNT, most commonly in carrion or spoiled food. Seven serotypes of BoNT have been discovered (A–G). All reported canine and feline cases of naturally occurring botulism have been associated with BoNT-C [28,29], excepting two canine cases of BoNT-D [30,31]. BoNT rapidly and irreversibly binds to neuronal surface receptors on nerve terminals, is internalized and prevents synaptic release of ACh at the NMJ, causing flaccid paralysis. As ACh release is also inhibited at autonomic synapses, signs of autonomic dysfunction (both sympathetic and parasympathetic) may be seen, but are usually milder in severity [32].

Animals with botulism often have a history of scavenging/carcass ingestion (either observed or assumed).

Cases may be seen in outbreaks if several animals have had access to the same source of BoNT. Botulism is more commonly reported in dogs than in cats. Any age or breed may be affected.

Signs of neurological dysfunction develop within hours to days of BoNT ingestion, and can be rapid and severe, depending on the amount of toxin and the susceptibility of the individual. Generalized LMN tetraparesis may progress to tetraplegia and paralysis of the muscles of respiration. Muscle tone and spinal reflexes are markedly reduced. Mentation and nociception are preserved. Cranial nerve and autonomic signs are more common in cases of botulism than in other diseases that cause acute generalized LMN signs, and often include facial paresis/paralysis, decreased jaw tone, diminished gag reflex, dysphonia/aphonia, mydriasis with diminished pupillary light reflexes, alterations in heart rate (bradycardia or tachycardia), megaesophagus, constipation, urinary retention, and decreased tear production [28].

Diagnosis is most commonly made on a consistent history and examination findings. Results of electrodiagnostic testing may be unremarkable, but can be useful in excluding other potential causes of acute generalized LMN signs. Confirmation of botulism by mouse bioassay, toxicological, bacteriological and serological methods has been reported in the dog [33], but these are unlikely to be useful in the emergency setting due to limited availability and/or length of time before results are received.

Treatment is supportive, primarily directed at maintaining adequate ventilation, providing nutrition and recumbency care, bladder management, eye care, and physiotherapy. Common sequelae include aspiration pneumonia, urinary tract infections, corneal and decubitus ulceration. The commercially available trivalent antitoxin used in humans with botulism acts against BoNT serovars A, B, and E [34], so will not be effective in canine and feline cases. Animals with botulism may recover fully within a few weeks, with no residual neurological deficits, provided they receive adequate supportive care.

Fulminant Myasthenia Gravis

Acquired myasthenia gravis (MG) is an immune-mediated disease in which autoantibodies are formed against the nicotinic ACh receptors on the postsynaptic membrane of the NMJ. The resultant decrease in functional receptors impairs neuromuscular transmission and leads to skeletal muscle weakness [35]. The inciting cause of autoantibody production may not be demonstrable (so-called “idiopathic” MG), but acquired MG has been associated with certain neoplasms (most notably thymoma [36]).

Acquired MG may present as one of three syndromes: focal, generalized or fulminant [37]. Focal and generalized MG are named according to whether the weakness affects only isolated muscle groups or all skeletal musculature, respectively. In both cases animals show signs of exercise intolerance or weakness that is exacerbated by exercise and abates with rest. Fulminating MG is a less common but more severe form; onset and progression of generalized muscle weakness are rapid and profound, with no improvement with rest. Tetraplegia with respiratory fatigue due to intercostal and diaphragmatic weakness is common. Megaesophagus, silent or overt regurgitation, frequently leads to aspiration, in part because of the weakness of the protective cough and gag reflexes, and the resulting bacterial pneumonia exacerbates the respiratory distress. Signs of cranial nerve dysfunction such as diminished palpebral reflexes and pharyngeal/laryngeal function (decreased gag reflex, dysphonia) are often seen.

Diagnosis of fulminant MG can be challenging; in the emergency setting, it is usually based on a combination of consistent history, clinical signs, and response to short-acting cholinesterase inhibitors. Paradoxically, this syndrome can occur after thymoma removal in patients which had subtle to absent weakness prior to surgery.

After the minimum database, thoracic radiographs should be obtained to look for evidence of megaesophagus, aspiration pneumonia, and/or a cranial mediastinal mass (suggestive of a thymoma). A positive response (improvement in strength) after challenge with a cholinesterase inhibitor such as edrophonium (Tensilon) (0.1–0.2 mg/kg IV dog or 0.25–0.5 mg/cat), or neostigmine (40 µg/kg IM or 20 µg/kg IV) is suggestive of MG, though the sensitivity and specificity of this test are low [38]. Dogs with fulminant MG may not have sufficient functional ACh receptors at the NMJ to respond [39]. Electrodiagnostic testing may yield results consistent with MG (decremental CMAP amplitude on repetitive nerve stimulation, increased jitter on single-fiber EMG), but it is rarely recommended in fulminant cases due to the high risk of aspiration pneumonia under general anesthesia.

Confirmation of diagnosis may be made by demonstrating circulating antibodies against the ACh receptor using an immunoprecipitation radioimmunoassay [38]. The assay has high sensitivity and specificity for diagnosing acquired MG in the dog and cat (positive if >0.6 nmol/L dog, >0.3 nmol/L cat) though as the result takes time to report, treatment of the fulminating form needs to be initiated on suspicion.

Administration of a cholinesterase inhibitor is the mainstay of therapy for fulminant MG in dogs and cats.

Dogs with fulminant MG generally require parenteral dosing due to frequent regurgitation (pyridostigmine 0.01–0.03 mg/kg/h IV, neostigmine 0.4 mg/kg IM). When oral or enteral administration is feasible, pyridostigmine may be given at a dose of 0.5–3.0 mg/kg in dogs and 0.25 mg/kg in cats, every 8–12 hours. As overdosing carries the risk of cholinergic crisis, and individuals are variably responsive to anticholinesterase therapy, the initial dose should be at the low end of the range and be titrated up to clinical effect.

The use of corticosteroids and other immunosuppressive drugs for the treatment of acquired MG remains controversial. In the initial stages of treatment of fulminant MG, they should be avoided as they have the potential to further predispose or exacerbate aspiration pneumonia and may contribute to muscle weakness [35]. Plasmapheresis or IVIg are commonly used in humans with fulminating MG [40,41]. Use in veterinary patients is limited by availability and cost, but use of both has been reported in dogs [42,43].

Animals with fulminant MG require intensive supportive care, almost invariably requiring mechanical ventilation, frequent turning, skin and eye care. Treatment of aspiration pneumonia requires parenteral broad-spectrum antibiotics, ideally selected culture and susceptibility testing results from tracheal wash samples (see Chapter 37).

Though dogs with acquired MG may go into remission spontaneously [44] or with thymoma removal [36], prognosis for fulminant MG in animals is guarded to poor, with respiratory failure being the most commonly reported cause of death [37,39,45].

Other Causes

Acute-onset generalized neuromuscular weakness due to NMJ blockade has also been reported due to many drugs, toxins, and venoms, such as cyanobacteria (blue-green algae), antibiotics (particularly aminoglycosides), organophosphates, black widow spider (North America), red back spider (Australia), Gila monster, hornet and many snake venoms (readers are referred to corresponding chapters of this textbook for more detailed discussion, Sections H and J). In coastal communities, puffer fish envenomation (tetrodotoxin) causes flaccid paralysis requiring ventilation, but usually only for 24 hours or so. In the authors' experience, many dogs and cats with acute lower motor neuron paresis of unknown cause can show signs of improvement, or even resolution of clinical signs, within a few days, so persevering with symptomatic and supportive treatment can be very rewarding even in the absence of a diagnosis.

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B. Respiratory Disease

28

Brachycephalic Syndrome

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Introduction

The term *brachycephalic* is applied to a group of feline or canine breeds with similar facial conformation involving a severe shortening of the muzzle, and therefore the underlying bones, and a more modest shortening and widening of the skull [1]. The French and English bulldogs are popular stereotypic examples of brachycephalic breeds. When pronounced, these anatomical changes can lead to increased resistance to airflow upon inspiration. Such animals are deemed to suffer from brachycephalic syndrome or brachycephalic obstructive airway syndrome (BOAS). While some feline breeds are considered brachycephalic, BOAS is rarely an emergency concern and is infrequently reported in this species [2–4]. Therefore, most of the following discussion will relate to brachycephalic dogs with BOAS.

Systemic Consequences of the Brachycephalic Obstructive Airway Syndrome

The various components of the BOAS can be classified as congenital or acquired defects. Those characteristics are presented in Table 28.1 and depicted in Figure 28.1 [5–16]. The contribution of the soft palate elongation and thickening to the development of BOAS has been outlined in three-dimensional imaging studies [17].

Various factors have been proposed to explain the abnormal soft palate anatomy seen in brachycephalic dogs with BOAS: fatty infiltration, muscular hypertrophy, tissue edema, muscle degeneration, and salivary gland proliferation [18,19]. Hypoplastic tracheae have traditionally been reported in patients with BOAS.

Interestingly, some puppies normalize their tracheal size as they grow [20]. It appears that tracheoscopy is a more reliable tool to diagnose hypoplastic trachea than computed tomography and/or radiographic assessment (which utilizes the ratio of tracheal lumen diameter to thoracic inlet length or thoracic tracheal luminal diameter to width of the proximal third of the third rib) [21,22].

Table 28.1 Reported incidence of various anatomical components of the brachycephalic obstructive airway syndrome.

Abnormality	Incidence
Congenital	
Elongated soft palate*	87–96%
Stenotic nares	58–85%
Hypoplastic trachea**	46%
Prominent nasopharyngeal turbinates	21–100%
Thickened tongue***	Unknown
Acquired	
Everted tonsils	56%
Everted sacculles	55–66%
Laryngeal collapse	53%
Increased oropharyngeal fat***	Unknown
Main stem bronchus collapse	88%

*Due to inflammation and vibration, soft palate elongation and thickening could also be an acquired factor.

**The tracheal diameter in some brachycephalic puppies might normalize by adulthood.

***These characteristics have proven to be contributors to upper airway obstruction and resistance to inspiratory airflow in humans with sleep apnea-hypopnea syndrome.

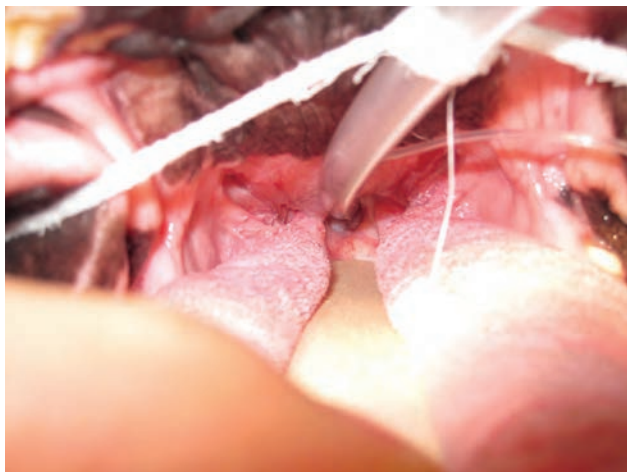


Figure 28.1 Laryngeal examination of an English bulldog with severe brachycephalic syndrome showing an elongated soft palate and everted laryngeal sacculi. The dog is anesthetized with orotracheal intubation prior to corrective surgery.

Patients affected by the BOAS demonstrate similar features as those human patients affected by the sleep apnea-hypopnea syndrome (SAHS). Humans suffering from SAHS also present with increased resistance to inspiratory flow, which worsens at night due to complete episodes of airway obstruction and hemoglobin desaturation, leading to chronic intermittent hypoxia (CIH). Because of physiopathological similarities with the BOAS, English bulldogs with BOAS have been used as a spontaneous model for SAHS. SAHS in humans is established as a systemic disorder and evidence is building to suggest that BOAS should also be regarded as a multisystem condition; overall, breeds with an extreme brachycephalic skull phenotype have a shortened life span when compared with breeds with less pronounced features [23] or height- and weight-matched dogs [24].

In order to overcome upper airway resistance during inspiration, patients with BOAS generate pleural pressures lower than those without upper airway obstruction. Those mechanical forces create strain on thoracic viscera that over time leads to inflammation and fibrosis. While there was no difference in alveolar-arterial gradients in a population of awake brachycephalic dogs when compared to non-brachycephalic dogs, those animals had higher packed cell volumes (48% versus 44%, respectively), which has been attributed to sleep desaturation and CIH [25].

Systemic hypertension is a common sequela of CIH in human SAHS patients [26]. Similar findings have been reported in a group of brachycephalic dogs where diastolic, mean, and systolic arterial blood pressures were significantly higher in brachycephalic than

non-brachycephalic breeds [25]. The underlying mechanisms are currently poorly understood; it has been postulated that these changes could be due to elevated levels of circulating endothelin, aldosterone, or angiotensin.

Significant pleural pressure changes generated with inspiration against upper airway obstruction in brachycephalic dogs with BOAS can be a cause of upper gastrointestinal tract disease, such as esophagitis, gastritis, and duodenitis with resultant regurgitation or vomiting. These animals are also prone to hiatal herniae. In humans, the severity of SAHS improved with medical management of upper gastrointestinal signs [27]. While hiatal hernia is not a life-threatening emergency, it has been associated with gastric dilation-volvulus in a single case report of a brachycephalic dog with historical and physical evidence of BOAS [28].

Chronic intermittent hypoxia is associated with inflammation, which can lead to a prothrombotic state. A retrospective evaluation of rotational viscoelastometry in brachycephalic dogs showed procoagulant features in a population of brachycephalic dogs compared to non-brachycephalic dogs [29]. These findings are believed to be the result of endothelial damage, elevated levels of circulating prothrombotic molecules, platelet priming, and increased blood viscosity.

Finally, a cohort of brachycephalic dogs was shown retrospectively to suffer from intracellular magnesium deficiency [30]. The physiopathological causes and clinical relevance of these findings are not currently well understood. It is important to keep in mind that not all brachycephalic dogs will be affected by BOAS, and that, among those suffering from the syndrome, there is a wide range of disease severity and subsequent pathological consequences.

Acute Upper Airway Obstruction: Current Concepts

Management of upper airway obstructive crisis in brachycephalic dogs with BOAS is a common challenge in the emergency and critical care setting. If they are affected by undiagnosed BOAS, some patients might be presented for an obstructive crisis for the first time. On the other hand, some patients will be presented for decompensation of previously diagnosed and sometimes treated BOAS.

In the emergency setting, brachycephalic dogs with an acute upper airway obstructive crisis should rapidly receive oxygen therapy (see Chapter 181), which can be implemented via either flow-by or face mask delivery. The presence of shock should be promptly evaluated and treated as necessary. Brachycephalic dogs with BOAS crisis will often require sedation in order to minimize

anxiety and turbulent airflow in their upper airway. Various agents can be used (Box 28.1). Some patients may present with such profound distress that orotracheal intubation might be required. A rapid-sequence intubation is then preferable. Induction agents such as propofol

(1–4 mg/kg IV to effect) or ketamine (5–10 mg/kg IV) can be used, and patient monitoring (electrocardiogram, arterial blood pressure, pulse oximetry) should be implemented simultaneously. The patient's temperature should also be evaluated.

Box 28.1 Management of acute upper airway obstructive crisis in dogs with brachycephalic obstructive airway syndrome.

First tier intervention	Evaluate airway patency	Oxygen therapy	Assess for presence of shock
	Consider orotracheal intubation if severe obstruction		Treat accordingly
Second tier intervention	Sedation Acepromazine (0.005–0.01 mg/kg IV) and/or butorphanol (0.3 mg/kg IV) <i>Consider induction of anesthesia and orotracheal intubation if no favorable response observed</i> Temperature control Maintain rectal temperature between 99–102.5 °F (37–39 °C)		
Third tier intervention	Evaluate oxygenation function Pulse oximetry measurement Arterial blood gases evaluation Consider thoracic imaging if hypoxemia documented		
Fourth tier intervention	Consider surgery if Patient distress cannot be alleviated medically or patient was intubated upon presentation and failed extubation		
Prevention of extubation failure in brachycephalic obstructive airway syndrome patients			
Nursing	Maintain patient in a quiet environment Maintain rectal temperature between 99–102.5 °F (37–39 °C) Keep orotracheal tube in place for as long as tolerated by patient Hold mouth open Rostral tongue retraction Prepare for reintubation		
Medical therapy	Consider use of sedation while avoiding oversedation Oxygen therapy		
Adjunct therapies	Laryngeal mask Nasotracheal tube for oxygen delivery High-flow oxygen therapy Temporary tracheostomy 24 h prior to extubation in patients undergoing mid- or long-term mechanical ventilation Consider the use of silicone tracheal stoma stents		
Chronic management of brachycephalic obstructive airway syndrome			
Respiratory signs	Weight loss if overweight Avoid heat or overexertion Surgical correction in patients with overt clinical signs despite medical management		

(Continued)

Box 28.1 Management of acute upper airway obstructive crisis in dogs with brachycephalic obstructive airway syndrome. (Continued)

Gastrointestinal signs	Gastric acidity reduction
	Omeprazole 0.5–1 mg/kg PO SID
	Famotidine 0.5–1 mg/kg PO BID
	Ranitidine 1–2 mg/kg PO BID
	Promotility agent
	Cisapride 0.1–0.5 mg/kg PO BID to TID
	Metoclopramide 0.2–0.5 mg/kg PO TID to QID
	Ulceration treatment
Blood pressure	Sucralfate 1 g/10 kg PO TID
	Measure arterial blood pressure
	Consider treatment if :
	Systolic arterial blood pressure >180 mmHg or
	Systolic arterial blood pressure >150 mmHg and evidence of target organ damage
	<i>Kidney: evaluate blood urea nitrogen, creatinine, proteinuria</i>
	<i>Eye: fundoscopic examination</i>
	<i>Brain: neurological examination</i>
Corrective surgery	<i>Heart/blood vessels: thoracic auscultation and radiographs, electrocardiogram, cardiac ultrasound</i>
	Brachycephalic obstructive airway syndrome
	Wedge rhinoplasty
	Staphylectomy
	Ventriculectomy
	+/- Folded palatoplasty
	+/- Laser excision of nasal turbinates
	Arytenoid lateralization in patients with laryngeal collapse
	Hiatal hernia correction

In a report of canine heat stroke, 25% of patients belonged to brachycephalic breeds (boxer, English bulldog, Shar Pei, Pekinese, dogue de Bordeaux, and Staffordshire bull terrier) while representing only 17% of the hospital general population [31]. This observation is mirrored by brachycephalic dog owners as well, who report their pets' intolerance to heat [32]. Every BOAS patient with an acute upper airway crisis should be carefully assessed for the presence of heat stroke due to inability to dissipate heat in the face of increased respiratory work. Brachycephalic dogs with an acute obstructive crisis and hyperthermia should be actively cooled (water spray and fans) to maintain their rectal temperature between 99 and 102.5 °F (37–39 °C). A summary of the proposed management of acute upper airway obstructive crisis in BOAS patients is presented in Box 28.1.

Obstructive crisis can also be observed upon extubation of brachycephalic dogs that underwent anesthesia with or without oropharyngeal surgery. During anesthesia, upper airway dilator muscle tone is decreased; upon anesthesia recovery, some patients may not tolerate the presence of the orotracheal tube while they still do not have sufficient muscle tone to maintain upper airway patency. This promotes airway collapse and increased resistance to airflow during inspiration. In addition, the presence of the orotracheal tube or concurrent oral, pharyngeal, or laryngeal surgical intervention might create edema in those areas. Brachycephalic patients should therefore be closely monitored for upper airway obstruction upon extubation.

A variety of techniques have been employed to minimize risk of extubation failure. Nursing care is

important, including maintaining the patient in a quiet postanesthetic environment (to avoid anxiety) and ensuring rectal temperature remains within the normal range (99–102.5 °F). Opening the mouth while retracting the tongue rostrally for as long as tolerated by the patient can facilitate extubation success by displacing the tongue away from the laryngeal opening. Adjunct therapies may include placement of a laryngeal mask to maintain upper airway patency. This device seems to be tolerated longer than orotracheal tubes. Laryngeal masks should not be used to replace orotracheal tubes, and their proper placement should always be monitored as they can easily get dislodged. Placement of nasotracheal tubes may also be used to facilitate oxygen delivery in the postanesthetic period. Use of nasotracheal tubes has been associated with minimal complications, such as coughing, vomiting, and regurgitation [33].

Medical intervention may also be required, including light sedation and oxygen therapy. High-flow oxygen therapy can be used to help maintain upper airway patency, similar to continuous positive airway pressure (CPAP) therapy employed in humans with SAHS. Some machines provide air with fractions of inspired oxygen ranging from 21% to 100% at high flow rates (up to 40 L/min); in order to facilitate tolerance by the patient, the air is humidified and warmed. Corticosteroid administration prior to extubation has not been investigated. While there is no evidence to support this practice, corticosteroids can be administered at an anti-inflammatory dose (0.5–1 mg/kg of prednisone equivalent per day), preferentially hours prior to extubation.

Finally, some patients with prolonged intubation and overt concerns for upper airway obstruction following intubation might benefit from a temporary tracheostomy. In this author's opinion, this procedure is often performed 24 hours prior weaning from to mid- or long-term mechanical ventilation. The use of a tracheostomy stoma stent has recently been described in a group of brachycephalic dogs [34]. Overall, the device appeared to be well tolerated. Data suggest against the use of the stents beyond 5 days in an attempt to prevent overt granulation tissue formation and stent displacement. A summary of interventions used to minimize the risk of extubation failure is presented in Box 28.1.

In the intensive care unit in one report, brachycephalic dogs were more likely to undergo mechanical ventilation than non-brachycephalic breeds [35]. The most common indication for ventilator therapy in brachycephalic dogs in that study was aspiration pneumonia, most likely owing to the frequency and severity of regurgitation and vomiting in brachycephalic dogs suffering from BOAS. Discharge rate was comparable to that reported for the general population of dogs undergoing mechanical ventilation.

Treatment of Brachycephalic Syndrome

Patients at risk for BOAS should undergo medical therapy prior to considering surgical intervention. As the volume of fat in the oropharyngeal region has been associated with an increased risk for SAHS in humans, it is fair to insure that dogs with signs of BOAS and an elevated body condition score should undergo a weight loss program. Additionally, those animals should not be exposed to high ambient temperatures, particularly in high humidity environments. Overexertion should be avoided. Management of upper gastrointestinal signs (vomiting and regurgitation) has been advocated in order to decrease the severity of clinical signs in humans with SAHS. A proposed protocol for the long-term management of BOAS is presented in Box 28.1 (management of gastrointestinal signs is adapted from [36]). Brachycephalic dogs should also have their arterial blood pressure monitored and those patients with systemic hypertension should be medically managed.

For BOAS patients who fail medical therapy, surgical correction should be considered. Some dogs that present for the first time with overt signs of BOAS might also benefit from surgical intervention. Patients that require intubation in the emergency room due to a BOAS crisis and subsequently fail extubation after initial medical therapies would be considered surgical candidates. Presently, BOAS surgical corrective interventions include wedge nasoplasty (rhinoplasty), soft palate resection (staphylectomy), and everted laryngeal sacculae resection (ventriculectomy or saccullectomy). Despite surgical correction of soft palate and nares abnormalities, spontaneous resolution of sacculae eversion is unlikely and saccullectomy should be considered at the time of surgery [37]. Figure 28.2 shows the laryngeal examination of an English bulldog following surgical intervention.



Figure 28.2 Laryngeal examination of the dog shown in Figure 28.1, following soft palate and laryngeal sacculae resection.

Future Directions

Brachycephalic dogs are becoming increasingly popular pet breeds [38]. While providing appropriate home and in-hospital care for BOAS patients can be challenging, the veterinary community faces other difficulties related to brachycephalic dogs. Diagnosis and grading the severity of BOAS remain a scientific and clinical challenge. Some brachycephalic dogs may have histopathological signs of BOAS (esophagitis, gastritis, or duodenitis) without overt clinical signs, such as vomiting or regurgitation [39]. Whole-body plethysmography (WBP) proved more sensitive than client judgment for diagnosing BOAS in

French bulldogs [40]. Therefore, WBP and waveform analysis may gain popularity as a BOAS diagnostic tool in the future [40,41]. A comprehensive owner questionnaire has recently been validated and may also prove helpful in staging owner-perceived severity of disease and response to experimental therapies [32].

Genetic analysis of brachycephalic traits has been performed [1], and the concept of altered breeding practices aimed at genetic improvement is gaining popularity in the field of brachycephalic dogs medicine. Adapting breeding standards would be an invaluable tool to prevent abnormal and potentially pathological phenotypes.

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29

Feline Upper Respiratory Complex

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Introduction

Feline upper respiratory infection (feline URI) is a common syndrome affecting cats in shelters, boarding facilities, and multiple cat households. A variety of viral and bacterial pathogens have been implicated and the development of disease is multifactorial. Simultaneous infection with multiple pathogens exacerbates the severity of illness [1,2].

Even though the mortality rate for affected cats is generally low, feline URI is an important cause of morbidity. Neonates and young kittens have an increased risk of mortality in situations with crowding and unhygienic conditions.

Causes/Infectious Agents

The majority of cases are caused by feline herpesvirus-1 (FHV-1) or feline calicivirus (FCV). Bacterial agents associated with the disease include *Bordetella bronchiseptica*, *Chlamydomphila felis*, and *Mycoplasma* species [2]. Some authors suggest involvement of other infectious agents as well. However, all pathogens have been isolated from both healthy and clinically ill cats [3].

Feline Herpesvirus-1

Feline herpesvirus-1 is a double-stranded, enveloped DNA virus. It generally induces more severe signs than the other organisms [1]. Only one serotype exists. It is fragile outside the host and can only survive for up to 18 hours in the environment. FHV-1 is susceptible to common disinfectants [2].

After acute infection, FHV-1 persists in a latent form in the trigeminal ganglia. Periodically, especially after stress, the virus is reactivated and the carrier starts shedding [4]. Shedding starts approximately 1 week after a

stressful event and lasts up to 1–2 weeks with a refractory period of several months after each reactivation [2].

Feline Calicivirus

Feline calicivirus is a single-stranded non-enveloped RNA virus [2]. A large number of different strains with variable pathogenicity exist. FCV can persist in the environment for several weeks and is less susceptible to disinfectants [4]. Some cats reportedly maintain a carrier state [5], although recent studies suggest that only a small percentage of cats are true persistent shedders. The majority of cats undergo reinfection from other cats [4].

Both viruses are primarily transmitted by direct contact, not aerosols. Shedding occurs through ocular, nasal, and oral secretions [2]. Indirect transmission may occur in situations with crowding. Acutely infected cats are the most important source of infection, but transmission also commonly occurs through non-clinical carriers [4].

Bordetella bronchiseptica

Bordetella bronchiseptica is an aerobic, gram-negative coccobacillus. It is a common respiratory pathogen in cats and other species and can cause opportunistic infections in people. *B. bronchiseptica* has historically been viewed as a secondary infectious agent but has recently been established as a primary pathogen [6]. It is more likely to cause disease in crowded and stressful environments. Transmission between cats and dogs is possible and therefore an important factor in disease control [2]. The organism may be shed for up to 19 weeks post infection [6].

Chlamydomphila felis

Chlamydomphila felis is an obligate intracellular gram-negative bacterium which does not survive outside the host. Shedding occurs in ocular secretions and

transmission therefore requires close contact. Although there is a risk for infection of exposed humans, it is not a common zoonotic infection [1,7].

Mycoplasma

Mycoplasma spp are gram-negative pleomorphic bacteria that lack a cell wall. The role of mycoplasma in feline URI is controversial. Many species are normal commensals in the upper respiratory tract but there is increasing evidence that some species play a primary or secondary role in URI and conjunctivitis [8–10]. *Mycoplasma* species have not been found in the lower airways of healthy cats and likely represent a pathological process when present [8].

Clinical Presentation

Feline URI is usually an acute illness, but chronic disease sequelae are possible [1]. Clinical signs range from mild to severe. Secondary bacterial infections can lead to complications, including lower respiratory infections (Table 29.1).

Table 29.1 Typical clinical manifestation based on pathogens involved.

Pathogen	Clinical Manifestation
FHV-1	Ocular and nasal discharge Sneezing Conjunctivitis (ulcerative) Keratitis Pyrexia, Lethargy
FCV	Oral ulceration Mild URI signs Pyrexia Limping Pneumonia
FCV-VSD	Peripheral edema, dermal ulceration, vasculitis SIRS, DIC, MODS, death
<i>B. bronchiseptica</i>	URI signs Coughing Pneumonia
<i>C. felis</i>	Conjunctivitis
<i>Mycoplasma</i> spp.	Conjunctivitis Ocular and nasal discharge

Feline Herpesvirus-1

Feline herpesvirus-1 causes upper respiratory signs including oculonasal discharge, conjunctivitis, sneezing, and occasionally hypersalivation and coughing. Affected cats show signs of depression, pyrexia, and decreased appetite. Initially, they have serous nasal and ocular discharge. With or without secondary bacterial infections, the discharge often becomes mucopurulent and cats develop crusting of nares and eyelids. Secondary bacterial infections reportedly enhance the virulence [2,11].

More serious signs including pneumonia and generalized systemic disease can occasionally be seen in neonates and immunosuppressed animals [11,12].

Feline herpesvirus-1 is also frequently associated with ulcerative keratitis. The role of FHV-1 in chronic ocular conditions such as eosinophilic keratitis, corneal sequestration, and uveitis is not completely clear. Skin lesions and ulceration have also been described [4,11]. Some authors believe that herpes infection can predispose cats to chronic rhinosinusitis as a result of damage to nasal turbinates or due to chronic immune stimulation [1,13].

Feline Calicivirus

Feline calicivirus most characteristically causes oral ulceration which typically develops on the tongue but can also occur elsewhere in the mouth or skin. Classic URI signs are reported as well, but these are usually milder than those seen with FHV-1 [2].

With some strains, lameness and pyrexia can be seen following FCV infection [5]. Full recovery usually occurs within 24–48 hours [2]. Some strains have a predilection for the lung and pneumonia has been described. It is believed that an immune-mediated reaction to FCV may cause chronic lymphoplasmacytic gingivitis/stomatitis [1].

Hypervirulent strains (FCV virulent systemic disease: FCV-VSD) have emerged and infect not only epithelial cells of the upper respiratory tract and oral cavity, but also endothelial cells, hepatocytes, pneumocytes, and pancreatic acinar cells [14]. Clinical signs of FCV-VSD infection include cutaneous edema, alopecia, crusting, and ulceration [12]. Edema develops most commonly on the head and limbs. Ulcerations are the result of severe vasculitis and are most prominent on the nose, lips, pinnae, periocularly, and on the distal limbs [15,16]. Affected cats can develop systemic inflammatory response syndrome, disseminated intravascular coagulation, multi-organ failure and death, with mortality rates described as high as 50–67% [5,12,16]. Outbreaks of FCV-VSD are sporadic and often involve shelter cats [1]. The disease is more severe in adult cats than in kittens. Vaccination does not seem to prevent infection with FCV-VSD [15,17,18].

Bordetella bronchiseptica

Bordetella bronchiseptica-related signs vary from mild upper respiratory signs to bronchopneumonia. A classic sign of bordetellosis in cats is coughing [2,6].

Chlamydophila felis

Chlamydophila felis is primarily a cause of conjunctivitis with only mild respiratory signs [2]. *C. felis* in combination with other organisms can lead to a more severe clinical presentation [19].

Mycoplasma

Mycoplasma spp are more prevalent in cats with conjunctivitis or upper respiratory disease than in healthy cats. Clinical signs include nasal and ocular discharge, sneezing, conjunctival hyperemia, and possibly keratitis [8,12].

Risk Factors

Feline URI is most commonly seen with crowding situations and stress. Stresses that may induce virus shedding include a change in housing, parturition, lactation, and corticosteroid therapy. Some cats may show clinical signs during reactivation. Other cats will be silent shedders [4]. One study showed that among adult cats, both intact and neutered males had a higher incidence of URI than spayed females [20].

Diagnosis

A diagnosis of feline URI is usually based on clinical signs. Any cat with an acute onset of URI signs and/or conjunctivitis and recent exposure to other cats should be suspected [1]. It is important to consider other differential diagnoses for URI signs such as toxic burns, foreign body, polyp, neoplasia, trauma, cleft palate, chronic rhinitis, and fungal infection [3,13].

Supportive treatment is similar, regardless of the pathogen involved. Diagnostic testing is most useful for catteries or animal shelters experiencing an increased incidence or severity of URIs [1].

Historically, virus isolation was attempted through cell culture. Immunofluorescence has also been used, particularly for FHV-1. In recent years, PCR has been commonly used. PCR is more sensitive than virus isolation, but there is great variability based on the laboratory and technique involved. FHV-1 can be detected as early as 1 day after infection and persists up to 3 weeks [2].

Interpretation of test results can be difficult. A positive result can support clinical disease, but can also indicate a shedding carrier or recent vaccination. False positives are common [3,4].

For FCV detection, reverse-transcriptase PCR is available but may be less sensitive due to the variability in strains, which may lead to false-negative results [4].

Polymerase chain reaction assays are also available for *B. bronchiseptica*, *C. felis* and *Mycoplasma* species, but are often not clinically useful. Since each of these organisms can be detected in healthy cats, the positive predictive value for these assays is low [13].

Several studies have compared different sampling sites including conjunctiva, nose, and oropharynx [21,22]. Detection rates of different organisms were similar between sites, with the exception of *B. bronchiseptica* [21]. The oropharynx was recommended as the preferred sampling site if only one sample can be taken. Obtaining samples at different sites significantly increased the detection rate for all pathogens [22].

Treatment (Table 29.2)

Supportive Treatment

The most important aspect of treatment is supportive care. Severe cases require hospitalization and fluid therapy. Many cats will not eat because of impaired sense of smell or oral ulceration. Warming food or offering highly palatable, aromatic foods might help [2]. Appetite stimulants can be used and some cats require nasogastric or nasoesophageal feeding tubes to ensure nutritional support [11].

Ocular and nasal crusting or discharges should be wiped away frequently to increase comfort. Steam inhalation or nebulization with saline may be helpful.

Cats with ocular lesions require topical treatment. Patients with severe respiratory compromise might require supplemental oxygen. Analgesia should be provided for cats with oral ulcers, lameness, or other complications of infection [1].

Antibiotics

In most cases of primary viral URI, antibiotic treatment is not necessary. In severe cases, broad-spectrum antibiotics can be given to control secondary bacterial infections [2]. For this purpose, beta-lactams (e.g. amoxicillin, amoxicillin-clavulanic acid) and azithromycin are reasonable choices [23].

Doxycycline is the antibiotic of choice for *B. bronchiseptica* infection. It is also a good antibiotic to treat infections with *C. felis* and *Mycoplasma* spp and achieves good airway penetration. Other antibiotics

Table 29.2 Drugs and recommended dosing for treatment of feline URI.

Drug	Class	Route of administration	Recommended dose	Comment
Antibiotics				
Doxycycline	Tetracycline	PO or IV	5 mg/kg q12h or 10 mg/kg q24h	Esophagitis and strictures possible Caution in pregnant and young animals
Azithromycin	Macrolide Antibiotic	PO	5–10 mg/kg q24h for 5 days, then q72h	Very long tissue half-life
Pradofloxacin	Fluoroquinolone	PO	7.5 mg/kg q24h	Enhanced gram-positive and anaerobic activity
Other antibiotics				
Enrofloxacin	Fluoroquinolone	PO, IV, IM	5 mg/kg q24h	Do not use >5 mg/kg in cats — may cause blindness
Trimethoprim-sulfamethoxazole	Potentiased sulfonamide	PO	15 mg/kg q12h	Anorexia, crystalluria, hematuria, leukopenias and anemias reported in cats
Antivirals				
Famciclovir	Acyclic nucleoside analog	PO	40–90 mg/kg q8h	Converted <i>in vivo</i> to penciclovir
Cidofovir	Acyclic nucleoside analogue	Topical	1 drop q12h for 10 days	Not commercially available — compounded as a 0.5% ophthalmic solution nephrotoxic in humans Do not use in cats intended for breeding
Other topical agents				
Idoxuridine		Topical	1 drop q4-6h for 2–3 weeks	
Trifluridine				
Vidarabine				
Aciclovir				
Interferons				
Feline IFN-omega	Immunomodulating cytokine	Topical	Dilute 10 million U vial in 19 mL 0.9% NaCl — 2 drops OU q4-6h	Hyperthermia, vomiting, diarrhea, increased ALT, bone marrow suppression reported Expensive
		PO	50 000–100 000 U q24h	
		SQ	0.75–1.5 million U/kg q24h	
Human IFN-alpha	Immunomodulating cytokine	PO	30-50 U/cat, q24h	Well tolerated orally Parenteral use associated with adverse effects
		SQ	10 000 U/kg (diluted in saline) q24h	
Lysine	Amino acid	PO	250–500 mg/cat q12h	Concurrent arginine depletion required

Source: Plumb's Veterinary Drug Handbook, 8th edn.

with good activity against bacterial agents include trimethoprim-sulfamethoxazole, azithromycin, enrofloxacin, and pradofloxacin [2].

Since dry pilling of doxycycline can cause esophageal strictures in cats, liquid compounds are preferable. Alternatively, pill administration can be followed with water [1]. Doxycycline should be avoided during pregnancy or in neonates. Enrofloxacin has been associated with sudden blindness and retinal degeneration in cats. The fluoroquinolone pradofloxacin is reportedly safe and has good efficacy against *C. felis* and *Mycoplasma* spp. Azithromycin and fluoroquinolones improve clinical signs but are less effective in clearing infection with *C. felis* than doxycycline [24].

Antivirals

No medications are available that were specifically developed for cats or feline viral infections. A large number of human oral and topical antiviral drugs have been used but often have poor activity against FHV-1 or are too toxic for cats [25]. Most medications are virostatic and only inhibit replication of DNA- or retroviruses. Antiviral treatments for FCV infections are not widely available for clinical use [5]. Famciclovir has been established as a potent and safe antiviral drug. Treatment with famciclovir results in clinical improvement in both acute and chronic herpesviral disease and decreases viral shedding [26,27]. It has proven efficacy in cats with ocular, upper respiratory, and cutaneous signs and is well tolerated in kittens [28].

Topical ophthalmic preparations that contain idoxuridine, trifluridine, vidarabine or aciclovir have been used to treat herpesviral keratitis, but the efficacy of these drugs is unknown. Frequent topical application (5–6 times daily) and prolonged use are required. A new topical alternative (cidofovir 0.5% compounded solution in artificial tears) shows greater promise and only requires twice-daily application. It is active against FHV-1 *in vitro* and in experimentally infected cats [12,25,29].

Feline herpesvirus-1 is reportedly susceptible to feline recombinant interferon-omega and recombinant human interferon-alpha. Interferons (IFNs) may be effective as non-specific antiviral agents and modulate cytokine cascades to decrease inflammation and signs associated with FHV-1 or FCV. They may be a treatment option for cats with persistent chronic viral URI that have failed conventional therapies [30,31]. These drugs have been administered parenterally, topically, and orally to cats with FHV-1 infection. Clinical responses to treatment vary and further research is needed to determine efficacy and safety [12].

Oral lysine may be useful in FHV-1-infected cats. Lysine is an essential amino acid that interferes with FHV replication *in vitro*. The antiviral mechanism is not completely understood. FHV-1 requires arginine for

viral replication. *In vitro* studies show that lysine supplementation reduces viral replication by about 50% with concurrent depletion of arginine. Therefore arginine restriction is necessary for lysine to be effective [25]. It may reduce the number of shedding episodes caused by reactivation. Evidence suggests that it is not effective in reducing clinical signs in cats with acute URI. It was also found ineffective as a preventative in shelter populations [32,33]. In privately owned cats, it can be used as an adjunctive therapy and nutritional supplement [3,25].

Prevention

Vaccination, stress reduction, and disinfection are most important for disease control. Vaccination for FCV and FHV-1 is considered a core vaccine [1]. Vaccines also exist for *C. felis* and *B. bronchiseptica* [34].

Both modified live and inactivated adjuvanted vaccines are available for injection. A modified live intranasal vaccine is available in some countries but is not widely used. Intranasal vaccines offer a more rapid onset of protection with the disadvantage that some cats develop mild respiratory signs [4].

The American Association of Feline Practitioners and World Small Animal Veterinary Association vaccination guidelines recommend the first vaccine in kittens around 6–9 weeks, with repeated doses every 3–4 weeks until 16 weeks of age. Booster vaccination is recommended after 1 year. Revaccination is recommended yearly or every 3 years, depending on the risk of infection [35,36].

Routine vaccination against *B. bronchiseptica* is not recommended and should be reserved for cats in high-risk situations. Transmission between dogs and cats is possible [6]. None of the vaccines prevent infection or the development of a carrier state. Vaccinated cats are reported to be less severely affected [4].

Besides limiting contact with infected cats, disinfection of surfaces and hand hygiene can help to reduce the incidence of feline URI. Cleaning and disinfection will destroy most of the pathogens; only FCV is difficult to inactivate. Diluted hypochlorite (household bleach) and a detergent mixture are reportedly effective [1,4].

Prognosis

Feline URI is highly contagious through direct contact and large outbreaks occur commonly in shelters and other situations with crowding. The mortality rate is usually low. Exceptions are kittens in poor housing situations and infection with FCV-VSD. Affected cats usually recover within 1–2 weeks, but reactivation can lead to recurrence of signs during stressful situations.

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30

Laryngeal Paralysis

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Introduction

Laryngeal paralysis is an upper respiratory disease that occurs when a patient is unable to abduct the arytenoid cartilages on inspiration. There are congenital and acquired forms, with acquired being the most common. Acquired laryngeal paralysis can occur secondary to trauma, neoplastic, or iatrogenic causes, and has also been associated with other disorders such as hypothyroidism, diabetes mellitus, and myasthenia gravis [1].

Idiopathic is the most common form of laryngeal paralysis, but may represent a form of progressive neuromuscular disease. This polyneuropathy syndrome is characterized by demyelination and axonal loss of long large-diameter nerves [2]. The recurrent laryngeal nerves are the longest nerves in the body and innervate the cricoarytenoideus dorsalis muscles, which are responsible for abduction of the arytenoids. As these nerves degenerate, patients have decreased abduction of their arytenoids and express more respiratory effort. Because this laryngeal paralysis- polyneuropathy syndrome can affect other nerves, these patients can also have progressive hindlimb weakness and/or muscle atrophy. A study showed dogs with co-existing neurological abnormalities are at a higher risk of developing postoperative complications after surgical treatment for laryngeal paralysis [2].

This disease occurs most commonly in large-breed dogs and is more common in males compared to females [3]. Although this disease is very rare in cats, it has been reported and the clinical presentation is similar to dogs (middle aged, change in voice, stridor, etc.) [4].

Clinical Signs

Patients with laryngeal paralysis typically present for increased respiratory effort and stridorous breathing.

Respiratory effort and associated sounds may be more marked on inspiration compared to exhalation. Other clinical signs include dysphonia, gagging, retching after drinking water or eating, coughing, and collapse or exercise intolerance.

Emergency Treatment

Patients with laryngeal paralysis are often in severe respiratory distress on presentation and require immediate treatment prior to diagnostic tests. This initial treatment is aimed at improving ventilation, reducing laryngeal edema, and minimizing stress. Improvement of ventilation is achieved with sedation and oxygen therapy. Sedation aims to reduce the respiratory effort and as a consequence, reduce the degree of pressure change experienced in the upper airway. This may allow the animal to maintain inspiratory airflow without causing laryngeal adduction and airway obstruction.

Butorphanol (0.1–0.3 mg/kg IV) and/or acepromazine (0.02–0.1 mg/kg IV) are commonly used sedative drugs in the initial stabilization of the patient with upper respiratory disease (see Chapter 32). Oxygen therapy via flow-by or mask may be effective during the initial stabilization period. Laryngeal swelling or edema is treated with non-steroidal drugs (NSAIDs) or glucocorticoids and time. Carprofen (2.2 mg/kg IV or IM for dogs) or dexamethasone SP (0.1 mg/kg IV, dogs and cats) are possible options. Additionally, these patients can be hyperthermic and will require efforts to reduce their temperature, such as wetting the fur and use of cooling fans (see Chapter 147). Active cooling should be stopped when the animal's temperature reaches 103°F. If the patient responds to initial stabilization therapy, full diagnostic evaluation can be performed and consideration for surgical management on an elective basis made.

If patients do not respond to these initial therapies, and severe respiratory distress persists or worsens, orotracheal intubation may be needed. Ideally, surgical intervention would occur soon after tracheal intubation to reduce the incidence of aspiration pneumonia, rather than maintaining the patient under general anesthesia for a prolonged period of time. If long-term management is required before surgical intervention, tracheostomy tube placement may be preferable to prolonged orotracheal intubation. Temporary tracheostomy tube placement prior to surgery in dogs with laryngeal paralysis has been shown to be a negative prognostic indicator and prolonged tracheal intubation in these patients makes them more likely to experience major complications [5]. General anesthesia alone places a patient at risk of aspiration pneumonia and this risk has been reported to be 17–50% [6,7]. A temporary tracheostomy tube requires intensive monitoring (see Chapter 180).

Emergency Diagnostic Tests

Once the animal is stabilized, a thorough history should be obtained and a complete physical examination completed. Laryngeal paralysis is often a chronic disease process that has had an acute exacerbation resulting in presentation to the emergency room. Every effort should be made to determine the cause(s) of this acute event. These causes are factors that promote increased respiratory rate and effort such as exercise and/or heat or co-existing respiratory disease such as aspiration pneumonia.

A minimum database, including thyroid testing, should be performed based on the patient's age and

co-existent diseases. This database should include chest radiographs for evaluation of aspiration pneumonia, non-cardiogenic pulmonary edema, and megaesophagus. Neck radiographs should be included to evaluate for other causes for upper airway obstruction, such as cervical tumors and trauma, or intraluminal laryngeal tumors or masses (Figure 30.1). Additionally, a neurological examination should be performed to document existing neurological co-morbidities that can put a patient at greater risk for developing postoperative complications.

A definitive diagnosis of laryngeal paralysis is made by direct visualization of the larynx under a light plane of anesthesia. This laryngeal examination is ideally done on an elective basis at the time of surgical treatment. Thiopental is the best agent for assessing laryngeal function, but due to lack of availability of this agent, propofol is the next best choice [8]. Doxapram HCl can be used to increase the respiratory rate and aid with laryngeal examination. Additionally, it is helpful to have an assistant verbally notifying the clinician when the patient is inspiring during laryngeal examination.

The diagnosis of laryngeal paralysis is made when examination reveals bilateral failure of arytenoid movement on inspiration. The diagnosis can be confounded by paradoxical movement, which is medial folding or inward movement of the cuneiform processes of the arytenoids on inspiration and passive return to normal position on expiration, giving the false impression of normal laryngeal movement [9]. Most patients with clinical signs will have bilateral paralysis, and those with unilateral paralysis have none to mild clinical signs [9].



Figure 30.1 Lateral neck radiograph of a dog presenting for signs of upper airway respiratory distress. Increased soft tissue opacity in the region of the larynx is evident, suggestive of a laryngeal mass that was later confirmed on laryngeal evaluation.

Long-Term Management

The best time to perform surgery for laryngeal paralysis is determined by a multifactorial decision-making process between the owner and clinician/medical team. If a patient's quality of life is severely affected by this disease, such that collapse, increased respiratory effort at rest and/or life-threatening events associated with laryngeal paralysis have occurred, surgery would be recommended. But many mildly affected individuals can be managed for a period of time by reducing stress, avoiding moderate or intense exercise, and avoiding heat.

Prognosis

Long-term outcome for dogs with laryngeal paralysis treated with a unilateral arytenoid lateralization is excellent and owner satisfaction is high, with the majority of owners reporting that the quality of the dog's life was improved [10,11]. The most common complication in patients with laryngeal paralysis undergoing surgical treatment is aspiration pneumonia [12]. This complication occurs in 5–24% of patients after surgical treatment and can occur in the immediate postoperative period and remains a risk for the remainder of the patient's life. Megaesophagus and use of postoperative opioids can increase the risk of aspiration pneumonia in patients after unilateral arytenoid lateralization [12].

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31

Tracheobronchial Injury and Collapse*Dana L. Clarke, VMD, DACVECC**University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA, USA***Anatomy and Physiology of the Trachea**

The trachea is composed of 35–45 C-shaped hyaline cartilaginous rings connected dorsally by the trachealis muscle [1–5]. Individual rings are attached to each other ventrally and laterally by the fibroelastic annular ligaments. It spans from the caudal aspect of the cricoid cartilage of the larynx to the cranial carina, which marks the origin of the mainstem bronchi. Its main function is to serve as a conduit for airflow from the upper to lower respiratory tract. Airflow velocity can be altered by contraction of the dorsal tracheal membrane under control of the vagus nerve which, in conjunction with the mucociliary escalator, is responsible for clearance of particulate matter from the airway via coughing and particle movement by mucus trapping and co-ordinated ciliary transport cranially [3–5]. Blood supply to the trachea is segmental, and originates from the cranial and caudal thyroid arteries [1–3,5].

In response to inflammation or trauma, the tracheal mucosal goblet cells increase mucous secretion. The thickened mucous layer, as well as cellular desquamation, create a mucosal barrier, allowing superficial defects to heal as early as 2 hours after injury [5–7]. Within 96 hours, the transitional epithelium becomes organized and differentiated into goblet cells and ciliated columnar epithelial cells [5–7]. Full-thickness wounds heal in a similar fashion if there is appropriate mucosal apposition [5]. Mucosal defects or retraction of the wound edges results in granulation tissue formation prior to epithelialization, which can reduce the luminal diameter of the trachea, leading to stenosis as well as impairment of function of the mucociliary escalator [5–7].

Emergency Management

As with other causes of upper airway obstruction, patients with acute tracheal trauma or airway obstruction from

tracheal collapse can present with varying severities of respiratory distress and compromise of oxygenation and ventilation. Sedation, control of anxiety, and oxygen supplementation are first-line therapies for patients presenting in respiratory distress secondary to upper airway obstruction and may effectively stabilize many patients. Since pneumothorax (see Chapter 44) can occur with tracheobronchial injuries, emergent thoracocentesis may be necessary in this patient population to ensure respiratory and cardiovascular stability (see Chapter 183). However, for patients whose distress is not controlled with medical therapies or those in such extremis that there is not enough time for medical management to be effective, heavy sedation and emergent intubation may provide life-saving relief of the airway obstruction. For emergency examination and stabilization of acute airway obstructions, see Chapter 32. For more detailed discussion of oxygen therapy and airway management, see Chapters 180 and 181).

If general anesthesia is needed for patient stabilization, to facilitate diagnostics to confirm the nature of tracheobronchial injury, or allow for definitive surgical intervention, intubation must be performed cautiously. If tolerated by the patient, clipping of the ventral neck prior to intubation should be considered in the event that emergent tracheostomy is necessary. If possible, a brief upper airway examination should be performed upon intubation to ensure appropriate laryngeal integrity and function. Anesthetic drug selection and measures to control anesthetic depth should be taken to maintain a plane of general anesthesia that allows the patient to ventilate on their own. Positive pressure ventilation and high airway pressures should be avoided to minimize the risk of continued air leakage from the traumatized airway, which can create or worsen pneumothorax and lead to cardiopulmonary instability or arrest. Care should also be taken on intubation to avoid further disruption of tracheal integrity. Materials necessary for thoracocentesis

and thoracostomy tube placement should be readily available when anesthetizing all patients with tracheobronchial injury (see Chapters 183 and 184).

Tracheobronchial Injury

Tracheobronchial injury, which may occur at any location along the trachea and principal bronchi, can result from intraluminal or extraluminal trauma and can range in severity from small lacerations to complete avulsions [3,6,8,9].

Extraluminal trauma most commonly results from bite wounds, penetrating foreign objects, and blunt force trauma, as with vehicle accidents [3,6,8–20]. A case of tracheal perforation from suture irritation after a ventral slot has also been described in a dog [21]. Cervical bite wounds account for 22–27% of all bite wound injuries, and tend to be associated with higher mortality rates [11,22,23]. In one study of cervical bite wounds in dogs and cats, 17% had trauma to the airway [11]. Tracheal avulsions of the intrathoracic trachea just cranial to the carina, as well as bronchial avulsions, have been described in cats. Avulsions are the result of blunt force trauma to the chest causing increased tracheal airway pressures against the closed glottis or causing movement of the mobile trachea against the more fixed carina [6,8,13–20]. After avulsion trauma, the tracheal adventitia and mediastinal tissues form a pseudoairway to allow continued respiration but can ultimately lead to stenosis of the avulsed ends of the trachea if untreated [8,13–17,19,20,24–26].

Intraluminal trauma is most often associated with endotracheal intubation, which has been well described in cats and rarely reported in dogs [6,8,19,27–31]. Injuries associated with intubation include overinflation of the endotracheal tube cuff, damage from the use of a stiffened stylet to facilitate intubation, failure to deflate the cuff prior to movement of the tube on extubation, movement of the patient's head or neck without disconnecting the endotracheal tube from the anesthetic circuit, and type of endotracheal tube used [27,28]. Most clinical feline patients with tracheal tears had a history of intubation for dental procedures [27,28]. Low-pressure, high-volume endotracheal tubes are likely safer than high-pressure, low-volume tubes. However, inflation of the cuff to prevent gas leakage rather than an arbitrary volume is likely more important than the type of tube [27,28,32]. Since the majority of the tracheal circumference is composed of the rigid tracheal cartilages, intraluminal injuries tend to occur in the dorsal tracheal membrane at the junction between the trachealis muscle and the cartilaginous ring along the trachea wherever the cuff was positioned during intubation [6,27,28]. A report of tearing along the midline of the trachealis muscle has been reported in a cat [31].

Clinical Signs and Physical Examination Findings

Both acute and chronic respiratory distress signs have been reported in animals with tracheobronchial injuries. In addition, a syndrome of delayed, chronic respiratory compromise has been reported in cats with tracheal avulsion injuries due to pseudoairway formation and a dog with necrosis of the trachea following intubation

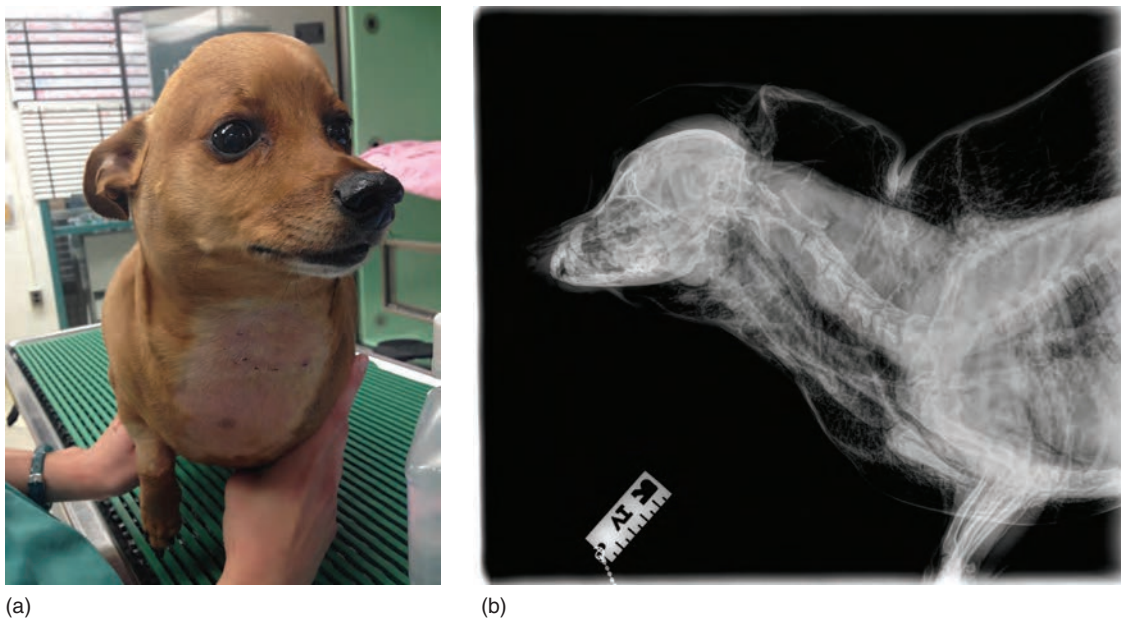


Figure 31.1 Picture (a) and lateral cervical radiograph (b) of a dog with a tracheal perforation secondary to ventral cervical bite wounds.

Table 31.1 Clinical signs and physical exam findings associated with tracheobronchial injury.

Acute respiratory distress	Delayed respiratory distress
Subcutaneous emphysema	Increased respiratory rate and/or respiratory effort
Increased respiratory rate and/or respiratory effort	Open mouth breathing
Inspiratory stridor	Orthopnea
Decreased bronchovesicular sounds consistent with pneumothorax	Expiratory dyspnea consistent with pseudoairway collapse under increased intrathoracic pressure upon expiration
Orthopnea	
Prolonged inspiratory phase with normal or increased expiratory push	Anorexia/weight loss
Hypersalivation	Dehydration
Coughing (with or without hemoptysis)	Exercise intolerance
Gagging/retching/vomiting	Other injuries consistent with prior trauma (broken nails, abrasions, lacerations)
Sublingual/pharyngeal swelling	

[6,8,10,13–18,24–26,30]. Animals with acute traumatic dyspnea secondary to tracheobronchial injury generally present within several hours of the injury whereas those with delayed clinical signs can present with respiratory compromise anywhere from 2 days to 3 weeks after the initial trauma [9,13,14,16–18,20,24–28].

The most common clinical sign in animals acutely affected by tracheal trauma is subcutaneous emphysema from air leakage from the damaged airway into the subcutaneous tissues, with or without obvious skin wounds (Figure 31.1) [6,8,11,27,28]. Since the most common cause of tracheobronchial injury is trauma, it is imperative that a global patient evaluation for cardiovascular, neurological, and urinary stability be performed concurrently with the respiratory evaluation and stabilization (see Chapter 2). Clinical signs and physical examination findings in animals with both acute and delayed respiratory distress secondary to tracheobronchial injury are listed in Table 31.1.

Diagnostic Testing

Cervical and thoracic radiographs are often the first-line diagnostic test in patients with suspected tracheobronchial injury once they are stable enough to have diagnostics performed. In a study of dogs and cats with cervical bite wounds, 17% of study animals had airway perforation, and all of these animals had subcutaneous emphysema or pneumomediastinum [11]. In two studies of cats with tracheal injuries secondary to intubation, all cats for which thoracic radiographs were performed had pneumomediastinum and subcutaneous emphysema [27,28]. One case each of pneumopericardium and pneumoretroperitoneum were also found [27]. Avulsion of the trachea from the larynx cranial or caudal to the

cricoid cartilage may be seen (Figure 31.2) [12]. When pseudoairway or tracheal stenosis as a late complication of prior tracheobronchial injury is present, radiographs may reveal the gas-filled diverticulum dorsal to the trachea, soft tissue opacity within the tracheal lumen consistent with stenosis, or incongruity of the tracheal margin [6,8,19]. Radiographs should also be evaluated for evidence of rib fractures, spinal column trauma, and other soft tissue injuries, such as pulmonary contusions, mediastinal widening from vascular trauma and hemorrhage and abdominal trauma.

**Figure 31.2** Lateral cervical radiograph of a dog with avulsion of the cricoid cartilage secondary to bite wounds and airway trauma.

Subcutaneous emphysema, pneumomediastinum, and/or pneumothorax can make radiographic detection of the precise location of airway perforation difficult. Computed tomography (CT), either with the patient under anesthesia or sedated, has been used to better characterize the nature of both acute and chronic consequences of tracheobronchial injury in dogs and cats, including complete tracheal avulsion, tracheal tear, and pseudoairway formation (Figure 31.3) [9,17,20,33].

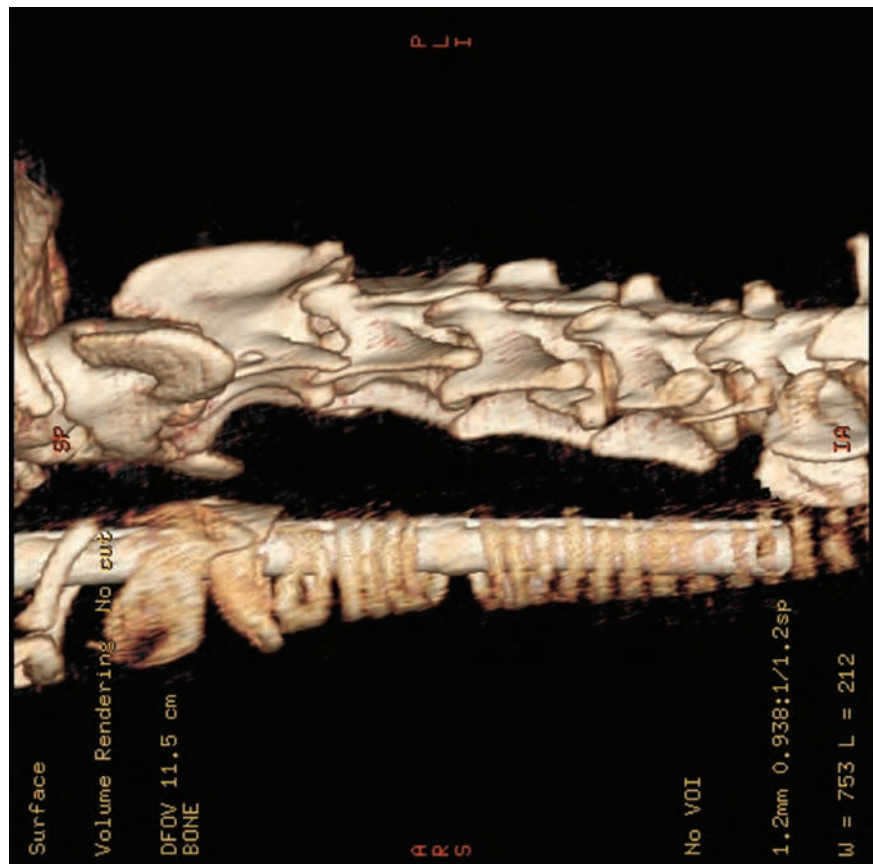
Tracheoscopy has been reported to have variable ability to visualize tracheobronchial traumatic lesions, which can appear like dorsal tracheal membrane mucosal lacerations, defects, raised blebs, or incongruity of the airway lumen [12,21,27,28,30]. In one study of cats with tracheobronchial injury secondary to intubation, tracheoscopy was able to confirm the location of the tear in all cats for which this procedure was performed but another study of a similar population of cats did not support these findings [27,28]. Case reports of dogs undergoing tracheoscopy for identification of tracheobronchial traumatic lesions showed similar variable utility [12,21,30]. Tracheoscopy has also proven beneficial for facilitation of intubation distal to a tracheal laceration in preparation for surgical repair in a cat [31]. Many modern video and fiberoptic bronchoscopes can be safely passed through a size 5 Fr

endotracheal tube with use of a bronchoscope adapter to maintain oxygen and inhalant anesthetic insufflation and carbon dioxide exhalation, making extubation unnecessary. For smaller animals or smaller endotracheal tube sizes, a video or fiberoptic ureteroscope can be used to facilitate tracheoscopy.

Treatment of Tracheobronchial Injuries

Tracheobronchial injuries can be managed with surgical intervention or conservative care. The decision about how to manage these patients often depends on the severity of their respiratory compromise, nature of the tracheobronchial injury, and response to supportive care with oxygen, sedation, and cage rest [3,6,8]. For patients that are cardiovascularly stable, respond to oxygen supplementation for resolution of their respiratory compromise, and do not have progressive subcutaneous emphysema or pneumothorax, conservative care can be attempted. The use of antibiotics should be guided by the type of primary tracheobronchial injury and common bacteria within the trachea and oropharynx (in cases of bite wounds) [34]. Oxygen therapy is believed to be helpful with subcutaneous emphysema and pneumomediastinum by decreasing the dissolved nitrogen concentration

Figure 31.3 CT volume rendering reconstruction showing the tracheal defect created by the bite wounds in the dog in Figure 31.1.



trapped within the soft tissues, increasing the rate of air resorption [35]. If needed, needle or catheter aspiration of the trapped subcutaneous air can be considered to improve patient comfort. Once the patient and air leakage have stabilized, discharge for rest and home monitoring can be considered since it can take 1–6 weeks for the subcutaneous emphysema to fully resorb [27].

For unstable patients with progressive subcutaneous emphysema or pneumothorax, or large tracheobronchial injuries, surgical intervention is indicated [3,6,8,27,28]. Based on the location of the injury, a ventral cervical midline or third-fourth intercostal right lateral thoracotomy approach is indicated. Careful dissection and tissue handling are imperative to avoid damaging the recurrent laryngeal nerves and segmental blood supply to the trachea [3,6,8].

For small tracheal lacerations, primary repair, with or without debridement, with a simple interrupted suture pattern at the junction of the tracheal ring and trachealis muscle is indicated [3,6,8]. Small lacerations can be difficult to visualize intraoperatively due to their dorsal location, so saline infusion and positive pressure ventilation to create bubbles can be helpful at localizing small defects [6]. For larger tracheobronchial defects, those requiring substantial debridement, or for management of tracheal avulsion injuries, pseudoairway formation, or tracheal stenosis, tracheal resection and anastomosis is the treatment of choice [3,6,8,10–18,20,21,29–31]. The amount of trachea that can be safely resected in dogs varies by age, with younger animals being less tolerant of significant resections compared to adult dogs (20–25% versus 25–50%) [3,5,6,8]. The amount of resection should be minimized as much as possible to reduce tension, as increased tension of the anastomotic site is associated with increased risk of stenosis and stricture formation [3,5,6,8]. Circumferential simple interrupted sutures, with or without tension-relieving sutures, are used to accomplish tracheal anastomosis. Intravenous anesthesia and oxygen insufflation should be used in patients undergoing tracheal resection to avoid surgeon inhalation of anesthetic gases [3].

Balloon dilation of a distal tracheal stenosis has been reported to be effective in one cat with tracheal avulsion injury, and ineffective in another [20,26]. Stenting of benign tracheal strictures has also been reported in two cats [36]. It is possible that additional case experience with balloon dilation and airway stenting will better define the role of these minimally invasive therapies for patients with tracheobronchial strictures or stenosis.

Tracheal and Bronchial Collapse

Tracheal collapse is a progressive, degenerative disease of the tracheal cartilages secondary to chondromalacia that is commonly seen in middle-aged to older toy

and small-breed dogs [37]. While the exact etiology and inheritance are unknown, hypocellularity of the tracheal cartilage with concurrent reduction in cartilage glycosaminoglycan, chondroitin, and calcium has been documented histologically [3,37–40]. Bronchomalacia describes similar pathological cartilage changes to the bronchi and bronchioles, and can occur as an isolated syndrome or in conjunction with tracheal collapse and can affect dogs of all sizes [41–43]. Widening of the dorsal tracheal membrane and flattening of the tracheal cartilages to varying degrees of severity cause airway narrowing and the inability to withstand changing intraluminal airway pressures with respiration [5,43–45]. The end result is airway inflammation and irritation, loss of function of the mucociliary escalator and squamous metaplasia, excessive mucus production, and airway obstruction [3,37,40,46].

Clinical Signs and Physical Examination Findings

Collapse of the trachea can occur at any location along the trachea and may be isolated to the cervical, thoracic inlet or intrathoracic trachea or can diffusely affect the entire airway. The location of airway narrowing, as well as the presence or absence of concurrent bronchial collapse, determines the clinical signs and severity of respiratory compromise. Up to 83% of dogs with cervical tracheal collapse have also been documented to have bronchial collapse [43,44]. Cervical tracheal narrowing results in increased work of breathing and noise on inspiration due to collapse of the weakened airway by the negative luminal pressure generated during inspiratory diaphragmatic contraction. Collapse of the intrathoracic trachea and bronchi occurs on expiration when increased intrathoracic pressure is the result of chest wall recoil and cranial diaphragmatic motion. Collapse at the thoracic inlet can result in either or both inspiratory and expiratory signs. The nature of the signs can be static or dynamic, depending on the extent of movement of the trachealis muscle and cartilages.

The clinical signs seen in many dogs with tracheal and/or bronchial collapse can be characterized as “obstructive” or “pure coughing,” although some animals with chondromalacia at multiple locations in the airway can have components of both coughing and obstructive signs. The classic “honking” noise heard, with respiration and panting, is typically seen with more obstructive airway disease, generally with collapse of the cervical or thoracic inlet trachea. The severity of the honk can be exacerbated by stress, activity, and excitement. Other signs of airway obstruction include stridor, stertor, gagging after eating and drinking, and exercise intolerance [37,39,44,47]. Conversely, pure coughing dogs tend to have a dry, hacking cough, which can also be high-pitched, and may or may not be productive [41,42].

These dogs do not tend to have exercise intolerance or respiratory distress. Coughing tends to be the result of bronchial and intrathoracic collapse. Many patients will have components of both coughing and obstruction, and determination of the more impactful problem can help guide diagnostics and therapy.

Diagnostic Testing

Static thoracic radiographs are useful to assess cardiovascular structures and the pulmonary parenchyma and lower airways, yet they can underestimate the severity of a dynamic disease process like tracheobronchial collapse, even when paired inspiratory and expiratory radiographs are taken [37,44,48,49]. In one study, static radiographs misdiagnosed the location of tracheal collapse in 44% of dogs and in 8% failed to diagnose tracheal collapse when compared to fluoroscopy [48]. Dynamic assessment of the entire airway, including the mainstem bronchi and nasopharynx, can be accomplished with fluoroscopy of the patient in either lateral or sternal recumbency. Evaluation of the nasopharynx is an important part of a complete upper airway fluoroscopic examination, as concurrent nasopharyngeal collapse has recently been recognized in dogs with tracheobronchial collapse [48,50]. Fluoroscopy is also useful at documenting cranial lung lobe herniation and tracheal kinking during coughing, both of which are reported in conjunction with tracheobronchial collapse and chronic coughing (Figure 31.4) [51].



Figure 31.4 Cranial lung lobe herniation and kinking of the thoracic inlet trachea during coughing induced during fluoroscopy in a dog with severe bronchial collapse and intrathoracic tracheal collapse.

Computed tomography (CT) also has diagnostic benefit in tracheal collapse, but it may not adequately assess dynamic disease processes like nasopharyngeal, laryngeal, and tracheal collapse when the patient is intubated and air movement is through the endotracheal tube and not the airway [52,53]. Dynamic CT with a clear plastic patient positioning device (MouseTrap) that restricts movement and facilitates oxygen supplementation has shown promising results in evaluation of upper airway obstruction without the need for anesthesia or sedation [52].

Tracheoscopy and bronchoscopy is the gold standard for evaluating and grading tracheal and bronchial collapse [42–44,53]. Since general anesthesia is required for endoscopic airway examination, recovery of patients with airway compromise must be considered before undertaking this diagnostic. If anesthesia is performed in patients with suspected or confirmed tracheobronchial collapse, airway examination should be performed prior to intubation since concurrent laryngeal paralysis has been documented with tracheal collapse (see Chapter 30) [44].

Cytology and aerobic culture should be considered in all dogs being anesthetized for diagnostic and therapeutic procedures associated with suspected or confirmed tracheobronchial collapse. Since many of these animals are small-breed dogs, endotracheal wash (ETW) or bronchoalveolar lavage (BAL) is easier to perform than transtracheal wash (TTW), which is generally reserved for dogs >10 kg [54]. Cytology is important to document airway inflammation since positive culture alone does not indicate infection as *Pasteurella*, *Staphylococcus* spp, *Streptococcus*, and *Klebsiella* have been cultured from the airway of normal dogs [34]. In dogs with tracheobronchial collapse diagnosed via tracheoscopy/bronchoscopy, as well as those undergoing tracheal stent placement, bacterial isolates include *Pseudomonas*, *Pasteurella*, *E. coli*, staphylococci, and *Enterobacter aerogenes* [43,55–57].

Treatment of Tracheobronchial Collapse

Medical management should be attempted in dogs with tracheobronchial collapse, unless they are in such a severe airway crisis that they will not survive without definitive intervention. Medical management is recommended since it has been shown to control clinical signs of tracheal collapse for more than 12 months in 71% of dogs [37].

Cough control is the mainstay of medical management for dogs with tracheobronchial collapse, especially in the patient population where cough, and not airway obstruction, is the predominant clinical sign. Hydrocodone homatropine (0.25–0.5 mg/kg PO q6–8h) and

butorphanol (0.5 mg/kg PO q6–8 h) are common opioids used for cough control. Both of these medications are more effective at preventing coughing than stopping it once started, so routine use should be recommended. The dose and frequency can be titrated to the lowest amounts once the patient's cough control is effectively controlled. It is possible for patients to develop tolerance to these medications over time which, when combined with the progressive nature of tracheobronchial collapse, will likely require increased dose and/or frequency over time. In patients with concurrent airway infection or pneumonia, coughing is necessary for clearance of the infection, so the aggressiveness of cough control should be adjusted in light of any infection.

Corticosteroids can be very helpful to manage the inflammation associated with recurrent airway collapse and coughing. Given the nature of the side-effects associated with prolonged steroid use, such as weight gain, hepatomegaly, muscle weakness, panting, and increased risk of thromboembolic events, and the negative impact these changes can have on patients with airway compromise, prolonged use of corticosteroids should be avoided [45]. Injectable dexamethasone (0.05–0.1 mg/kg IV/SQ/IM q12–24 h) can be used for an acute coughing or obstructive crisis whereas an oral tapering course of prednisone (0.25–0.5 mg/kg PO q12 h or 0.5–1 mg/kg PO q24 h) is indicated for intermittent management of airway inflammation as well as after placement of a tracheal stent. The benefit of oral versus inhaled steroids with tracheobronchial collapse is yet to be determined, but can be considered for patients in whom avoidance of systemic steroids is desirable and who are tolerant of the face mask.

The use of bronchodilators is also controversial in managing dogs with tracheobronchial collapse since they have no effect on larger airways and the role of bronchoconstriction in bronchial collapse is unknown. Bronchodilators are generally reserved for dogs with confirmed bronchial collapse or concurrent lower airway disease. Methylxanthine derivatives, such as theophylline (10–20 mg/kg PO q12 h) or aminophylline (5–10 mg/kg IM, IV q8 h), are preferred to B2 agonists such as terbutaline or albuterol due to their effectiveness and risk of tachyarrhythmias with sympathomimetic agents. Theophylline and aminophylline have multiple drug interactions, so drug compatibility must be confirmed before initiating therapy. Inhaled bronchodilators may have a role as rescue drugs during a coughing crisis.

Prosthetic extraluminal tracheal rings made from polypropylene syringes/syringe cases or commercially available rings from New Generation Devices (www.ngdvet.com) can be used in dogs with cervical or thoracic inlet tracheal collapse. In dogs that also had concurrent intrathoracic tracheal collapse, prosthetic

rings were still beneficial at improving respiratory distress and no difference in survival rate was seen when compared to those with cervical collapse alone treated with extraluminal rings [58]. The rings are secured to the dorsal and lateral external surface of the cartilaginous rings with non-absorbable sutures, using care to avoid the recurrent laryngeal nerves and segmental blood supply [37,44,57]. Complications associated with the procedure include infection, tracheal necrosis, ring penetration into the airway, tension pneumothorax, and laryngeal paralysis in 10–30% of patients [3,37,44,57,59].

Tracheal stenting is a minimally invasive technique that can be considered in dogs with tracheal collapse at any location in their trachea or which are poor candidates for surgical intervention. Since the procedure can be performed quickly, its utility has also been documented in dogs presenting in severe respiratory crisis that is not amenable to medical management [60,61]. The complications seen with laser cut and balloon expandable stents, including foreshortening, migration, fracture, and excessive airway irritation, have been reduced with the use of stents made specifically for the canine trachea (www.infinitemedical.com) [62–69].

Stent sizing is determined under general anesthesia and positive pressure ventilation to ascertain maximal tracheal diameter and the length of trachea requiring stenting. Therefore, since sizing decisions need to be made once the patient is anesthetized, multiple stent sizes should be readily available for immediate placement. Both fluoroscopic and bronchoscopic placement methods have been described (Figure 31.5) [69]. As with tracheoscopy, the use of a bronchoscope adapter allows continued oxygen insufflation during stent positioning and deployment. Despite advances in tracheal stent design and placement techniques, significant complications such as fracture, migration, failure of stent incorporation into the mucosa, chronic airway infections, and granulation tissue ingrowth can still occur.

While many complications can be managed medically, or in the case of clinically significant stent fracture, new stent placement, tracheal stenting should not be done cavalierly and clients need to be well educated about long-term monitoring and possible complications such as recurrent infections, granulation tissue formation, and stent fracture [70].

Patients will experience a mild, soft, dry cough for 4–6 weeks after tracheal stenting. After this time, clients are advised to learn their dog's "new" cough and to be diligent with recheck examinations (including radiographs) as well as with any change in the nature, frequency, or severity of coughing. Long-term cough suppression, generally at least twice daily, is needed in most tracheal stent patients and should be anticipated by the client. In

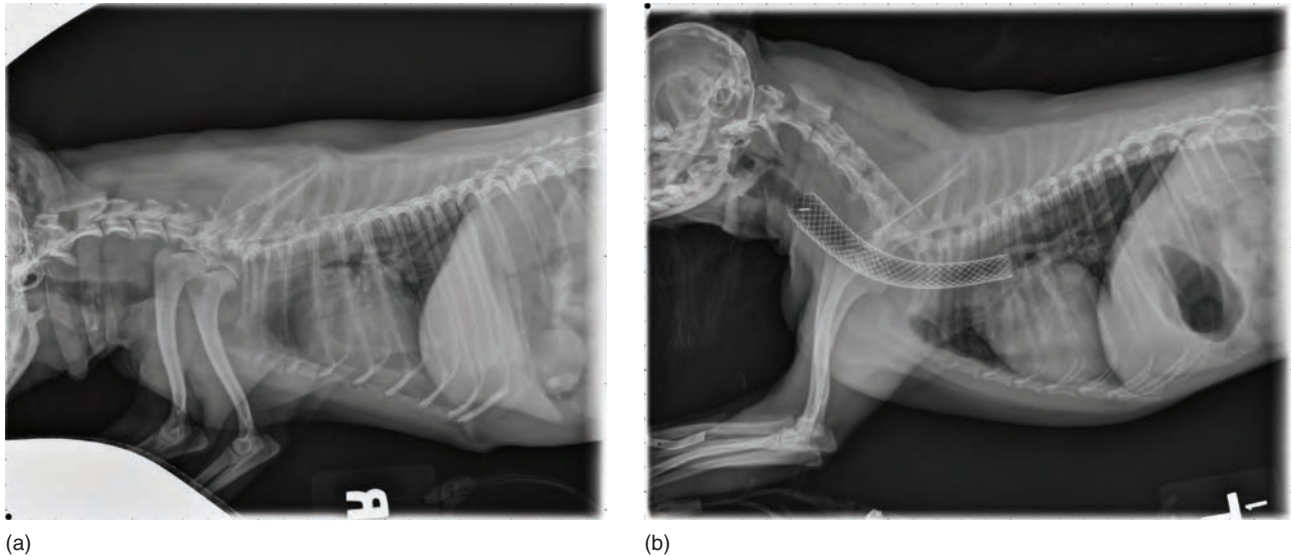


Figure 31.5 Lateral radiographs showing pre- (a) and post-tracheal (b) stent placement in a dog.

addition, routine thoracic radiographs are recommended every 3–4 months for the first year after stent placement and then every 6 months thereafter to monitor for complications such as fracture and granulation tissue so they can be addressed before causing airway obstruction and the need for emergency intervention.

Should additional anesthetic procedures be needed for tracheal stent patients in the future, care should be taken to gently intubate the patient and minimize cuff

overinflation and head/neck manipulation to avoid trauma to the airway and stent.

Even with the complications associated with stenting, it is still a viable method for relieving life-threatening airway obstructions and improving quality of life [61,69,71]. Stenting for bronchial collapse is its infancy, and currently only a single case report exists documenting stenting of concurrent bronchomalacia and left atrial enlargement [72].

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32

Acute Airway Obstruction*Dana L. Clarke, DVM, DACVECC**University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA, USA***Emergency Examination**

In animals with upper airway obstruction, respiratory sounds, breathing patterns, and clinical signs can help determine the location of the obstruction, especially in patients that are too unstable for examination and must have an auditory and visual exam performed from afar. Stridor is defined as high-pitched inspiratory noise that is compared to “breathing through a straw” and is generally seen when inspiring against a narrowed portion of the airway. Stertor is lower pitched, snorting or snoring-like noise that is associated with inspiration or exhalation. Honking with inspiration or panting is classically seen in dogs with cervical or thoracic inlet tracheal collapse (see Chapter 31).

Gagging, especially after eating and drinking, is common in patients with laryngeal and tracheal disease. Coughing is common in patients with laryngeal and tracheal disease, as well as mainstem bronchial collapse, chronic lower airway disease, and pulmonary parenchymal disease. Coughing associated with bronchial collapse tends to be paroxysmal and may be followed by a terminal retch and/or panting. Excluding a cardiogenic origin for coughing is important early in the management of the patient with respiratory distress.

The respiratory signs can also be characterized as static or dynamic. Static signs occur with a fixed obstructive process that impacts all phases of respiration, whereas dynamic signs occur with either inspiration or exhalation, and can vary in severity with patient position, stress, and anxiety. Inspiratory noise or distress is associated with obstruction of the upper airway rostral to the thoracic inlet since the generation of negative intraluminal airway pressures upon inspiration collapses the diseased structure into the airway and results in prolongation of the inspiratory phase of respiration. In contrast, expiratory noise or distress and prolonged expiratory phase of respiration is the result of increased intrathoracic pressures

upon exhalation that collapse or obstruct the diseased thoracic trachea, mainstem bronchi, or tertiary airways. Retrospective evaluation of dogs and cats presented for emergency treatment of respiratory distress found that inspiratory noise in dogs and cats, as well as inspiratory distress in dogs, was significantly associated with disease localized to the upper airway [1].

Diseases of the nose, choanae, and nasopharynx can result in sneezing, reverse sneezing, nasal discharge (unilateral or bilateral), snoring, and an inability to rest or breathe when not panting (dogs) or open mouth breathing (cats). Laryngeal disease can be associated with both stridor and stertor, coughing, and gagging, especially when eating or drinking [2–5].

Other clinical signs seen in patients with upper airway obstruction include orthopnea (head and neck extension), panting, and, in severe cases, cyanosis. Cats will only open mouth breathe with severe respiratory compromise, so a panting cat must be handled very delicately. Panting in dogs can be normal or due to an extrarespiratory problem (e.g. hyperadrenocorticism), a sign of increased work of breathing, or associated with hyperthermia, which is a common complication of upper airway obstruction and requires prompt recognition and treatment (see Chapter 147).

Emergency Stabilization

Oxygen therapy and sedation, including control of anxiety, are the mainstays of therapy for all patients with upper airway obstruction, regardless of the etiology. If these strategies do not improve patient comfort, oxygenation, and ventilation, or for patients that present in respiratory failure, immediate intubation may be needed (see Chapter 180). When orotracheal intubation is not possible, tracheostomy is indicated as a life-saving procedure.

Oxygen therapy can be delivered using a variety of methods (see Chapter 181). Since many upper airway obstruction patients are intolerant of handling due to exhaustion of their physiological reserves, use of an oxygen cage is often the preferred method for provision of high percentages of inspired oxygen while minimizing patient contact and stress. The clinician must closely observe the patient in the cage since the ability to hear changes in the amount of stridor or stertor is compromised. Similarly, temperature regulation can be challenging with large-breed dogs in oxygen cages, especially those that are panting, so patient and ambient temperature must be monitored closely. Alternate methods for providing oxygen supplementation include flow-by, use of a face mask, nasal catheters or prongs, a covered plastic E-collar to serve as an oxygen tent, and orotracheal/tracheal intubation. Many upper airway obstruction patients will not tolerate the presence of the mask over their face. In addition, nasal oxygen supplementation is often of limited benefit for patients panting heavily or those with obstruction distal to the nasal passage.

Since the self-perpetuating cycle of inflammation and edema leading to progressive airway obstruction can be extremely distressing for patients, control of anxiety via sedation and anxiolytics is essential for upper airway obstruction patients. Acepromazine is an effective anxiolytic and sedative for cardiovascularly stable patients. Since physical examination is often limited in these animals, which precludes assurance of cardiovascular stability, low doses of acepromazine should be used at first, then repeated as indicated, bearing in mind that it takes 15 minutes after intravenous administration to achieve maximal effect (0.005–0.02 mg/kg IV, 0.01–0.05 µg/kg IM) [6]. Dexmedetomidine is an effective, reversible sedative and anxiolytic that should also be used with caution in patients with cardiovascular disease or instability. However, low doses are effective at controlling anxiety (0.5–2 µg/kg IV dogs or 3–5 mg/kg IM dogs and cats) [6]. Its reversal agent, atipamezole, should be readily available for intramuscular administration (or IV in a life-threatening emergency) in an equal volume to that of the dexmedetomidine administered. Butorphanol (0.1–0.5 mg/kg IM or IV) provides sedation, cough suppression, and analgesia, and is reversible with naloxone (0.01–0.02 mg/kg IV or IM) [6].

Management of inflammation and edema is another important aspect of emergency treatment of acute airway obstruction. The glucocorticoid dexamethasone sodium phosphate (0.05–0.2 mg/kg IV, IM, SQ) is most commonly used [6]. However, it should be used with caution in patients with poor perfusion, recent non-steroidal anti-inflammatory (NSAID) administration, or those for whom neoplasia, such as lymphoma, is

a high differential for the source of the airway obstruction as steroid administration may obscure the cytological diagnosis.

If there is concern for significant hyperthermia ($T > 104^{\circ}\text{F}$) that is unresponsive to sedation and improved patient heat dissipation, cooling measures to prevent secondary heat related illness should be considered. Placing a fan in front of the patient with or without wetting the animal with lukewarm water may help maximize heat lost via radiation and evaporation [7–9]. For more specific therapy in hyperthermic patients, see Chapter 147.

Diagnostics

Adequate oxygenation and ventilation should be determined as soon as possible for all patients with acute airway obstruction. When patient stability permits, pulse oximetry provides a rapid, non-invasive assessment of oxygen saturation. Arterial blood gas sampling is the gold standard for assessment of oxygenation and ventilation, but is often not possible in patients with respiratory distress, so venous blood gas analysis can be used to assess for acid–base disturbances, including respiratory acidosis from hypoventilation. A PvCO_2 value greater than 50 mmHg in the absence of poor perfusion is consistent with hypoventilation. When the obstruction is chronic (> 3 –5 days), there may be compensatory bicarbonate retention by the kidneys in effort to normalize the pH (see Chapter 107).

Thoracic radiographs are important in all patients with respiratory disease, but can only be obtained when fragile upper airway obstruction patients are stable. Three-view thoracic radiographs are helpful to evaluate for cardiogenic and non-cardiogenic pulmonary edema, pneumonia, intrathoracic tracheal and bronchial collapse, and neoplasia. Radiographs of the cervical trachea, larynx, and nasopharynx aid in the diagnosis of laryngeal and tracheal masses, extraluminal tracheal or laryngeal compressive disease, nasopharyngeal collapse or masses, cervical and thoracic inlet tracheal collapse, and foreign bodies. Radiographs can miss or underestimate the severity of collapse of the nasopharynx, trachea, and mainstem bronchi, so fluoroscopy is helpful for dynamic assessment of airway diameter changes and collapse along the upper airway during all phases of respiration and coughing, if indicated.

Computed tomography (CT) is the best imaging modality for nasal and nasopharyngeal disease, but often requires general anesthesia, which carries significant risk in patients with upper airway disease upon recovery if definitive intervention is not pursued concurrently. Studies using a clear plastic patient positioning device

that allows for oxygen supplementation and restraint (MouseTrap) during CT have shown preliminary utility for CT evaluation of dynamic disease processes such as laryngeal paralysis, intraluminal airway masses, and tracheal disease [10,11].

Heavy sedation or anesthesia of these patients should only be considered for severe obstruction that cannot be medically managed or when definitive treatment can be performed after confirmatory diagnostics. If the underlying cause of the obstruction is not addressed, extubation may not be possible. If sedation of the acute upper airway obstruction patient is indicated for stabilization or diagnostics, an upper airway examination for laryngeal function, integrity, and masses should be routinely performed, even if laryngeal disease is not considered to be the primary pathology. If possible, anesthetic protocols that do not impair laryngeal function should be used (see Chapter 30). An assistant is imperative to confirm appropriate phase of respiration with laryngeal motion in order to rule out paradoxical laryngeal motion, which is inward arytenoid movement secondary to negative inspiratory pressure that can be misinterpreted as laryngeal function.

Additional diagnostics that are helpful in upper airway obstruction patients include endotracheal wash or bronchoalveolar lavage (BAL), tracheobronchoscopy, retroflexed rhinoscopy, and antegrade rhinoscopy.

Complications of Upper Airway Obstruction

The secondary complications that can result from upper airway obstruction influence patient morbidity and

mortality, even with prompt intervention for the primary disease process. Heat stroke (see Chapter 147), non-cardiogenic/neurogenic pulmonary edema (see Chapter 39), and aspiration pneumonia (see Chapter 37) are some of the most serious secondary complications of upper airway obstruction. Diligent monitoring for multiple organ dysfunction and failure that can result from heat stroke, hypoxemia, and pulmonary parenchymal disease is an important aspect of the ongoing care needed for patients with airway obstruction.

Diseases Causing Upper Airway Obstruction (Table 32.1)

Diseases of the Nasal Passage and Nasopharynx

For in-depth discussion of nasal diseases and their role in upper airway obstruction in cats, see Chapter 29. In dogs, since panting allows them to bypass breathing through the nasal passage, nasal disease rarely causes acute airway signs and is generally attributable to a more chronic disease process.

Brachycephalic airway syndrome (BAS) is a common source of upper airway obstruction in dogs, and is attributed to one or more anatomic components of the disease process, including stenotic nares, elongated soft palate, tracheal hypoplasia, nasopharyngeal turbinates, and the secondary complications of the anatomic abnormalities, including everted laryngeal sacculles, laryngeal collapse, and chronic gastrointestinal signs [12–18]. For detailed discussion of BAS, see Chapter 28.

There are a variety of nasopharyngeal diseases that contribute to upper airway obstruction, including polyps,

Table 32.1 Diseases of the upper respiratory tract that can cause upper airway obstruction.

Nasal passage/nasopharynx	Larynx/pharynx	Trachea/bronchi
Chronic rhinitis (bacterial, fungal, viral)*	Laryngeal paralysis	Tracheal collapse
Brachycephalic airway syndrome (BAS)	Laryngeal collapse	Tracheal stricture/stenosis
Nasopharyngeal infection*	Inflammatory/granulomatous laryngeal disease	Tracheal/bronchial foreign body
Nasopharyngeal foreign bodies*	Laryngeal neoplasia	Tracheal neoplasia
Nasopharyngeal stenosis*	Pharyngeal foreign body	Tracheal membrane hemorrhage
Nasopharyngeal collapse*	Laryngeal edema (prolonged or traumatic intubation)	Tracheobronchial trauma/avulsion
Nasopharyngeal polyps*		
Nasopharyngeal neoplasia*		

*In dogs, panting will bypass the nasal obstruction, so nasal obstructive signs will only be evident at rest or when they are not panting. Since cats are obligate nasal breathers, open mouth breathing or panting from nasal or nasopharyngeal disease is indicative of severe obstruction.

stenosis, infection, foreign bodies, and neoplasia. Nasopharyngeal *Cryptococcus* infection has been reported in cats and *Blastomycosis* infection reported in one dog [19–21]. A variety of nasopharyngeal foreign bodies, including bones, a stone, sewing needles, and a pet fish, have been reported as causes of acute upper airway obstruction in cats and dogs. Removal can be achieved with soft palate retraction, basket retrieval using retroflexed rhinoscopy, and nasal flushing [21–27].

Nasopharyngeal polyps cause upper airway obstruction in approximately 28% of cats with nasopharyngeal disease, and are sporadically reported to cause obstructive signs in dogs [28–31]. Benign polyps arise from the auditory tube or middle ear mucosa and are believed to be of either congenital or infectious etiology [28,31–38]. They are generally refractory to medical management, so surgical removal via ventral bulla osteotomy (VBO) is recommended over traction-avulsion removal, which can have a recurrence rate of 40–50% [32,34,37,39,40].

Nasopharyngeal stenosis (NPS) is an uncommon cause for upper airway obstruction in dogs and cats that may be due to a congenital or acquired membranous narrowing of the nasopharynx caudal to the choana and rostral to the caudal border of the soft palate [40–44]. An acquired NPS can be a complication of chronic rhinitis, aspiration (chemical) rhinitis, trauma, and neoplastic infiltration. Surgical correction with an oral approach through the soft palate, endoscopic or fluoroscopic-guided balloon dilation, and stent placement are described techniques for resolution of NPS (Figure 32.1) [43–49]. Restenosis of NPS can occur regardless of the correction technique chosen, but is less likely in patients for whom stents are placed. However, erosion of the soft palate, hair entrapment, granulation tissue, and dysphagia are all reported

with nasopharyngeal stenting and must be considered when recommending treatment for this frustrating disease process [44,50,51].

Nasopharyngeal collapse (NPC) is a disease process that has only recently been recognized in dogs and a cat [52,53]. Clinical signs in dogs with NPC include coughing, stertorous breathing, and gagging. Since mouth breathing in dogs will bypass NPC, it is unlikely to be the sole source of acute airway obstruction in this species. However, given its association with brachycephalic airway syndrome and tracheal collapse, it is likely a contributing factor to signs seen in these complex upper airway diseases.

Lymphoma, mast cell tumor, squamous cell carcinoma, adenocarcinoma, and fibrosarcoma have been reported in the canine nasopharynx [21]. Lymphoma and adenocarcinoma have been reported in this region in cats, but less frequently than in dogs [21,54,55]. Adequate surgical margins in such a confined area are difficult to achieve, making chemotherapy and radiation more beneficial treatment modalities.

Diseases of the Larynx and Pharynx

Laryngeal paralysis is the most common laryngeal source of acute upper airway obstruction in dogs. For in-depth discussion of laryngeal paralysis, see Chapter 30.

Repeated, traumatic, or prolonged intubation can contribute to laryngeal edema formation and upper airway obstruction, especially in cats given their propensity for laryngospasm and small diameter of the rima glottis. Tracheostomy and anti-inflammatory medications may be indicated when extubation is not possible due to the severity of laryngeal edema.

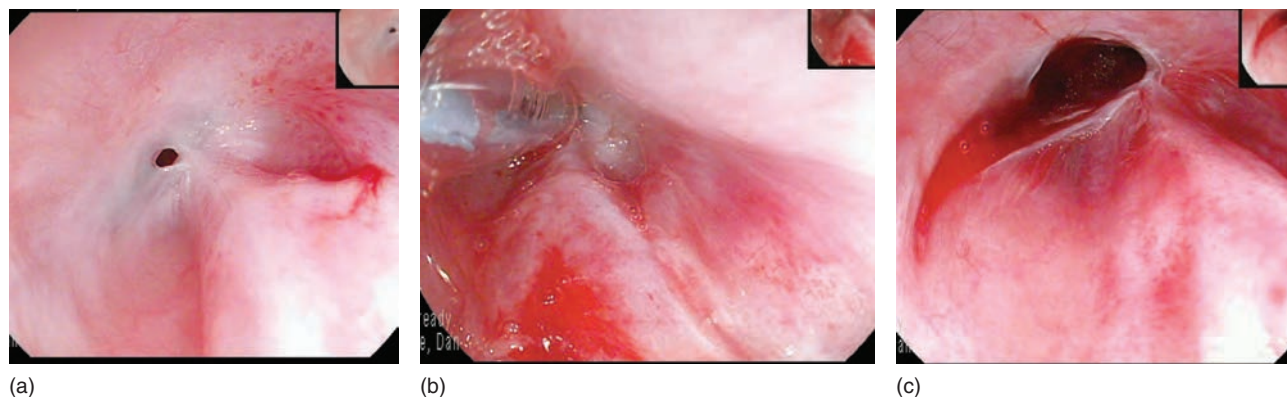


Figure 32.1 Retroflexed rhinoscopy appearance of nasopharyngeal stenosis (NPS) (a). Balloon dilation of NPS as seen on retroflexed rhinoscopy (b). Post-balloon dilation appearance of NPS (c).



Figure 32.2 Grade 3 laryngeal collapse seen during airway examination of a 10-year-old Yorkshire terrier presenting for stridor and respiratory distress.

Laryngeal collapse is an uncommon cause of upper airway obstruction in dogs that is a secondary complication of chronically increased negative airway pressures, most often reported in association with BAS. It has also been recognized with laryngeal paralysis, nasopharyngeal obstruction, and trauma, and in non-brachycephalic breeds diagnosed with laryngeal collapse including Norwich terriers and English bull terriers [56–58]. Chronically increased airway resistance and work of breathing cause cartilage fatigue and degeneration of varying degrees of severity (stage 1–3). Stage 1 is laryngeal saccule eversion, which is a commonly recognized secondary complication of BAS. Stage 2 is loss of rigidity and collapse of the cuneiform processes of the arytenoid cartilages, and stage 3 is complete laryngeal collapse characterized by midline collapse of the corniculate processes (Figure 32.2) [56]. Stage 1 laryngeal collapse is amenable to surgical intervention, but more advanced stages have variable response to surgery, and may ultimately end up requiring permanent tracheostomy [56,59–61].

Inflammatory and granulomatous laryngeal disease is an uncommon, poorly understood cause for upper airway obstruction in small animal patients [36,55,62–67]. On direct visualization, the larynx and vocal folds may be thickened and erythematous; nodules may be seen on the arytenoid cartilages or rima glottis [62,64–66]. These changes can be difficult to distinguish from laryngeal neoplasia, so fine needle aspiration or biopsy may be necessary. Treatment may involve temporary or permanent tracheostomy, surgical excision of polypoid or

mass-like lesions, corticosteroids, and antimicrobials and antibiotics [36,55,62–65].

Lymphoma, squamous cell carcinoma, carcinoma, and adenocarcinoma have been reported in the feline larynx [36,56,66,68,69]. In dogs, additional reported neoplasia types include melanoma, chondrosarcoma, plasmacytoma, and rhabdomyoma [56,68,70–74]. Laryngectomy and permanent tracheostomy may be necessary given the difficulty of complete excision in this area [68,74,75]. The prognosis for laryngeal neoplasia is guarded, and depends on tumor type, invasiveness, treatment response, and metastasis [69].

Diseases of the Trachea and Bronchi

Tracheal collapse secondary to chondromalacia is the most common tracheal cause of upper airway obstruction in dogs. For a detailed description of this disease process, see Chapter 31. Tracheal trauma resulting in airway obstruction and secondary stricture or stenosis are also discussed in the same chapter.

Aspiration of foreign material or parasitic migration into the trachea and bronchi can result in coughing, gagging, head and neck extension, and respiratory distress. A variety of objects have been removed from the canine and feline trachea, including grass awns, plastic material, stones and gravel, and *Cuterebra* spp in cats (Figure 32.3) [76–80]. Bronchoscopic retrieval is reported to have an 86% success rate in dogs and 40% success rate in cats [76]. When bronchoscopic retrieval fails, surgical excision, grasping forceps used under fluoroscopic guidance, and inflated Foley catheter or angioplastic balloon extraction techniques have also been described [76–81].

Intraluminal tracheal narrowing, secondary to anti-coagulant rodenticide toxicity and a tracheal hematoma, has been reported as a rare cause of upper airway obstruction [82–84]. Tracheal strictures, secondary to tracheal trauma, are another uncommon cause of upper airway obstruction and are discussed in Chapter 31.

Tracheal Neoplasia

Osteochondroma is the most common canine tracheal neoplasia, but chondrosarcoma, adenocarcinoma, leiomyoma, and osteosarcoma have also been described [68,85]. Lymphoma is the most common tracheal neoplasia in cats, with various forms of carcinoma (adenocarcinoma, squamous cell carcinoma, basal cell, and neuroendocrine carcinoma) also reported [66,69,73,86–88]. Tracheal resection and anastomosis, endoscopic snaring, radiation, chemotherapy, and palliative intraluminal stenting are treatment modalities described for tracheal neoplasia [66,85,86,89].



(a)



(b)



(c)

Figure 32.3 Radiograph of a tracheal foreign body in a French bulldog with a 2-month history of intermittent respiratory distress (a). Endoscopic visualization of the cherry pit bronchial foreign body (b). Retrieval of the cherry pit using a stone basket used for cystic calculi retrieval (c).

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33

Exacerbations of Chronic Bronchitis

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Introduction

A variety of disorders can lead to decompensation in a dog with chronic bronchitis and result in emergency presentation to the veterinarian. It is important to establish that the diagnosis of chronic bronchitis has been confirmed and to determine response to previous treatment while investigating potential causes for deterioration in the dog's condition and instituting appropriate therapy.

Disease Syndrome

Chronic bronchitis is a disorder characterized by airway inflammation. Clinically, it is recognized by the presence of daily cough for greater than 2 months in the absence of a specific etiology. It occurs in middle-aged to older dogs and any breed or sex can be affected [1]. Dogs with bronchitis are generally in good systemic health despite the presence of chronic cough, which can be dry or productive, depending on the amount and character of secretions produced. Respiratory rate is typically normal although as disease progresses, increased expiratory effort can be noted. Harsh bronchovesicular sounds, expiratory wheezes, or diffuse inspiratory and expiratory crackles can be heard [1]. The latter finding, along with expiratory effort, makes it difficult to distinguish the dog with chronic bronchitis from the dog that has cough related to bronchomalacia. The association between airway inflammation and airway collapse is unclear but in some cases, both disorders are found concurrently.

Diagnosis

Diagnosis of chronic bronchitis requires exclusion of all other causes of cough. In particular, bronchomalacia and

airway infection can result in similar clinical presentation. A minimum database (CBC, chemistry profile, and urinalysis) is usually normal in all three conditions. Similarly, thoracic radiographs can appear relatively normal with any of these conditions or a diffuse bronchial pattern could be noted. Loss of thoracic volume is relatively common due to poor lung inflation and obesity. Classically, a bronchial pattern with increased numbers of visible airway walls and increased thickness of the airways is anticipated in dogs with chronic bronchitis [2], although these are subtle findings.

Airway sampling through tracheal wash or bronchoalveolar lavage is required to rule out infection and confirm inflammatory airway disease as the cause for cough. Airway cytology in the dog with bronchitis demonstrates non-degenerate neutrophils, absence of intracellular bacteria, and sometimes increased mucus or Curshmann's spirals. Results of bacterial culture are sometimes challenging to interpret because aerobic bacterial culture can reveal light growth of bacteria [3]. Specific evaluation for *Mycoplasma* is recommended through culture or PCR.

Diagnosis and exclusion of airway collapse as a contributor to cough typically requires fluoroscopy and bronchoscopy. Fluoroscopy has the benefit of providing dynamic assessment of airway diameter in the cervical and thoracic region during respiration and during cough, but the low resolution of image quality can make identification of bronchomalacia difficult. Also, because left and right lobar bronchi are variably affected by collapse, fluoroscopy might need to be performed in multiple positions for complete evaluation of the airways. Bronchoscopy is a valuable tool for confirming the presence of airway inflammation and visualizing airway collapse but the requirement for anesthesia as well as specialized equipment and training makes this test undesirable in some situations.

Treatment (Table 33.1)

Chronic bronchitis is typically treated with prednisone 0.5–1.0 mg/kg PO BID, with downward tapering of the dose with alleviation in cough. Rarely, dexamethasone might be used in place of prednisone at 0.05–0.10 mg/kg PO SID to BID. The goal of therapy is to reduce dosing to every other day and to discontinue therapy if possible. In many cases, continued corticosteroid therapy can be required and a bronchodilator might be added to improve corticosteroid responsiveness. The dosage recommended for extended-release theophylline is 10 mg/kg PO BID. Alternately, some dogs can be better managed on inhaled corticosteroids, with or without theophylline.

There are several disorders that can result in exacerbation of signs of bronchitis and various disorders that can complicate the disease. Repeat diagnostic testing or additional investigation can be required to define the reason for worsened disease, while in other cases, altered management strategies are needed for better control of clinical signs.

Causes of Exacerbation

Airway Collapse

The relationship between airway collapse and chronic bronchitis is unclear [4]. It could be theorized that sustained inflammation of the airways from chronic bronchitis, could lead to degradation of airway cartilage and loss of airway smooth muscle tone that would normally preserve opened airways during alterations in respiratory flow. Airway collapse might develop in an animal with poorly controlled chronic bronchitis as a sequel to the disease process. Conversely, it is possible that airway collapse is a primary problem that causes airway inflammation through mechanical trauma at the internal surface of the bronchi and repetitive airway injury.

Table 33.1 Drug doses for the management of chronic bronchitis in dogs.

Drug	Dosage
Prednisone/prednisolone	0.5–1 mg/kg PO BID
Dexamethasone	0.05–0.1 mg/kg IV SID
Terbutaline	0.01 mg/kg IV, IM or SQ
Theophylline (extended release)	10 mg/kg PO BID
Sildenafil	1–3 mg/kg PO BID to TID

BID, twice a day (*bis in die*); IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SID, once a day (*semel in die*); SQ, subcutaneous; TID, three times a day (*ter in die*).

As mentioned earlier, confirmation of airway collapse as a contributor to clinical signs requires advanced imaging, including fluoroscopy and bronchoscopy. Clinical findings that should raise concern about coincident airway collapse in a dog previously diagnosed with bronchitis include development of a honking cough or detection of an end-expiratory snap on auscultation. Additional findings suggestive of bronchomalacia include newly detected inspiratory and expiratory crackles and worsened expiratory effort. Perhaps most importantly, the animal that deteriorates during a corticosteroid trial should be suspected of having either an infectious cause of cough or airway collapse. In these cases, judicious use of antibiotics and/or bronchodilators should be considered.

In the emergency situation, management of airway collapse is controversial. Bronchodilators such as terbutaline, which directly relax airway smooth muscle, are unlikely to be effective because dogs do not have active bronchoconstriction with inflammatory airway disease. Also, while a drug such as extended-release theophylline might reduce respiratory effort and improve expiratory airflow, its effect will not be immediate. In the dog with airway collapse exacerbating chronic bronchitis, judicious use of sedation, cough suppressants, and oxygen is most likely to be efficacious.

Mucus Obstruction

Chronic bronchitis is characterized by an increase in airway mucus production, and accumulation of mucus can lead to worsened ventilation:perfusion mismatch. Recovery from anesthesia after airway sampling in an oxygen-enriched environment is advisable.

Mucus obstruction is generally well controlled by corticosteroid therapy, but some dogs can develop inspissation of mucus and worsening airway obstruction despite therapy. Use of antihistamines, atropine, or diuretics can precipitate this. Worsened crackles and development of a moist cough in a previously stable animal could indicate that secretions have become excessively mucoid and thick. Radiographs in an affected dog could show patchy alveolar infiltrates and a ventral distribution is not uncommon because mucus will accumulate in ventrally dependent regions. Radiographic findings could be reminiscent of aspiration pneumonia, and unfortunately clinical findings and bloodwork do not always help to differentiate between the two conditions. An elevated white blood count with band response might be more suggestive of aspiration or possible infection, although this is not seen in all dogs [5].

Management of mucus obstruction requires liquefaction of secretions. Any drugs that promote drying of the airways should be discontinued if possible. Saline

nebulization can be administered using an ultrasonic or compressed air nebulizer to create particles 2–5 microns in size that will travel into small airways. Use of a direct mucolytic such as N-acetylcysteine by nebulization is not typically advised due to the tendency for this drug to induce bronchoconstriction and airway toxicity. If needed, consider administration of terbutaline prior to nebulization at 0.01 mg/kg IV, IM, or SQ, and use a low concentration of N-acetylcysteine for inhalation (1–2 mL of 10% solution diluted in the nebulizer cup) once daily. Coupage is performed by gently pounding both sides of the thorax with cupped hands in order to mobilize secretions. This therapy might be needed at home to prevent mucus trapping.

Bronchiectasis

Chronic airway inflammation that goes untreated can result in destruction of airway walls and airway dilation, which predisposes a dog to mucus impaction and possibly recurrent infection. Clinically, bronchiectasis in conjunction with bronchitis can result in hypoxemia with labored breathing. Radiographs are not highly sensitive for detection of bronchiectasis but lack of normal airway tapering can be detected in some dogs (Figure 33.1). Documentation of bronchiectasis is improved by use of CT or bronchoscopy.

Treatment of resultant hypoxemia and mucus obstruction involves oxygen stabilization and institution of nebulization and coupage to remove secretions. Use of antibiotics is controversial in the absence of repeat airway cultures but some dogs appear to improve with antibiotic therapy in conjunction with airway therapy.



Figure 33.1 Lateral radiograph of a dog with bronchitis that demonstrates diffuse thickening of airway walls and lack of tapering to the bronchi, indicative of bronchiectasis, particularly in the cranial lung lobe (arrows).

Infection

Respiratory Infection

In humans with chronic obstructive pulmonary disease (COPD), infection with bacteria, viruses, or both is considered a common cause of worsened clinical signs, responsible for substantial morbidity as well as more frequent hospitalizations [6,7]. However, COPD in humans is most commonly initiated by smoking, which results in airflow limitation and increased susceptibility to infection with organisms such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* [7]. The etiology of canine bronchitis is not understood, and the role of bacterial infection in worsening of signs in dogs with chronic bronchitis is unknown, although it seems likely that this is a rare occurrence. However, it is possible that dogs with bronchitis occasionally develop infection or pneumonia.

A recent study of dogs with pneumonia implicated underlying viral infection in 35% of cases [8]. It is conceivable that viral infection could worsen clinical signs in a dog with bronchitis or could predispose that dog to bacterial infection. Further investigations are required but in the interim, the potential infectious nature of disease should be considered when evaluating dogs presented for worsened cough or respiratory difficulty.

Laryngeal dysfunction is relatively common in dogs with chronic cough [9], and aspiration events are one of the more common causes of pneumonia in dogs. Pneumonia signs can result from acid injury or from bacterial infection associated with aspiration. A history of vomiting, regurgitation, seizure, or loss of consciousness prior to development of respiratory difficulty or tachypnea can be found, and radiographic evidence of cranial lung lobe infiltrates or middle lung lobe disease is considered suspicious for aspiration [5,10]. If aspiration pneumonia is suspected as a cause for exacerbation of disease, use of terbutaline would be advised initially to combat acid-induced bronchoconstriction. Stabilization in oxygen might also be warranted although aspiration injury has been reported to predispose to oxygen toxicity in an experimental model of aspiration in rabbits [11]. Therefore, the fraction of inspired oxygen concentration should be limited to that needed to prevent hypoxemia and excessive respiratory effort.

Intravenous fluids may be indicated, and if airway infection seems likely, broad-spectrum antibiotic coverage should be utilized that targets gram-positive, gram-negative, anaerobic, and mycoplasmal organisms. In addition, the dog should be closely monitored for development of acute respiratory distress syndrome.

Systemic Infection

Chronic bronchitis requires treatment with corticosteroids and the possibility of systemic immunosuppression

resulting in increased risk of infection must be considered. Urinary tract infections have been documented in animals on chronic corticosteroid treatment [12] and a urine culture is warranted in the dog with chronic bronchitis that presents for evaluation of systemic illness.

An alternate site for systemic infection is endocarditis. This might be particularly of concern in small-breed dogs with myxomatous mitral valve disease. Increased intensity to the murmur or development of a new murmur in a dog in conjunction with systemic signs such as anorexia, fever, or limping should trigger suspicion for endocarditis. Importantly, a heart murmur can be absent in up to 40% of dogs with endocarditis [13] so clinical suspicion for bacteremia is important. Routine bloodwork would be expected to show leukocytosis, thrombocytopenia, hypoalbuminemia, and elevated liver enzymes. Pyuria was reported in 60% of dogs [13]. Aerobic and anaerobic blood cultures are recommended along with echocardiography to confirm the diagnosis of endocarditis. Testing for *Bartonella* should be considered in culture-negative cases that demonstrate aortic valve involvement. Appropriate therapy requires intravenous use of broad-spectrum antibiotics for 5–7 days followed by extended oral therapy. Dogs should be monitored closely for development of congestive heart failure.

Pulmonary Hypertension

Chronic lung disease with global hypoxemia is one potential cause of pulmonary arterial hypertension (PAH) [14]. The incidence of PAH in dogs with chronic respiratory disease is unknown and it is likely that multiple factors play a role in generation of elevated pulmonary circulatory pressures. The most common clinical consequence of PAH is syncope. Other causes of collapse such as arrhythmias, seizures, and metabolic disorders must be ruled out, and documentation of PAH is most commonly achieved with Doppler echocardiography. Detection of elevation in the velocity of tricuspid regurgitation ($>2.8\text{ m/sec}$) or pulmonary insufficiency ($>2.2\text{ m/sec}$) is consistent with pulmonary hypertension. Use of the modified Bernoulli equation ($\Delta P = 4 \times \text{velocity}^2$) provides an estimate of an RV-RA pressure gradient exceeding 32 mmHg for tricuspid regurgitation and $>20\text{ mmHg}$ for a PA-RV gradient with pulmonic insufficiency. Clinical signs would be anticipated in dogs with moderate-to-severe PAH (pressure gradient exceeding 50 mmHg).

Pulmonary arterial hypertension occurring as a complication of chronic bronchitis is likely a permanent

condition caused by alterations in the morphology of the vasculature. Stabilization in oxygen is recommended and in some cases, home oxygen therapy can be employed to improve daytime activity levels. For dogs with moderate-to-severe PAH (pressure gradient exceeding 50 mmHg) or for any dog that displays clinical signs consistent with PAH, therapy with sildenafil should be considered [15]. Recommended starting dosages are 1–3 mg/kg PO BID-TID.

Obesity Hypoventilation Syndrome

Progressive weight gain is a substantial problem in animals with respiratory disease and is particularly problematic to manage in dogs that require long-term corticosteroid use for control of inflammation. Use of inhaled corticosteroids can reduce the likelihood of progressive obesity but all dogs being treated for chronic bronchitis are at risk.

Obesity hypoventilation syndrome results in chronic elevations of CO_2 in the blood. In the normal dog, increased CO_2 augments respiratory drive, but in dogs that have been chronically hypercapnic, central chemoreceptors are insensitive to elevations in CO_2 and ventilation is stimulated by the effects of hypoxemia on peripheral chemoreceptors. In rare instances, placing a chronically hypercapnic dog into oxygen will worsen ventilation and gas exchange because the hypoxic stimulation of respiratory drive is lost and respiratory failure ensues. This can be recognized by a decreasing respiratory rate and decreased respiratory effort in a hypoxemic, hypercapnic dog receiving oxygen therapy. In such cases, positive pressure ventilation can be required. Oxygen therapy is limited to a level that maintains acceptable ($\text{SpO}_2 > 90\%$) but not normal ($\text{SpO}_2 > 95\%$) oxygen saturation.

Emergency Management of Disease Exacerbations

Dogs with bronchitis can have waxing and waning clinical signs related directly to inflammation or can develop additional or secondary disease processes. Physical examination features can be helpful in determining the need to perform repeat blood tests and radiographs or to obtain advanced testing such as echocardiography, CT, or bronchoscopy. Stabilization in an oxygen-enriched environment, judicious use of antibiotic therapy, implementation of airway therapy, or intensification of anti-inflammatory therapy might be required, depending on the most likely etiology of disease exacerbation.

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Feline Lower Airway Disease

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Introduction

Feline lower airway disease (FLAD) generally refers to chronic inflammatory conditions of the lower airway. Feline asthma and chronic bronchitis fall under this umbrella term, and there are several parasitic conditions affecting the lower airways that should be considered as differentials. Although these are chronic conditions, acute exacerbations of disease can result in emergent presentation to the veterinary hospital.

Clinical signs of feline respiratory distress may include tachypnea, open mouth breathing, cyanosis, extension of the neck, abduction of elbows, pronounced abdominal component to the respiratory pattern, and frequent changing of body positions. Distress associated with FLAD is the result of narrowed lower airways whether by bronchoconstriction or obstruction due to structural changes or excessive secretions.

Parasitic diseases often affect the lower airways and the pulmonary parenchyma which can lead to mixed respiratory signs. However, these conditions cannot be differentiated from feline asthma and chronic bronchitis based solely on presentation and clinical signs. Even with further diagnostics, parasitic disease can be difficult to differentiate from feline asthma.

Patient History

Chronic cough is the most common historical complaint in cats with feline lower airway disease [1–3]. Tachypnea, dyspnea, abnormal respiratory noises, wheezing, vomiting, and lethargy have also been frequently reported [1–3]. Importantly, these signs overlap with those reported in cats diagnosed with either heartworm-associated respiratory disease (HARD) or lungworms [4–9], making differentiation based on historical findings impossible. While vomiting is a common historical

finding, particularly of asthma and HARD, this clinical sign can often be confused with coughing in cats. Any reports of vomiting or hairball-associated vomiting in cats by the owners should prompt further questioning to differentiate this from coughing.

A thorough general medical history is recommended with emphasis on environment, travel/change of environment, heartworm prevention, and any medical treatment recently administered (e.g. deworming targeting lungworms). Patients with lungworms may experience acute exacerbation of disease after antiparasitic administration.

Initial Assessment

Assessment of respiratory pattern and character along with thoracic auscultation can allow for rapid anatomical localization of the respiratory problem. Expiratory respiratory distress and an abdominal component, or “abdominal push,” are characteristics of lower airway disease. Thoracic auscultation often reveals expiratory wheezes, and crackles may be appreciated in some cats, particularly after a coughing episode. Cats with parasitic bronchial disease may also have parenchymal involvement which could manifest as inspiratory crackles and increased inspiratory effort [7,8].

Emergency Treatment

Oxygen supplementation and sedation are the primary components of initial stabilization. If significant expiratory effort and wheezes are noted, bronchodilator therapy should also be considered. Sedation is aimed at reducing the anxiety associated with respiratory distress. Butorphanol can be used with minimal risk, and if additional sedation is necessary, this can be combined with either low-dose acepromazine or a benzodiazepine [10].

Oxygen supplementation can be provided in a variety of ways (see Chapter 181). The choice of which oxygen delivery method to employ often relies on availability, severity of the patient's condition, and what the patient will tolerate without causing undue stress. Flow-by oxygen is widely available and generally well tolerated. This involves physically holding the oxygen tubing near the patient's nose and mouth, but though it is well tolerated, it is also the least efficient method of oxygen delivery. A tight-fitting face mask can increase the FiO_2 being delivered but many cats will not tolerate this, particularly during episodes of respiratory distress. Flow-by oxygen and face masks are short-term oxygen delivery methods that are frequently employed during the initial examination and stabilization of the patient and when transporting patients.

An oxygen cage provides a lower stress method of oxygen supplementation while still allowing monitoring of the patient. Oxygen cages provide an environment where the oxygen concentration, ambient temperature, and humidity can be regulated. Oxygen should be supplemented at an FiO_2 of at least 40%, humidity should be maintained at 40–50%, and temperature should be kept at approximately 70°F [11]. For feline patients, oxygen cages are preferred by the author for oxygen supplementation when available.

Bronchodilators are a key component of therapy for cats experiencing bronchoconstriction. Indicators of bronchoconstriction on physical examination include wheezing, expiratory distress, and significant “abdominal push.” Short-acting bronchodilators should be chosen in emergency situations; beta-2 adrenergic agonists are the most widely utilized. Anticholinergic options, such as ipratropium bromide, are also available but less commonly used. Combination of albuterol and ipratropium bromide has been reported to be synergistic [12]. Albuterol can be administered as a metered-dose inhaler, using a spacer designed for cats (Figure 34.1), or nebulized. Administration of albuterol via a metered-dose inhaler and delivery via nebulization have been shown

to be equally as efficient when cats were challenged with a bronchoprovacant [12]. Success of inhalant therapy is largely dependent on patient cooperation. Alternatively, terbutaline (0.01 mg/kg IV, IM or SC) can be administered easily and with minimal patient handling [13]. This is the author's preference for emergency management of asthmatic cats.

Many cats with feline lower airway disease will be stabilized with the above therapy. Glucocorticoids at an anti-inflammatory dose may be required in these initial stages to address airway inflammation. It should be noted that use of glucocorticoids could potentially interfere with obtaining a diagnosis if this has not been achieved. Additionally, response to glucocorticoids does not narrow the differentials for the underlying etiology of feline lower airway disease as all have the potential to respond to this therapy.

Differential Diagnosis

Feline lower airway disease typically refers to feline asthma and chronic bronchitis. Other differentials that have similar presentations and clinical pictures include heartworm-associated respiratory disease and lung-worm disease. Additionally, *Toxocara cati* infection can produce similar clinical findings, but it remains unclear whether this infection leads to emergent respiratory presentation.

Feline Asthma

Feline asthma is a chronic inflammatory airway disease that is estimated to affect approximately 1–5% of cats [14]. Current evidence supports an allergic etiology where sensitization to aeroallergens and subsequent exposure to those allergens result in classic features of allergic asthma such as eosinophilic airway inflammation, airway hyperresponsiveness, and airway remodeling [15,16]. In-depth discussion of the pathogenesis of feline asthma has been detailed elsewhere [15] and is beyond the scope of this chapter. Bronchoconstriction is a key feature of this condition, and therefore cats may experience acute episodes of expiratory respiratory distress that are responsive to bronchodilator therapy.

Thoracic radiography findings may include a bronchial or bronchointerstitial pattern or be within normal limits [1–3,17,18]. Additionally, some cats may have evidence of flattening of the diaphragm which could suggest air trapping and lung lobe collapse, typically the right middle lung lobe, which is presumed to be due to atelectasis and mucus trapping [2,18]. Bronchoalveolar lavage (BAL) cytology is characterized by eosinophilic airway inflammation.



Figure 34.1 A spacer and mask for delivery of a bronchodilator (albuterol metered-dose inhaler) to cats.

Chronic Bronchitis

Chronic bronchitis is infrequently associated with respiratory distress as bronchoconstriction is not a component of this condition; however, with severe disease, cellular infiltration, excessive mucus production, and structural changes can occur which lead to a more fixed airflow limitation. Chronic bronchitis is considered to be the result of a previous airway insult, such as persistent respiratory infection or chronic exposure to airway irritants. A bronchial pattern is commonly seen on thoracic radiographs. Chronic bronchitis is characterized by non-degenerate neutrophilic airway inflammation noted on BAL cytology and excess mucus production. Culture of BAL fluid is recommended as secondary infection can occur.

Despite this condition being characterized by neutrophilic inflammation, it is still somewhat difficult to definitively differentiate it from feline asthma as airway damage from chronic asthma may result in a component of neutrophilic inflammation [16]. Structural changes that can be noted on bronchoscopy, such as bronchiectasis and bronchomalacia, can occur secondary to long-standing inflammation [19] and this alteration is not reversible. These structural changes along with excess mucus secretion can lead to a presentation of respiratory distress in cats with chronic bronchitis.

As bronchoconstriction is not a feature of chronic bronchitis, significant improvement in response to bronchodilator therapy is not expected. Treatment is directed at controlling airway inflammation with glucocorticoids and addressing any secondary infections.

Lungworm Disease

Lungworms should be considered as a differential diagnosis in cats presenting with signs of feline lower airway disease. The most commonly discussed lungworms in cats are *Aelurostrongylus abstrusus* and *Capillaria aerophila*. Recently, an additional lungworm, *Troglostrongylus brevior*, has been identified in domestic cats [7,8].

Lungworm infection can have similar presenting complaints and clinical features to feline asthma and chronic bronchitis. Clinical signs can include coughing, wheezing, dyspnea, labored abdominal breathing, tachypnea, sneezing, and nasal discharge [7–9]. Radiographic findings in cats with lungworm disease are non-specific and have been reported to include bronchial thickening/bronchial pattern, bronchointerstitial pattern, unstructured interstitial pattern, and poorly defined small nodules [7,9]. Peripheral eosinophilia may be present as well as eosinophilic inflammation on BAL cytology. Analysis of feces by the Baermann technique is considered the diagnostic of choice for lungworm infection [7,20]. It is

very sensitive [20] and widely available. However, results take 24 hours to obtain, and optimum sensitivity requires repeating the test three times if the test is negative [7].

There are several treatment protocols available [7] and treatment should be directed based on the particular lungworm identified. It is worth noting that respiratory distress may also be seen as a result of parasite death and secondary inflammation once treatment has begun.

Heartworm-Associated Respiratory Disease

Heartworm-associated respiratory disease can be difficult to differentiate clinically from feline asthma and lungworm infection. Clinical signs of coughing, open mouth breathing, labored breathing/dyspnea, vomiting, diarrhea, syncope, and sudden death have been reported in studies of naturally occurring feline heartworm disease [5,6,21,23]. Adult heartworm infection is relatively uncommon in cats, with an overall reported feline heartworm antigen-positive rate of 0.4–0.9% [21,23]. This rate increases to 5% in cats with consistent clinical signs [5]. Prevalence of seropositivity ranges widely, depending on geographical location as well as whether the population evaluated is largely asymptomatic (7.8–12%) or demonstrating consistent clinical signs (13.3–44%) [5,6,21,23]. A history of living indoors only should not be reason to dismiss this condition from the differential [5,6,21].

Peripheral eosinophilia and basophilia may be noted in some cats [5,24]. Abnormalities noted on thoracic radiographs may include a bronchointerstitial pulmonary pattern, interstitial pulmonary pattern, and/or enlargement of the caudal lobar arteries [5,22,24]. Bronchoalveolar lavage cytology is typically classified as eosinophilic inflammation [24]. If computed tomography is evaluated, changes that have been associated with HARD include increased interstitial densities, decreased total lung volume, and pulmonary artery enlargement [24].

Treatment of these patients typically involves glucocorticoid therapy at anti-inflammatory doses. There is mixed evidence for the occurrence of bronchoconstriction in HARD patients; an *ex vivo* bronchial ring study documented decreased bronchial contractility to bronchoprovocants while a study using plethysmography in cats documented changes supportive of bronchoreactivity [25,26]. Therefore, what benefit bronchodilator therapy may have is not clear.

Toxocara cati

Lung disease associated with *Toxocara cati* infection has been described [27,28]. Cats experimentally infected with *Toxocara cati* were reportedly asymptomatic [28], but the condition remains an important consideration since changes noted on complete blood count, thoracic

radiography, and bronchoalveolar lavage are similar to disease discussed above. It could be difficult to diagnose lung pathology associated with *Toxocara cati* since abnormalities were seen in cats that did not develop concurrent intestinal parasites, and cats on an appropriate preventive also developed abnormalities [28]. These cats developed eosinophilia on complete blood

counts, and thoracic radiography revealed a bronchial pattern and/or pulmonary artery enlargement [28]. Eosinophilic bronchoalveolar lavage cytology was also documented [28]. This could represent a background disease condition that has the potential to further complicate diagnosis. Further observations from clinical cases are needed.

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Puppy Pneumonia

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Introduction

Puppies are frequently presented to the emergency room with signs of respiratory distress. Infectious respiratory disease is by and large the most common reason for distress in puppies, constituting part of the “kennel cough” or canine infectious respiratory disease complex (CIRD) [1]. Less common causes for respiratory distress are seen, including heart failure secondary to congenital heart disease (Figure 35.1) and neoplasia (Figure 35.2). The term CIRD encompasses all causes of respiratory infections in

dogs but bacterial and viral etiologies predominate. Most cases of CIRD result in tracheobronchitis and potentially purulent nasal discharge. A smaller proportion of these puppies develop pneumonia as well, which is referred to as “community-acquired” pneumonia to distinguish it from the aspiration or hematogenous pneumonias also seen in puppies [2].

Within the United States, infectious respiratory diseases in puppies are becoming more common than more traditional infectious problems such as parvovirus. This paradigm shift has developed as a result of active transport situations where puppies are shipped around the country. This applies not only to non-reputable breeders but also to well-meaning rescue organizations. Transport is in itself a stressful process that may be worsened by mixing puppies from multiple sources of origin. Respiratory infections are transmitted via aerosol, which means infections can and will spread rapidly. While vaccination is effective against diseases such as parvovirus and canine distemper virus, *Bordetella* vaccination is less effective and it may not even be the causative agent in CIRD.

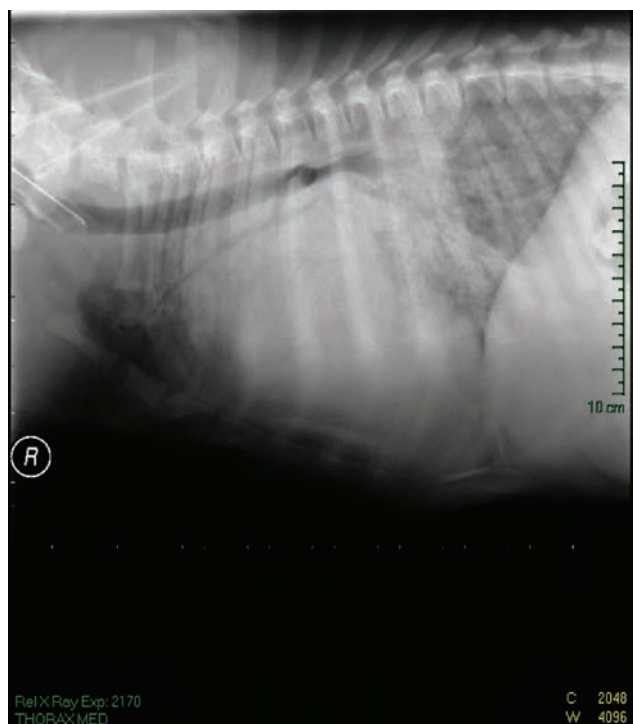


Figure 35.1 A lateral thoracic radiograph from a Gordon setter puppy with respiratory distress associated with heart failure from a patent ductus arteriosus.

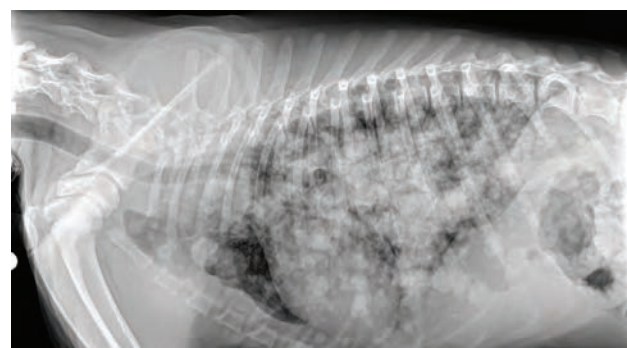


Figure 35.2 A lateral thoracic radiograph from a 5-month-old giant schnauzer-standard poodle X with metastatic disease from a nephroblastoma. Note the nodular pattern.

Clinical Approach

Puppies with community-acquired pneumonia typically present with overt evidence of respiratory distress, potentially accompanied by other clues including dehydration, lethargy, fever, and inappetence. A working list of differential diagnoses of common reasons for respiratory distress in puppies is helpful for the ER veterinarian. Infectious causes of respiratory distress are most common, often associated with fever and/or purulent nasal discharge. Alternative rule-outs for distress include congestive heart failure secondary to congenital cardiac diseases (see Figure 35.1), non-cardiogenic pulmonary edema (e.g. secondary to electrocution or choking) (Figure 35.3), and some relatively rare but important conditions such as neoplasia (see Figure 35.2), bleeding secondary to anticoagulant rodenticide toxicity, or thoracic trauma. Pattern recognition and historical clues can be very helpful to gauge the relative likelihood of these conditions in specific cases. Cases of suspected CIRD should be considered a contagious risk until proven otherwise and appropriate biosecurity measures should be instituted (e.g. isolation from other dogs) whenever possible.

The clinical approach to specific cases will vary depending on a number of factors. The severity of clinical symptoms is one of the most helpful guides. A bright puppy without evidence of significant respiratory embarrassment or volume depletion and with a good appetite could reasonably be considered fit for empirical therapy as an outpatient. In contrast, a weak, dehydrated and febrile animal would likely benefit from hospitalized care given the risk of becoming septic and not surviving

its disease. The financial capabilities of owners will also govern the completeness of diagnostics and treatments provided. Another consideration may be if the puppy is no immediate risk to infecting other animals in the household, compared to a group ('herd health') type scenario where an infected animal poses an immediate risk to others. Definitive confirmation of a causative agent may be more desirable in the latter situation.

Diagnostic Testing

There may be some situations where no diagnostics are strictly necessary or even financially possible for owners, although in most circumstances a variety of tests can be considered, even if not all are pursued. Supportive information can be gleaned from an emergency laboratory database, including packed cell volume, total solids, blood smear evaluation, and blood glucose estimation. Respiratory-specific diagnostics include imaging of the thorax, airway sampling for cytology and culture, as well as specific tests focused on pathogen identification.

Thoracic radiographs are helpful to rule out other differential diagnoses and evaluate the extent of pulmonary pathology. Puppy pneumonia is classically characterized by a diffuse but ventrally distributed alveolar pattern (Figure 35.4). This differs from the classic pattern seen with aspiration pneumonia resulting in alveolar infiltrates usually in single lung lobes. Puppies that have radiographic changes more consistent with aspiration pneumonia may have an unrecognized underlying process leading to a vomiting or regurgitating event (e.g. persistent right aortic arch, parvoviral enteritis,

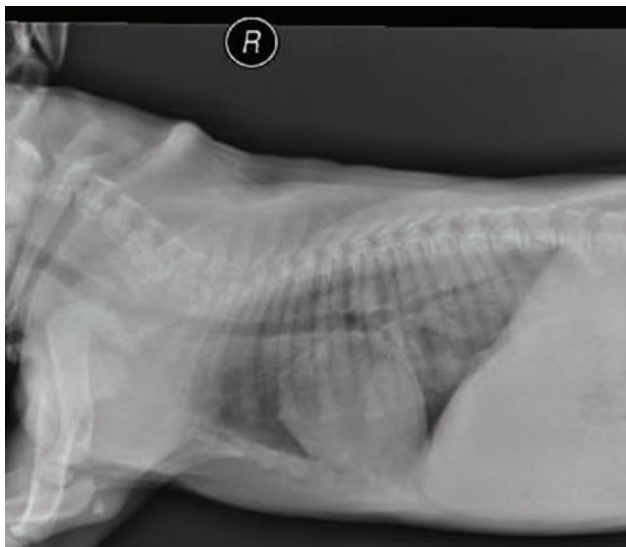


Figure 35.3 A lateral thoracic radiograph from a mixed breed puppy with non-cardiogenic pulmonary edema. Note the dorsal caudal infiltrates.

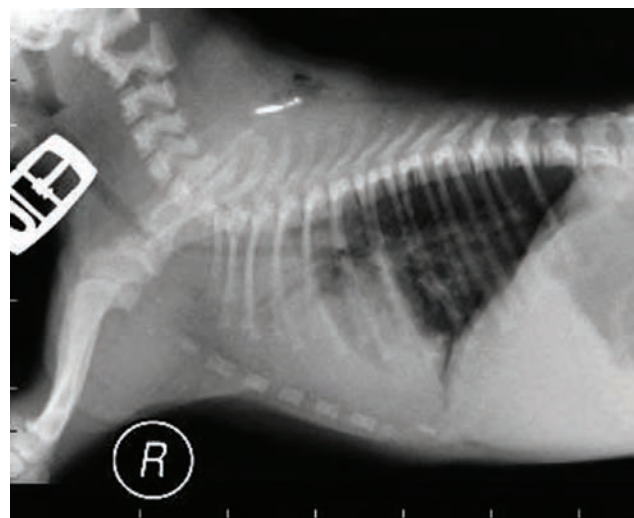


Figure 35.4 A lateral thoracic radiograph from a puppy with severe community-acquired pneumonia.

intussusception, parasitism). The diagnostic plan for these dogs will vary compared to that of dogs with CIRD.

Airway sampling is tempting to confirm diagnosis, identify specific pathogens implicated in individuals, and guide therapy through antimicrobial susceptibility. Depending on the technique employed, general anesthesia is typically necessary and the risk of anesthesia should be weighed against the benefit of data obtained from airway sampling. Another consideration is that there can be a frustrating time delay between collecting samples and obtaining results. In this time period, empirical therapy may have proven effective or not, potentially limiting the usefulness of such tests in the straightforward CIRD case.

The authors typically will perform endotracheal washes (ETW) in most puppies. Briefly, this involves inducing anesthesia, securing the airway with a sterile endotracheal tube, and passing a sterile urinary catheter (e.g. 5 Fr red rubber) down the lumen of the endotracheal tube. A small aliquot of sterile 0.9% sodium chloride (isotonic to preserve cellularity) is introduced rapidly into the airway via the endotracheal tube before being suctioned back. An assistant can perform coupage in an attempt to improve the diagnostic yield of such airway samples. Briefly tipping the patient's body such that the head momentarily faces downwards off an exam table may also enable collection of more airway secretions into a sterile collection cup. The sample collected can be submitted for cytology and culture/susceptibility testing. In larger puppies, transtracheal washes may be considered. In children with cystic fibrosis, deep oral swabs are considered viable alternatives to more invasive airway sampling techniques. Deep oral swabs have some associations with endotracheal washes in adult dogs but disparate results in puppies [3].

Airway cytology in cases of pneumonia will typically be consistent with neutrophilic inflammation with visible intracellular bacteria (bacilli more commonly than cocci). No causative organisms may be seen with certain species of bacteria (e.g. *Mycoplasma*) and with viral diseases. Oral commensal bacteria (e.g. *Simonsiella*) are also frequently seen in samples collected with an orotracheal approach.

Bacterial culture results in cases of puppy pneumonia are generally evenly divided between *Bordetella* and gram-negative bacteria [2]. More fastidious organisms such as *Mycoplasma* may be missed by standard culture and require special growth media. A convenient additional option for identifying causative organisms in puppies with suspected CIRD is the use of quantitative PCR from pharyngeal swabs [1]. Quantitative PCR for *Bordetella* can also be performed accurately on BAL fluid [4].

Viral causes of CIRD, including canine influenza and canine distemper virus, may also be identified using commercially available quantitative PCR panels. Canine influenza is an emerging pathogen of concern for adult dogs mainly, but has particular relevance for shelter situations. It is spread as an aerosol through coughing and sneezing and potentially via fomite spread (e.g. kennel surfaces) [5]. Dogs are most contagious for up to 4 days after exposure but persistence of infectious load can occur for weeks longer. Antibodies to influenza viruses can be detected via commercially available serological tests. Serology can be used for previous exposure to virus as well as surveillance of clinical cases [6]. Clinically overt cases of influenza are very common but mortality is less common.

Care for these dogs is largely supportive in nature, with antiviral drugs (e.g. oseltamivir) not being recommended in clinical cases [7]. Dogs with infection should be isolated for up to 21 days and strict hygiene policies need to be implemented (e.g. cleaning cages, personal protective clothing).

Treatment Options

Antimicrobials are the mainstay of therapy in cases of puppy pneumonia. Antimicrobial therapy would ideally be guided by culture and susceptibility. Since not all puppies will undergo culture and there is a delay of a few days in obtaining results, empirical choices will need to be made. Depending on the severity of patient illness, antimicrobials can be administered orally, parenterally or via aerosol. Potential antimicrobial choices are summarized in Table 35.1.

Table 35.1 Potential antimicrobial options for puppies with CIRD.

Drug name	Dose range	Frequency	Route	Indications
Doxycycline	5–10 mg/kg	12–24 hours	PO or IV	Infection
Amoxicillin-clavulanate	12–15 mg/kg	12 hours	PO	Infection
Enrofloxacin	10–20 mg/kg	24 hours	PO or IV	Infection
Amikacin	15 mg/kg	24 hours	IV	Infection
Gentamicin	6 mg/kg	24 hours	Inhaled	Persistent cough

CIRD, canine infectious respiratory disease; IV, intravenous; PO, by mouth (*per os*).

Most antimicrobials are chosen for the elimination of acute infection and/or to prevent secondary bacterial pneumonia in cases of primarily viral disease. One study in puppies found amoxicillin-clavulanate to be appropriate based on culture/susceptibility in all cases of *Bordetella bronchiseptica* [2]. Resistance patterns vary with geography and the best empirical choice may differ from hospital to hospital. Consideration for potential adverse effects is important in neonates, with chondrotoxicity a specific concern in growing large-breed dogs specifically. The authors typically manage outpatient cases (never requiring hospitalization) with doxycycline. Inhaled antimicrobials are generally avoided in more systemically sick puppies. Aerosolized aminoglycosides may have a role in dogs with chronic *Bordetella* infections where epithelial adherence of *Bordetella* may lead to chronic cough.

In addition to antimicrobials, overall care of the compromised puppy may include IV fluids to ensure normal fluid balance with dextrose supplementation of fluids if nutritional intake is below normal. Puppies with more severe respiratory compromise might require oxygen therapy (see Chapter 181). A variety of techniques are possible, the availability of which varies from hospital to hospital. Oxygen cages, oxygen masks, nasal lines, and even intubation for ventilation may be necessary. Nebulization and coupage are frequently recommended in puppies, yet there is a lack of compelling evidence to suggest a clear benefit to the technique.

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Prognosis

Prognosis is generally favorable in puppies with CIRD, depending on their illness severity and the appropriateness of their supportive care. A failure to respond relatively quickly to therapy (e.g. within 1–2 days) is considered a poor sign, as would be the development of acute respiratory distress syndrome leading to refractory hypoxemia. Long-term sequelae are uncommon. In a small group of patients chronic pneumonia may develop that is associated with a failure to thrive. Alternatively, small airway disease may be seen in some dogs associated with exercise intolerance and air trapping.

Brachycephalic Dogs

Brachycephalic puppies, such as bulldogs, deserve special comment as they appear to be more commonly affected with pneumonia. Resolution of pneumonia may be more challenging due to relative tracheal hypoplasia, and upper airway obstruction limiting airflow. Interestingly, a recent report has described that bulldogs with apparent tracheal hypoplasia may have resolution of this anatomic abnormality as they age. Practically, hospitalization and close monitoring of brachycephalic puppies with pneumonia are warranted, and the prognosis may be more guarded.

36

Coughing and Hemoptysis

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Introduction

Cough is a common yet non-specific condition in animals presenting to the emergency service as either a chief complaint or part of the pertinent medical history. Despite the prevalence of acute cough, most published reports in veterinary medicine have focused on chronic cough. A 2010 study evaluating chronic cough (>2-month duration) found the majority (77%) were due to large airway disease, predominantly chronic bronchitis and tracheobronchomalacia [1]. To the author's knowledge, there have been very few controlled studies evaluating the risk factors or responsible etiologies for acute cough or hemoptysis. Infectious tracheobronchitis, laryngeal paralysis, tracheal collapse, congestive heart failure, and pneumonia comprise the vast majority of clinical cases presenting for cough on an emergency basis.

Physiology

Coughing is a normal protective mechanism by which the respiratory tract can expectorate foreign material or excess secretions from the airway. The cough reflex can be separated into two phases: the sensory phase and the motor phase.

The sensory phase begins with activation of receptors within the airway which initiate afferent nerve impulses, primarily via the vagus nerve to the brainstem. There are both mechanical and chemoreceptors within the airway responsible for initiating the cough reflex [2].

Perceptually, we can appreciate the difference between mechanoreceptor activation and chemoreceptor activation [3]. Mechanoreceptor activation is an often more violent, non-voluntary action, whereas chemoreceptor activation results in the sensation of an "urge to cough."

Mechanical receptors predominate within the larynx, trachea, and large bronchi. These are myelinated afferent nerves, allowing for very rapid conduction of action potential, and are primarily responsible for protecting the airway from aspiration [3,4].

Chemoreceptors (C-fibers) are the more prevalent of the two receptor types, and have been identified within all segments of the respiratory tree, including the larynx, carina, terminal bronchioles, and alveoli [3,4]. C-fibers primarily respond to chemical stimuli, such as capsaicin, bradykinin, adenosine, prostaglandin E₂, citric acid, hypertonic saline solution, sulfur dioxide gas, chlorine gas, and lung inflammation [4]. These have unmyelinated axons and hence conduct action potentials more slowly than the mechanical receptors. They are less responsive to mechanical stimulation, but can also amplify a cough reflex initiated by mechanoreceptors [3].

Once action potentials reach the medulla of the brainstem, the sensory stimulation elicits a series of events, collectively referred to as the motor phase. This motor pattern of the reflex cough is regulated differently than for tidal breathing in multiple ways [4]. Anatomically, for instance, the neuronal pathways invoked with the cough reflex reside alongside other neuronal pathways involved with swallowing [4].

The motor phase is further composed of an inspiratory phase, compressive phase, and expulsive phase. At first, inspiratory muscle activation results in thoracic wall expansion. The compressive phase is characterized by glottic closure and contraction of the expiratory muscles such as the diaphragm, which increases intrathoracic pressure. Finally, during the expulsive phase, the vocal cords and epiglottis open, resulting in the rapid escape of pressurized air from the thoracic cavity [2]. Hemoptysis is associated with cough from a variety of causes.

Differential Diagnosis

Nearly any disease resulting in laryngeal, tracheal, bronchiolar, or pulmonary pathology can elicit coughing and may need to be considered with the appropriate concurrent patient signalment, physical exam findings, and available diagnostic results. Even non-airway diseases such as gastroesophageal reflux have been associated with cough in both people and dogs [5]. Trauma or cardiopulmonary diseases such as left-sided congestive heart failure, pulmonary hypertension, pulmonary fibrosis, chronic bronchitis, and pulmonary thromboembolism also should be considered [6].

Hemoptysis

Hemoptysis, defined as the expectoration of blood or bloody mucus from the respiratory tract at or below the larynx, is rarely encountered in veterinary medicine (Box 36.1). A retrospective case series of 36 dogs presenting with hemoptysis found bacterial bronchopneumonia to be the most common cause [7]. Other attributable causes in veterinary medicine have included bacterial or fungal pneumonia, leptospirosis, heartworm disease, neoplasia, immune-mediated thrombocytopenia, anticoagulant rodenticide toxicity, foreign body, trauma, lung lobe torsion, pulmonary thromboembolism, left-sided heart failure, and even a recent report of pneumonic plague [7–11].

Infectious Tracheobronchitis

Viral infectious tracheobronchitis, commonly referred to as kennel cough, is a respiratory syndrome affecting the larynx, trachea, bronchi, and nasal mucosa which

Box 36.1 Approach to a dog with a presenting complaint of hemoptysis.

- Complete physical examination with focus on evidence of other spontaneous bleeding and/or presence of respiratory distress; provide supplemental oxygen or intubate and ventilate if respiratory distress present; review history for possible trauma.
- Evaluation of clotting status; platelet count (immune-mediated thrombocytopenia), prothrombin time (anticoagulant rodenticide) and activated partial thromboplastin time (disseminated intravascular coagulation).
- Thoracic radiographs; evaluate for pulmonary infiltrates or mass lesion.
- Consider computed tomography or bronchoscopy if origin is not evident from other testing.

is composed of multiple etiological agents in both dogs and cats. Canine parainfluenza virus and canine adenovirus remain the two most common agents in dogs, although many other pathogens have been implicated [12–15]. Independent from viral causes, several bacterial isolates including *Bordetella bronchiseptica*, *Mycoplasma*, and *Streptococcus equi* also contribute to this syndrome [14,15]. Typical clinical signs consist of a dry, non-productive cough and/or nasal discharge.

Infectious tracheobronchitis is associated with an excellent prognosis, with most affected animals recovering spontaneously within several days to weeks. Prevention through regular immunization has been considered the most effective management option, although controversy exists about how much protection vaccines might convey [16]. Treatment may not be required, except for severely affected patients.

Bacterial pneumonia can be part of the infectious tracheobronchitis syndrome or the result of aspiration pneumonia, foreign body, or ventilator-associated causes. Aspiration pneumonia should be highly considered in patients with a history of vomiting and the presence of an alveolar pulmonary pattern, particularly affecting the right middle lung lobe. Investigators have concluded that samples collected from deep oral swabs are not an appropriate alternative to tracheal wash [17]. Transtracheal aspirate, bronchoalveolar lavage or transcutaneous fine needle aspirate of a severely consolidated lung lobe could be considered for cytology and culture submission.

Foreign Body

Inhaled or migrating pharyngeal or tracheal foreign bodies, most commonly grass awns and plant material, can also result in the development of bacterial pneumonia, cough, and/or hemoptysis. Cases of foreign body-associated pneumonia often occur in young, athletic breeds, with a history which may consist of chronic or recurring respiratory signs despite antibiotic therapy. *Pasteurella*, *Streptococcus*, *Nocardia*, *Actinomyces*, and anaerobic bacterial isolates have been cultured from affected sites [18]. Definitive diagnosis and treatment may require CT imaging and surgical intervention, but the prognosis is often favorable.

Although much less common, fungal pneumonia such as aspergillosis, histoplasmosis, and blastomycosis may be considered in those patients that live in or have traveled to endemic areas [19].

Other tracheal foreign bodies such as cuterebra, transected endotracheal tubes, bone, and stones have been reported in the literature [20–22]. Survey radiography may identify radiodense or soft tissue opacity, often at the level of the carina. Bronchoscopic retrieval or

surgical excision is required for foreign body removal [20–22].

Anatomical Disruption

Anatomical disruption is a common category of diseases resulting in cough and/or hemoptysis and includes laryngeal paralysis, tracheal collapse, lung lobe torsion, and even tracheal intussusception [23].

Laryngeal paralysis is a common acquired condition affecting the recurrent laryngeal nerves or cricoarytenoid dorsalis muscles, with some reports suggesting up to 25% prevalence in all dogs undergoing anesthesia (see Chapter 30) [24]. Feline laryngeal paralysis has also been characterized, although the disease is much less prevalent [25].

Tracheal collapse is a common cause of cough in dogs and can affect the cervical trachea, intrathoracic trachea or both regions (see Chapter 31). The clinician may have a high index of suspicion based on the breed disposition and characteristic “honking” cough, but fluoroscopy or bronchoscopy is required for definitive diagnosis [26,27]. Immediate stabilization is typically achieved with sedation and supplemental oxygen, although some dogs may require endotracheal intubation. Long-term management including intratracheal stents or tracheal rings is indicated for severely affected patients, but does not negate the need for medical management including antitussives and other medical management tools [28].

Lung lobe torsion is rare, but large deep-chested dogs, Afghan hounds, and Pugs may be overrepresented [29,30]. Radiographic evidence of lung lobe torsion may include lobar opacity, pleural effusion, vesicular emphysema, and focally narrowed or blunted lobar bronchi. [30,31]. The prognosis for dogs with lung lobe torsion is generally fair to guarded with surgical intervention [29,30].

Neoplasia

Neoplasia affecting the intrathoracic or extrathoracic respiratory tract can result in coughing and/or apparent hemoptysis. Upper airway masses in cats such as squamous cell carcinoma, lymphoma, and adenocarcinoma can be relatively simple to diagnose but have a grave prognosis, with a median survival time of 5 days and only 7.4% alive at 1 year [32]. Primary lung tumors in dogs such as bronchoalveolar carcinoma, adenocarcinoma, histiocytic sarcoma, and squamous cell carcinoma have a variable prognosis depending on the tumor type, size, histological grade, and presence of metastatic disease but generally range from 8 to 18 months [33]. Unlike dogs with primary pulmonary tumors, most dogs with disseminated disease carry a worse prognosis [33].

Diagnostic Approach

During initial patient triage, the emergency clinician is tasked with determining whether the patient is experiencing any respiratory distress. Dyspneic patients should be supported with supplemental oxygen (see Chapter 181). Using physical exam parameters, the clinician should attempt to localize the source of dyspnea to the upper airways, lower airways, lung parenchyma, pleural space, thoracic wall, or non-respiratory causes [34]. In addition, the cervical region should be critically evaluated for lymphadenopathy, enlargement of the thyroid gland, or other potentially compressive soft tissue swelling. Successfully localizing the source of the respiratory distress will aid both in developing an appropriate list of differential diagnoses and determining the most immediate therapeutic intervention [34].

If hemoptysis is present, the first diagnostic consideration is to assess primary and secondary hemostatic systems. Categorizing the hemoptysis as coagulopathic or non-coagulopathic will aid the clinician in organizing appropriate disease differentials and selecting the most appropriate next diagnostic options (see Chapters 67, 69, and 70). CBC, manual platelet count, prothrombin time, and activated partial thromboplastin time should be performed in any patient with hemoptysis. Additional tests of coagulation such as buccal mucosal bleeding time or coagulation factor analysis should be undertaken as deemed clinically necessary.

Survey cervical radiographs may be useful in identifying tracheal collapse, metallic foreign body, or intraluminal opacity that could be consistent with foreign material, polyp, abscess, or a neoplastic process. The clinician is advised that laryngeal radiography is notoriously hard to interpret. Bronchoscopy may be required in those patients that require more focused evaluation of the tracheal lumen or mainstem bronchi and, of course, is useful for removal of foreign objects or biopsy of masses.

Thoracic radiographs should be evaluated for the position of the carina, intrathoracic airway diameter, overall cardiac size, left atrial size, enlargement of pulmonary arteries and/or veins, abnormal pulmonary parenchymal patterns, space-occupying lesions within the thoracic cavity, or enlarged mediastinal lymph nodes. Echocardiography should be considered for patients with cardiomegaly, left atrial enlargement, distended pulmonary veins, or perihilar alveolar pulmonary pattern. Dogs with hemoptysis will usually have abnormal radiographs, either from the source of the hemorrhage or due to aspiration of blood into airways.

Sedation for laryngeal exam and/or endotracheal tube placement should be considered for patients with dyspnea attributed to upper airway disease, but the heavy sedation required for effective orolaryngeal examination

may cause significant respiratory depression. Therefore, diagnostics to rule out concurrent cardiac or pulmonary disease are typically considered before a sedated orolaryngeal exam.

When performing a laryngeal exam, the clinician should consider drugs which minimally affect normal laryngeal motion (see Chapter 30). Thiopental has been previously recommended [35], but is not currently available. A more recent investigation recommended that concurrent ketamine should be avoided with propofol due to increased respiratory depression and its inability to reduce the propofol dose [36]. Propofol by itself has been associated with decreased arytenoid movement, significant respiratory depression, and apnea [35], which can impede normal laryngeal abduction. During sedated laryngeal examination, doxapram has been advocated to increase intrinsic laryngeal motion, which may be helpful in differentiating normal dogs from dogs with laryngeal paralysis [37,38].

In addition, there are commercially available respiratory disease diagnostic panels for the detection of most canine and feline viral pathogens. During laryngeal examination, the clinician may consider collecting deep pharyngeal swabs and conjunctival swabs for future submission to commercial diagnostic laboratories as indicated.

Treatment

Therapeutic principles for managing patients with cough are always directed towards identifying and effectively treating any primary disease. The finding that bacterial pneumonia was the most common cause of hemoptysis in dogs suggests that use of empiric antibiotics may be warranted until additional diagnostic information is ascertained (see Chapter 37) [7].

If the cough is highly productive, antitussive therapy may be contraindicated so as to not impede the normal respiratory clearance mechanisms. For non-productive coughs, antitussive treatment could be considered if the cough impairs normal daily function or if an underlying cause is not identified. Symptomatic antitussive treatment consists of opiate derivatives with the intended goal of inhibiting the central mediators of the cough reflex [3]. Interestingly, the antitussive effect does not appear to be related to the binding of traditional opiate receptors [3].

Commonly prescribed veterinary medications include codeine (1–2 mg/kg PO q6–12h), hydrocodone (0.25 mg/kg PO q6–12h), butorphanol (0.1–0.2 mg/kg PO q6–12h), and dextromethorphan (0.5–1 mg/kg PO q8–12h) [39].

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Bronchopneumonia

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Introduction

Pneumonia is defined as inflammation of the pulmonary parenchyma [1–3]. It is a common diagnosis with varying etiologies and a spectrum of severity. Bronchoalveolar inflammation is a characteristic physiological feature of pneumonia. It is typically caused by infectious agents that bypass normal or impaired host airway defenses or that enter the lungs hematogenously [3].

Types of Pneumonia

Bacterial Pneumonia

The normal flora of the oral cavity, trachea, and upper respiratory tract is similar to the organisms identified in many cases of bacterial pneumonia, suggesting that pneumonia often occurs when these agents overcome airway defenses. In normal dogs and cats, respiratory tract defenses include the nasal turbinates, larynx, mucociliary escalator, cough, bronchus-associated lymphoid tissue, and alveolar macrophages.

Bacterial pneumonia often occurs as a sequela of acute or chronic lung injury caused by inflammation or structural disease. Aspiration of gastrointestinal tract contents (see below) is one of the most common causes of bacterial pneumonia in dogs. Dogs with severe tracheal collapse, chronic bronchitis or bronchiectasis may be at higher risk of developing bacterial pneumonia as a complication of the primary lung or airway disease. Similarly, cats with bronchial disease, including feline asthma, may also be at increased risk.

Young and unvaccinated dogs may develop primary community-acquired pneumonia (CAP), with *Bordetella bronchiseptica* the most common bacterium identified (see Chapter 35) [1]. Co-infection with viruses such as

canine adenovirus type 2, parainfluenza, canine influenza or distemper occurs in the majority of cases.

B. bronchiseptica may also cause upper respiratory tract infections in cats [4].

The most common cause of feline bacterial pneumonia is hematogenous spread via the bronchial or pulmonary circulation [5]. Hematogenous pneumonia has also been reported in dogs, but is much less common. *Staphylococcus* and *Streptococcus* spp are common pathogens identified in hematogenous pneumonia; this likely occurs secondary to intravenous catheters or bacterial endocarditis.

Mycoplasma is a type of bacterial pathogen implicated as a cause of pneumonia in cats, although its role in dogs is less convincing. Its presence in airway cultures from cats with pulmonary disease, but not in healthy cats, suggests that it may be a primary pathogen in feline pneumonia [6].

Inhalation of foreign bodies such as plant materials or grass awns has been reported as a cause of bacterial pneumonia in dogs and cats. Foreign bodies in dogs are found most commonly in the right bronchus whereas in cats the trachea or carina is the most common location [7]. Lobar consolidation or a lung abscess, pyothorax or pneumothorax are possible complications as foreign material migrates through the pulmonary parenchyma or pleura. Grass awns have been associated with *Pasteurella*, *Nocardia*, *Streptococcus*, *Actinomyces*, and anaerobic bacteria [7,8].

Impaired defenses can also play a role in the development of bacterial pneumonia. Primary ciliary dyskinesia, genetic immunoglobulin deficiencies, and X-linked severe combined immunodeficiency (SCID) have all been reported in dogs [9–11]. Viral diseases such as feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) can increase susceptibility to secondary bacterial infections. Patients receiving chemotherapeutic drugs also face similar susceptibilities.

Aspiration Pneumonia

Various underlying causes predispose dogs to aspiration pneumonia, including vomiting or regurgitation, neurological or laryngeal disease, and following sedation or anesthesia [2,12,13]. Of dogs presenting with aspiration pneumonia, 68% have a single underlying cause, with esophageal disorders being most common [12]. Often the aspiration event is unseen and the diagnosis is presumptive. Aspiration pneumonia is a rare finding in cats [5].

Following an aspiration event, initial injury to the airway epithelium and pulmonary parenchyma occurs if the gastric pH is less than 2.5. Sterile chemical pneumonitis predisposes to secondary bacterial infection with opportunistic pathogens from the normal pharyngeal flora [13]. The most common bacterial isolates are *Escherichia coli* and *Klebsiella* spp, with *Staphylococcus* and *Streptococcus* spp occurring less frequently [14–16].

Viral Pneumonia

Viruses are primary etiological agents of pneumonia, inducing inflammation of the respiratory epithelium and parenchyma. They cause immunosuppression and create an ideal environment for secondary bacterial adhesion and colonization [17,18]. Canine infectious respiratory disease (CIRD) is one of the most common infectious diseases in dogs, with a multifactorial etiology (canine parainfluenza virus, canine adenovirus type 2, canine distemper virus, coronavirus, canine influenza virus (CIV), *Bordetella bronchiseptica*, *Mycoplasma* spp, and *Streptococcus equi* sp. *zooepidemicus*) (see Chapter 35) [19–21]. A recent study showed that while viral infections were frequently present in dogs with bacterial pneumonia, no difference in severity of disease or length of hospitalization was noted [22]. However, this might not take into consideration some newer viral infections such as the H3N2 canine influenza virus, which has only been recently documented in the United States.

Feline infectious respiratory disease is most commonly caused by feline herpesvirus-1 (feline rhinotracheitis virus) or feline calicivirus. These viruses are mainly shed via ocular, nasal, and oral secretions and are prevalent in multicat households and younger animals (see Chapter 29) [23,24]. Carrier states contribute to prevalence despite availability of vaccines. The H3N2 canine influenza virus has also been reported in cats.

Fungal Pneumonia

Pulmonary mycotic infections can be due to opportunistic organisms such as *Aspergillus* spp or primary pathogens such as *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, or *Cryptococcus*

neoformans. The respiratory tract is commonly affected through inhalation of air-borne fungal spores. These fungal diseases are commonly found in soil and tend to be endemic to certain areas. As the most common mycosis in cats, cryptococcosis does not appear to have a defined endemic region [25]. Histoplasmosis is the second most commonly reported systemic fungal disease in cats, and along with blastomycosis is endemic to the Ohio, Missouri, and Mississippi river valleys [26,27]. Coccidioidomycosis is endemic to the south-western United States, Mexico, and Central and South America [28].

Aspergillosis most commonly affects the nasal cavity and sinuses of mesocephalic and dolichocephalic dogs [29]. Necrotizing pleuritis and spontaneous pneumothorax secondary to *Aspergillus* have also been reported [30]. Disseminated fungal infections can also cause ocular, dermatological, neurological, orthopedic, and gastrointestinal signs. For example, cryptococcosis has a high predilection for the CNS in dogs and an altered mental status was found to be a negative prognostic indicator [31].

Protozoal Pneumonia

Although protozoal pneumonia is rare, *Toxoplasma gondii*, an obligate intracellular coccidian, is one of the most common causes. Three infectious stages including oocysts, tachyzoites and bradyzoites occur, with cats being the definitive host [32]. Transmission usually occurs via ingestion of feces or water containing oocysts or of tissue containing tachyzoites and bradyzoites [33]. In cats with systemic disease, 97.7% have respiratory involvement [34].

Parasitic Pneumonia

Primary lung parenchymal parasites include trematodes (*Paragonimus kellicotti* – dog and cat) and nematodes (*Filaroides hirthi* and *Filaroides milksi* – dog). Parasites that invade the airways include *Aelurostrongylus abstrusus*, *Angiostrongylus vasorum*, *Crenosoma vulpis*, *Capillaria aerophila*, and *Oslerus osleri*. Some intestinal nematodes normally migrate through lung tissue during their life cycle (e.g. *Ancylostoma*) while others may aberrantly migrate into the lungs.

Physical Examination Findings

Patient history and physical examination findings vary with the underlying cause and severity of disease. Pneumonia can be subclinical, cause mild to severe respiratory distress, or lead to fulminant disease with acute respiratory arrest. In addition to general malaise, other signs may include a cough, which can be productive as

exudate is being cleared, or harsh in animals with tracheitis or bronchial compression (e.g. due to hilar lymphadenopathy). Ocular or nasal discharge, sneezing, fever, oral ulcerations or changes in the respiratory rate/pattern can also be seen. Generally, cats are more difficult to diagnose as many lack systemic illness or clinical signs referable to the respiratory tract [5].

Most dogs have normal vital signs, but 68% are found to have abnormal lung sounds [35]. It is notable that fever is not consistently present in dogs with pneumonia. In severe cases of pneumonia, patients may develop secondary sepsis or systemic inflammatory response syndrome (SIRS) and as a result present with hemodynamic compromise.

Diagnostics

A presumptive diagnosis of pneumonia is generally made from the patient history, clinical examination findings,

and thoracic radiographs. However, to confirm the diagnosis, the presence of pulmonary inflammation and an underlying agent must be confirmed.

Diagnostic Imaging

If the patient is stable enough, orthogonal three-view thoracic radiographs should be obtained. When the pneumonia is bronchogenous in origin (aerosolized pathogen or aspiration), thoracic radiographs most commonly demonstrate a cranioventral alveolar/interstitial pattern, which can be diffuse or lobar [5,36]. Aspiration pneumonia most commonly involves the right middle, left cranial, and right cranial lobes [13]. Hematogenous pneumonia tends to have a caudodorsal distribution [37]. Fungal pneumonia typically has a diffuse or nodular interstitial pattern and hilar lymphadenopathy (Figure 37.1) [38]. Radiographic changes can lag up to 24 hours behind clinical signs. Fluoroscopy can be used to evaluate for tracheal or bronchial collapse.

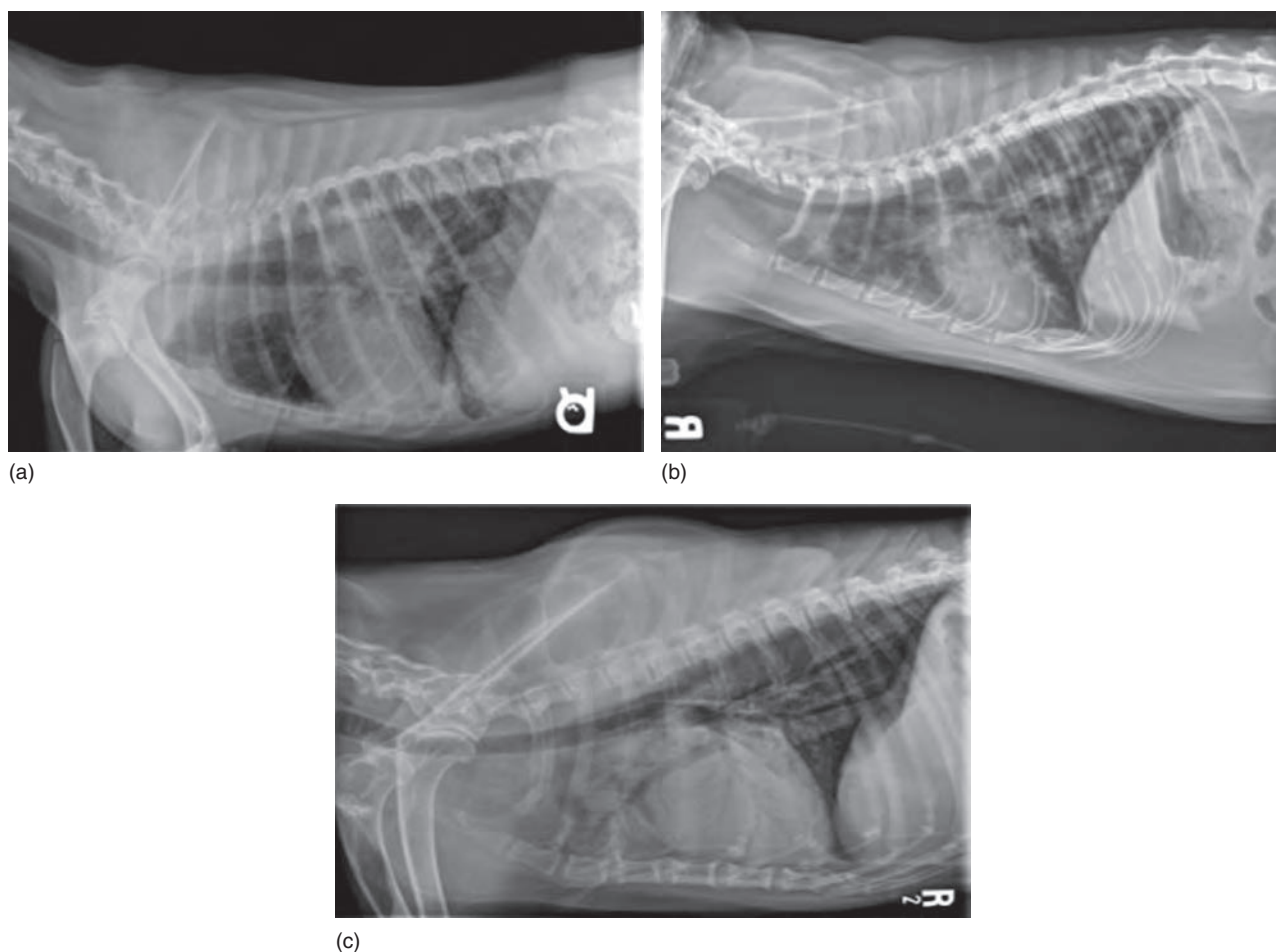


Figure 37.1 Lateral thoracic radiographs displayed. (a) Dog diagnosed with fungal pneumonia. Note the miliary bronchointerstitial pattern with tracheobronchial lymphadenopathy. (b) Cat diagnosed with toxoplasmosis. Note the multilobar patchy interstitial to nodular alveolar patterns throughout all lung lobes. (c) Dog diagnosed with aspiration pneumonia. Note the multilobar ventral alveolar pattern.

Thoracic ultrasound can also be used to supplement radiographs in cases of consolidated pulmonary infiltrates, possible abscesses, concurrent pleural effusion or intrathoracic masses. An echocardiogram should be performed if secondary pulmonary hypertension or bacterial endocarditis is suspected.

Advanced imaging such as CT may provide better three-dimensional imaging to document the presence of pulmonary parenchymal and small airway infiltrates and to exclude alternative diagnoses such as masses or thromboembolism.

Tracheobronchoscopy may be beneficial in cases of suspected foreign bodies, allows diagnosis of structural or functional airway disorders, and may facilitate fluid or tissue sampling from the airways [2].

Clinicopathological Evaluation

The complete blood count (CBC) may reveal an inflammatory leukogram, but this was present in only 57% of dogs with pneumonia in one study [1]. Chemistry and urinalysis profiles may support an underlying disease but offer no direct correlation with pneumonia [2].

C-reactive protein was found to be significantly higher in dogs with bronchopneumonia compared to other respiratory diseases [39], but is not expected to distinguish pneumonia from concurrent infectious, inflammatory or neoplastic conditions.

Polymerase chain reaction (PCR) and virus isolation assay panels are available through various diagnostic laboratories for suspected viral infections. Serological testing is available for a variety of viral, fungal, and protozoal pathogens. Antigen tests using serum or urine have demonstrated high sensitivity in identifying fungal infections [40,41].

A Baermann fecal examination should be performed in cases of suspected parasitic pneumonia.

Blood cultures should be considered in patients suspected of hematogenous pneumonia, SIRS or sepsis. Although not routinely performed, one study reported positive blood cultures in 49% of critically ill dogs and cats [42].

Lung Function and Hemodynamic Monitoring

Pulse oximetry and arterial blood gases are practical ways to evaluate the oxygenation status of the patient. Hypoxemia ($\text{PaO}_2 < 80 \text{ mmHg}$ or $\text{SpO}_2 < 94\%$) is commonly present, but hypercarbia is rare [13,35,43]. Hypoxemia is often due to ventilation:perfusion (V/Q) mismatch but can also involve shunt or diffusion impairment.

Blood pressure and electrocardiogram monitoring should be considered if there is any suspicion of hemodynamic compromise.

Airway Sampling for Cytology and Microbiology

Airway sampling is key to confirming pneumonia and guides antimicrobial use. Methods for sampling of the lower airways include bronchoalveolar lavage (BAL), transtracheal wash (TTW), and endotracheal wash (ETW).

During bronchoscopy, airway mucosal biopsy specimens can be obtained and BAL can be performed to collect samples from specific lung lobes for cytology and culture. Although BAL has increased sensitivity compared to a TTW [44], it is impractical in the emergency room setting if the patient is dyspneic due to the need for prolonged anesthesia and special equipment.

Transtracheal wash and ETW require less equipment and are minimally invasive. TTW is performed with light sedation and local anesthesia. A catheter is placed percutaneously into the cervical trachea; this technique is best suited to medium or large dogs. ETW is performed by briefly intubating the trachea with a sterile endotracheal tube under general anesthesia, and is best suited to small dogs and cats. The cardiovascular and respiratory status of the patient should be evaluated prior to performing any type of airway sampling.

The use of deep oropharyngeal swabs as a surrogate for ETW was not diagnostically helpful in puppies with community-acquired pneumonia [45]. Ultrasound-guided fine needle aspirates (FNA) of the pulmonary parenchyma tend to have high diagnostic yield if there are consolidated lesions or focal masses, but may be less helpful in animals with diffuse lung disease [46–48]. Potential complications of FNA, including pneumothorax, hemoptysis or death, are rare [46,47,49].

Aerobic culture and susceptibility testing should be performed, as most bacterial isolates from airways of dogs and cats are aerobic [5,50]. Anaerobic bacteria have been noted in some cases, such as with migrating grass awns, so these cases may prompt submission of an anaerobic culture. Although its role as a primary bacterial pathogen in pneumonia is still controversial [37], *Mycoplasma* culture or PCR may be submitted, especially in samples from cats with lung disease [51]. Fungal culture may be submitted if warranted by the clinical presentation.

In patients with pneumonia, cytological examination usually reveals mixed inflammatory cells, including neutrophils, some or many of which may have degenerative changes. Increased populations of macrophages may be seen in cases with chronic disease. Eosinophils may be present in cases with fungal or parasitic pneumonia. Intracellular bacteria confirm the diagnosis of bacterial pneumonia, but may not be identified on cytology, even though the culture results are positive.

Occasionally, other agents can be identified on airway cytological exam, including *Toxoplasma* tachyzoites, lungworm larva, or fungal organisms [52–54].

Treatment

Treatment of pneumonia must take into consideration the type of pneumonia, the underlying cause, and the severity of clinical signs.

Antimicrobials

Antimicrobials are the cornerstone of treatment for bacterial pneumonia, but veterinary guidelines for empiric antimicrobial therapy are lacking [14]. First-time or mild cases of pneumonia may be empirically treated as outpatients with oral first-line antimicrobials such as amoxicillin/clavulanate, doxycycline, or azithromycin. However, if the patient has findings consistent with hypoxemia and/or gastrointestinal tract dysfunction, hospitalization with parenteral antimicrobials and supportive care should be recommended [1]. Broad-spectrum coverage with combinations of intravenous antimicrobials such as ampicillin with enrofloxacin or ticarcillin/clavulanate with enrofloxacin is shown to have >90% susceptibility in cases of bacterial respiratory disease [50]. If severe pneumonia is nosocomial in origin or the patient has a prior history of antimicrobial therapy, third-line drug combinations such as clindamycin with a third-generation cephalosporin, or even carbapenems, may be indicated. If an airway wash is performed, antimicrobials should be adjusted based on microbiological susceptibility results. De-escalation of antimicrobials is recommended in the 2015 ACVIM Consensus statement on therapeutic antimicrobial use [55].

Other types of pneumonia may require treatment with antiviral, antifungal or antiparasitic drugs (Table 37.1).

Supportive Care

Oxygen should be provided for patients with hypoxemia, via either nasal cannula or an oxygen cage with an FiO_2 of 40–60% (see Chapter 181). Oxygen should be humidified to prevent desiccation of the airway mucosa. Oxygen supplementation is weaned when the patient can breathe comfortably in room air. Patients in severe respiratory distress and those with hypoxemia despite supplemental oxygen, hypoventilation or onset of respiratory fatigue may require mechanical ventilator support.

Fluid therapy is administered because hydration promotes clearance of pulmonary exudates. In addition to intravenous fluids, frequent nebulization with sterile saline droplets that are small enough to enter the bronchi (2–5 μm) also promotes clearance of exudates. Coupage of the thoracic wall may be performed to trigger breaths with a bigger tidal volume and stimulate coughing.

N-acetylcysteine acts as a mucolytic by breaking the disulfide bonds in mucus and is routinely given intravenously (diluted, administered slowly) to pneumonia

patients at the authors' facility. It should never be nebulized as it causes bronchoconstriction and epithelial toxicity. The use of diuretics and cough suppressants should be avoided as they oppose the goals of promoting hydration and expectoration of debris and mucus, respectively. While bronchodilators are controversial, they may be utilized in cases of underlying feline asthma, and have been shown to improve ciliary activity and have anti-inflammatory properties [3].

Consideration should be given to treatment of the underlying cause of pneumonia. Recumbent patients should be repositioned or turned every 4–6 hours to minimize atelectasis, which can encourage proliferation of bacteria in collapsed airspaces. Frequent walks to stimulate coughing by increasing tidal volumes should also be encouraged. The use of antacids, antiemetics or prokinetics may be beneficial. Surgical intervention may be required in cases of an inhaled foreign body or pulmonary abscess.

Long-Term Therapy

Supportive care should be continued in hospital until the patient is cardiovascularly stable and breathing comfortably in room air. The patient should be able to eat and drink without any vomiting, especially in cases of aspiration pneumonia. The transition to oral medications may occur once the patient's lung function has improved to normal and they are bright and alert with a good appetite. The duration of treatment with antifungal, antiprotozoal, and antiparasitic agents varies with clinical status, thoracic radiographs, and recheck serological testing, as needed.

For treatment of patients with bacterial pneumonia, antimicrobials are traditionally continued for 3–6 weeks or longer, or 1–2 weeks beyond resolution of radiographic changes [37]. Clinical signs of disease typically resolve significantly earlier than radiographic changes.

Evidence regarding duration of treatment in veterinary medicine is lacking [55], and shorter courses of therapy may be considered in some cases. Recent studies regarding stable outpatient community-acquired pneumonia in humans have shown no difference between short and extended courses of antimicrobials in regard to clinical success or mortality [56,57]. It is argued that shorter duration of antimicrobials may provide improved owner compliance and reduce the likelihood of adverse drug effects or resistance. Studies in veterinary medicine have shown that short courses of antimicrobials are effective for management of lower urinary tract infections [58,59]. However, these data cannot be extrapolated to critically ill, oxygen-dependent pneumonia patients, and we do not advise that they should be extended to high-risk outpatient populations such as young puppies with pneumonia or immunosuppressed patients. The emergency clinician is urged to use clinical judgment as to the duration of antimicrobial therapy in these patients.

Table 37.1 Common recommended therapies for pneumonia.

Bacterial Pneumonia	Stable outpatient	Amoxicillin-clavulanic acid: 13.75 mg/kg PO q12h
	Broad spectrum	Enrofloxacin: 10–15 mg/kg PO/IV q24h (Dog) 5 mg/kg PO/IV q24h (Cat) And Ampicillin: 22 mg/Kg IV q8h Or Ticarcillin/clavulanic acid: 50 mg/kg IV q6h Or Piperacillin/clavulanic acid: 4mg/kg bolus + 3.2 mg/kg/hr or 50-100 mg/kg IV q6h
	Additional therapeutics	N-Acetylcysteine: 70 mg/kg IV q6h Terbutaline: 0.01 mg/kg SC/IM/IV q4–6h
Parasitic Pneumonia		Fenbendazole: 50 mg/kg PO q24h for 10–14 days
Fungal Pneumonia	Blastomycosis	Itraconazole: 5 mg/kg PO q12h for 15 days, then 5 mg/kg PO q24h for 60–90 days, 1 month past resolution (Dog) 5 mg/kg PO q12h for 60 days, 1 month past resolution (Cat) Or Fluconazole: 5 mg/kg PO q12h for 60 days, 1 month past resolution (Dog)
	Histoplasmosis	Itraconazole: 5–10 mg/kg PO q12–24 for 4–6 months, 2 months post resolution (Dog & Cat) Or Amphotericin B: 0.25–0.5 mg/kg IV q48h, cumulative dose of 5–10 mg/kg (Dog), 4–8 mg/kg (Cat)
	Cryptococcus	Fluconazole: 10 mg/kg PO q12h, until resolution of signs (Cat) Or Flucytosine: 250 mg total PO q6–8h, 1–9 months (Cat, >3.75 mg) 50–75 mg/kg PO q8h, 1–12 months (Dog) And Amphotericin B: 0.25–0.5 mg/kg IV 3×/week, until cumulative dose 10 mg/kg (Dog & Cat) 0.5–0.8 mg/kg SQ 2–3×/week (Dog & Cat)
	Coccidiomycosis	Itraconazole: 5 mg/kg PO q12h up to 12 months (Dog) 25–50 mg per cat PO q12–24h up to 12 months Or Fluconazole: 5 mg/kg PO q12h up to 12 months (Dog) 25–50 mg per cat PO q12–24h up to 12 months Or Amphotericin B: 0.4–0.5 mg/kg IV 3×/wk cumulative dose 8–11 mg/kg (Dog)
Viral Pneumonia	Feline herpes virus	Famciclovir: 40–90 mg/kg PO q8h (Cat)
Protozoal Pneumonia	Toxoplasmosis	Clindamycin: 10–20 mg/kg PO q12h for 2–4 wks (Dog) 12.5 mg/kg PO q12h for 2–4 wks (Cat)

Prognosis

Survival of patients with bacterial pneumonia has been reported as being between 77% and 88%, depending on the inciting cause and severity of disease [1,12,14]. In one study, the prognosis for survival

was reported to be independent of radiographic evidence of disease, but this was later refuted by a study that documented a difference in survival based on the number of lung lobes affected radiographically [12,13]. No additional prognostic factors have been determined at this time.

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38

Cardiogenic Pulmonary Edema

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Introduction

Cardiogenic pulmonary edema is a common sequel to severe left-sided heart disease in the dog and cat and is a frequent cause of emergency room visits. In these patients, neurohormonal activation leads to sodium and water retention and expansion of the plasma volume by as much as 30% (see Chapter 51). This increased volume is accompanied by increased pressure within the pulmonary venous and capillary system. As intracapillary pressure rises above plasma colloidal osmotic pressure, fluid leaks across the capillary membrane and into the interstitial and alveolar space. In general, pulmonary venous pressures >25 mmHg are sufficient to produce pulmonary edema.

Clinical signs associated with cardiogenic pulmonary edema include increased respiratory rate and effort and orthopnea. In patients with extremely severe edema, a productive cough associated with pink-tinged nasal discharge or sputum can occur. Of note, isolated coughing, in the absence of other respiratory signs, is usually indicative of primary airway or respiratory disease as opposed to cardiogenic pulmonary edema [1].

Treatment strategies for cardiogenic pulmonary edema are largely empirical (Figure 38.1). The primary focus in the emergent situation is to alleviate respiratory distress. This is achieved by reduction and redistribution of preload using diuretics and venous vasodilators, along with efforts to improve cardiac output, maintain blood pressure, and protect kidney function. At the same time, it is important to minimize adverse side-effects, remove aggravating factors, and consider how best to transition the acute patient that has been successfully stabilized to chronic therapies.

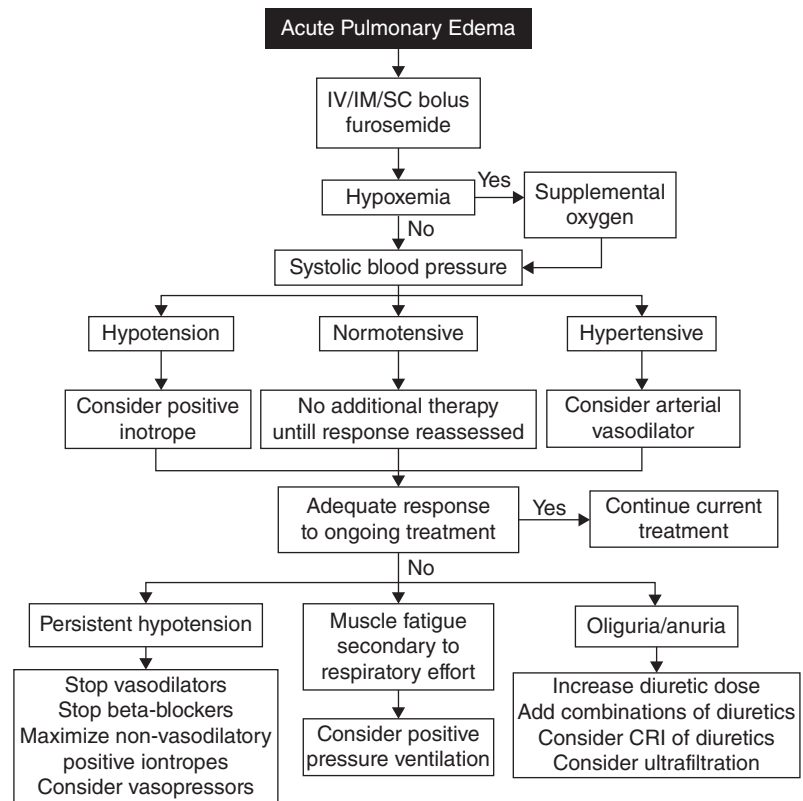
Diuretics

Virtually all patients with emergent cardiogenic pulmonary edema require diuretics. Furosemide is the most commonly administered diuretic due to its potency, injectable formulation, and rapid onset of action. Furosemide inhibits intraluminal sodium and chloride absorption in the ascending loop of Henle, resulting in natriuresis and diuresis. When administered intravenously, onset of action occurs within 5 minutes with peak effect in 30 minutes and duration of action 120–180 minutes. Typical initial IV/IM/SC dose for the dog is 2–4 mg/kg and for the cat 1–2 mg/kg (Table 38.1). Following the initial dose, the patient's respiratory rate and effort, urine production, SaO₂, and blood pressure should be closely monitored. Due to the relatively short duration of action, repeated boluses of furosemide are administered every 1–3 hours until clinical improvements are noted. In the author's experience, dogs and cats with cardiogenic pulmonary edema typically require 1–4 boluses of IV furosemide in order to improve respiratory rate and effort. Once these improvements are noted, the frequency of subsequent furosemide boluses is reduced over the next 24–36 hours to q6–8h and then replaced with oral dosing q8–12h as the patient is readied for hospital discharge on chronic oral maintenance therapy.

These standard recommendations are subject to a great deal of modification based on the individual patient's medication history, severity of respiratory distress, underlying heart disease, and renal function.

Furosemide has several important pharmacokinetic and pharmacodynamic properties that influence its diuretic efficacy in the emergent patient. It is effective only when attached to the intraluminal surface of the

Figure 38.1 Algorithm for treatment of acute cardiogenic pulmonary edema. CRI, constant rate infusion. See text for details. Reproduced with permission of John Wiley & Sons.



sodium-chloride transporter in the loop of Henle. In order to gain access to the transporter, furosemide is secreted from the blood into the tubule lumen using an organic ion transporter located in the proximal convoluted tubule. The efficacy of this process is regulated by renal perfusion, competition by other organic anions, such as NSAIDs, and the degree to which furosemide is bound to albumin in the circulation. Thus, in patients with poor cardiac output, concurrent NSAID therapy, or severe hypoalbuminemia (<2.0 – 3.0 g/dL), the furosemide dose may need to be increased. As previously indicated, the duration of action after a single furosemide injection is relatively short.

The use of constant rate infusions (CRI) of furosemide has been investigated in healthy dogs [2,3]. In comparison to IV or SC boluses, an 8-hour CRI administration of an equivalent dose of furosemide increases the amount of diuresis. Whether or not CRI is superior to intermittent boluses in dogs or cats with cardiogenic pulmonary edema requires further study. Disappointingly, in humans, furosemide CRI was not associated with an improvement in symptoms, increase in 72-hour urine volume, or shorter length of hospital stay versus intermittent boluses [4]. The author will occasionally utilize furosemide CRI in patients with a history of recurrent heart failure that are already receiving high doses of chronic oral furosemide and are suspected of having some degree of diuretic resistance.

Other diuretics, such as hydrochlorothiazide and spironolactone, are less potent than furosemide and are rarely used as life-saving therapy in patients with emergent cardiogenic pulmonary edema, unless there is poor response to initial or repeated furosemide doses.

Vasodilators

Blood pressure is regulated through vascular tone (i.e. resistance) and cardiac output (i.e. flow). In patients with normal or increased blood pressure, vasodilatory drugs should be considered as first-line agents along with diuretics to help alleviate congestion. Venous vasodilators, such as nitroglycerin, increase venous capacitance and redistribute preload to the central venous reservoirs to reduce capillary pressure and genesis of edema. Arterial vasodilators, such as hydralazine, ACE inhibitors, and pimobendan, decrease ventricular afterload, increase cardiac output, and improve cardiac function. Mixed or balanced vasodilators, such as nitroprusside, act on both veins and arteries. Nitroglycerin and nitroprusside relax vascular smooth muscle by increasing concentrations of cGMP, which results in vasodilation.

Nitroglycerin is typically provided as a topical paste and is applied to hairless cutaneous surfaces of the inner ear pinna or inguinal region. The effectiveness of absorption,

Table 38.1 Commonly used agents for the treatment of cardiogenic pulmonary edema.

Drug class	Mechanism of action	Dose
<i>Diuretics</i>		
Furosemide	Loop diuretic	Dog: 2–4 mg/kg IV/SC/IM q1–3h for acute pulmonary edema; 0.2–0.5 mg/kg/h IV for acute pulmonary edema; 1–4 mg/kg q8–12h PO for chronic therapy Cat: 1–2 mg/kg IV/SC/IM q2–3h for acute pulmonary edema; 1–2 mg/kg q12–24h PO for chronic therapy
<i>Vasodilators</i>		
Nitroglycerin paste	Nitrate	Dog: 0.25 inch/5 kg cutaneously q6–8h Cat: 0.125–0.25 inch/cat cutaneously q6–8h
Nitroglycerin	Nitrate	Dog/cat: 4–20 µg/kg/min IV CRI
Nicardipine	Ca channel blocker	Dog/cat: 0.5–5 µg/kg/min IV CRI
Nitroprusside	Nitrate	Dog: 0.5–5 µg/kg/min IV
Hydralazine	Arterial vasodilator	Dog: 1–3 mg/kg PO q12h (titrate to effect) Cat: 0.5–0.8 mg/kg PO q12h
Enalapril	ACE inhibitor	Dog: 0.5 mg/kg PO q12–24h Cat: 0.25–0.5 mg/kg PO q12–24h
Benazepril	ACE inhibitor	Dog: 0.25–0.5 mg/kg PO q24h Cat: 0.25–0.5 mg/kg PO q24h
<i>Positive inotropes</i>		
Pimobendan	Ca sensitizer	Dog: 0.25 mg/kg PO q12h; 0.15 mg/mL IV single injection Cat: 1.25 mg/cat PO q24h
Dobutamine	Sympathomimetic	Dog: 2.5–20 µg/kg/min IV Cat: 0.5–10 µg/kg/min IV
Dopamine	Sympathomimetic	Dog/Cat: 5–10 µg/kg/min IV
Milrinone	Phosphodiesterase inhibitor	Dog: 30–300 µg/kg IV bolus followed by 1–10 µg/kg/min IV
<i>Vasopressors</i>		
Norepinephrine	Catecholamine	Dog/Cat: 0.1–1 µg/kg/min IV
Phenylephrine	Alpha-1-antagonist	Dog/Cat: 0.5–5.0 µg/kg/min IV
<i>Sedatives</i>		
Acepromazine	Phenothiazine	Dog: 0.005–0.02 mg/kg SC/IM/IV Cat: 0.005–0.02 mg/kg SC/IM/IV
Butorphanol	Opioid	Dog/Cat: 0.1–0.3 mg/kg IV/IM
Morphine	Opioid	Dog: 0.1–0.5 mg/kg SC/IM Cat: 0.05–0.2 mg/kg SC/IM
Methadone	Opioid	Dog/Cat: 0.05–0.2 mg/kg IV/IM/SQ

IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SQ, subcutaneous.

especially in heart failure patients that are typically vaso-constricted, is probably low. Nitroprusside is a balanced arterial and venous vasodilator that is administered using constant rate IV infusion. Its high potency and short half-life allow for precise titration to a target decrease in systolic arterial blood pressure of 10–20% from baseline, or 90–100 mmHg in normotensive animals. Due to its

potential to cause hypotension, nitroprusside is reserved for instances where invasive or frequent non-invasive arterial blood pressure monitoring is available. At the time of writing, manufacturing shortages in nitroprusside have greatly increased the cost of drug and unfortunately limited the availability of this very effective treatment.

Hydralazine is a potent and rapid-acting injectable or orally administered arterial vasodilator with a poorly understood mechanism of action. It is primarily used in dogs with cardiogenic pulmonary edema due to mitral valve regurgitation in order to reduce afterload and subsequently reduce volume of regurgitation. The dose should be titrated upwards over 24–48 hours while monitoring systemic blood pressure. ACE inhibitors, such as enalapril and benazepril, are arterial vasodilators and commonly prescribed in both dogs and cats with emergent cardiogenic pulmonary edema. Specifically, in dogs with edema due to dilated cardiomyopathy or mitral regurgitation, enalapril was associated with improved clinical signs and lower pulmonary capillary wedge pressure [5]. Renal function, blood pressure, and hydration status must be closely monitored when prescribing ACE inhibitors, especially in those animals with pre-existing renal dysfunction, severe dehydration, or receiving other vasodilatory agents simultaneously.

Pimobendan is an arterial vasodilator that relaxes arterial smooth muscle by preventing the breakdown of cAMP. Increased cAMP inhibits myosin light chain kinase and thereby prevents the cross-bridging of actin and myosin in arterial smooth muscle. Pimobendan is available in tablet or capsule form. When administered orally to emergent patients with cardiogenic pulmonary edema, there is rapid onset of vasodilatory action. At time of writing, an injectable form of pimobendan meant as a single injection to help initiate treatment of acute heart failure is available in Australia and some parts of Europe.

The decision whether to administer arterial or mixed vasodilators to patients with cardiogenic pulmonary edema is based on arterial blood pressure. Most dogs and cats with cardiogenic pulmonary edema due to myxomatous mitral valve disease or hypertrophic cardiomyopathy, respectively, have normal to increased systolic blood pressure at presentation, and are eligible for vasodilatory therapy. Patients that present with cardiogenic pulmonary edema and concurrent hypotension, as in cases with severe systolic dysfunction (i.e. dilated cardiomyopathy) or outflow tract obstruction (i.e. aortic stenosis), are not candidates for therapeutic vasodilation. In humans with acute heart failure, concurrent systemic hypotension, defined as systolic blood pressure <85–90 mmHg, is a poor prognostic indicator.

Positive Inotropes

Positive inotropes are drugs that increase contractility. Positive inotropes indirectly help to alleviate cardiogenic pulmonary edema by increasing forward cardiac output, improving renal perfusion and diuretic delivery to the kidney tubule, and helping maintain adequate blood

pressure in the presence of vasodilatory therapy. In the emergency setting, the most commonly used positive inotropes are the calcium-sensitizing and arterial vasodilator agent pimobendan and the short-term intravenous sympathomimetic agents dobutamine and dopamine.

Pimobendan improves cardiac contractility by increasing the affinity of cardiac troponin to calcium ion binding, which in turn regulates strength of systolic contraction. As previously discussed, pimobendan also elicits relaxation of arterial smooth muscle and decreases afterload. The rapid onset and potent action of pimobendan make it a useful and commonly administered drug in dogs with emergent cardiogenic pulmonary edema due to mitral valve disease or dilated cardiomyopathy. Most cases of cardiogenic pulmonary edema in cats are caused by diastolic dysfunction, and pimobendan is rarely used unless concurrent systolic dysfunction is documented by echocardiography.

Dobutamine and dopamine bind to myocardial beta-1 receptors and enhance cardiac norepinephrine release, which increases cytosolic calcium ion concentration and improves contractility. Due to the short half-life of both of these sympathomimetics, constant rate infusion is required. Dobutamine or dopamine typically are titrated to effect based on surrogate markers of cardiac output, such as blood pressure, heart rate, capillary refill time, and urine output. High doses of either agent can cause sinus tachycardia or ectopic tachyarrhythmias as well as peripheral alpha-receptor-mediated vasoconstriction. Once cardiogenic pulmonary edema begins to resolve, the infusion of dobutamine or dopamine is gradually decreased over a 12–24-hour period and chronic oral administration of pimobendan is started. Due to rapid development of tolerance, infusions of dobutamine or dopamine are rarely continued past 48 hours.

Milrinone is another positive inotrope. Its principal mechanism of action is to increase cytosolic calcium ion concentration through increased cAMP. In peripheral arterial smooth muscle, milrinone elicits vasodilation and hence is similar to pimobendan in its combined positive inotropy and arterial vasodilatory effects. In dogs, milrinone is administered by IV bolus followed by IV infusion over 12–36 hours. Experience with milrinone in veterinary patients is limited and it is usually reserved for cases with severe systolic dysfunction that are poorly responsive to sympathomimetics. Potential side-effects include systemic hypotension and arrhythmias.

Digoxin is a weak positive inotrope with a narrow therapeutic window. Due to its long-half life and propensity for toxicity, intravenous or oral digoxin is rarely used as a first-line positive inotrope in the emergency setting. In cases with cardiogenic pulmonary edema and atrial fibrillation, rapid oral loading of digoxin to help slow the ventricular heart rate can be performed with great care (see Chapter 53).

Vasopressors

In cases with severe underlying cardiac dysfunction and reduced cardiac output, systemic hypotension might exist despite use of positive inotropes. Systemic hypotension complicates the resolution of cardiogenic pulmonary edema by limiting the use of diuretics and vasodilators. Treatment of systemic hypotension employs specific IV vasopressors (i.e. vasoconstrictors) such as high-dose dopamine, norepinephrine, or phenylephrine. Patients with cardiogenic pulmonary edema and concurrent low cardiac output and systemic hypotension are extremely challenging to stabilize due to the inability to aggressively diurese or vasodilate.

Sedatives

The respiratory distress and shortness of breath that accompany cardiogenic pulmonary edema can cause a high degree of anxiety that makes handling and treatment difficult in some patients. Sedation with butorphanol, morphine, or acepromazine may be useful. Care must be taken to avoid oversedation, hypotension, and bradycardia.

Oxygen Therapy

Cardiogenic pulmonary edema is associated with variable degrees of hypoxemia, depending on the degree of

diffusion impairment, ventilation status, and presence or absence of concurrent pulmonary or heart disease (i.e. intracardiac shunts). Supplemental oxygen therapy using flow-by, nasal cannulation, oxygen mask, or oxygen cage is indicated in cases with $\text{SaO}_2 < 94\%$ while breathing room air (see Chapter 181). The effect of supplemental oxygen on hemodynamics is complex. In human patients, hyperoxia can be associated with systemic vasoconstriction, bradycardia, and decreased cardiac output, especially in those with systolic dysfunction. Thus, human patients with cardiogenic pulmonary edema but still adequate oxygen saturation (i.e. $\text{SaO}_2 > 90\%$) are not routinely given supplemental oxygen [6].

Other Therapies

Ultrafiltration is a non-pharmacological therapy that can help resolve cardiogenic pulmonary edema. Ultrafiltration involves removal of isotonic fluid and reduction of plasma volume by an extracorporeal filter system. Blood is pumped through the ultrafiltration circuit and, driven by hydrostatic pressure, fluid and solute components cross a filter and are removed. In human patients, ultrafiltration is not consistently superior to diuretic therapy in alleviating clinical signs or protecting renal function. Studies in veterinary patients are needed. Patients with fatigue due to the increased respiratory effort associated with cardiogenic pulmonary edema or those with intractable anxiety or distress may require mechanical ventilation (see Chapter 188).

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39

Neurogenic Pulmonary Edema

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Introduction

Neurogenic pulmonary edema (NPE) is a form of non-cardiogenic pulmonary edema that is characterized clinically by rapid onset of respiratory distress after a central nervous system insult. The four major causes of NPE recognized in veterinary medicine are head trauma, seizures, electrocution, and upper airway obstruction [1].

Pathogenesis

Pulmonary edema subsequent to a brain insult is a well-recognized phenomenon that occurs in a variety of species. The histological changes in the lungs can occur within minutes of the brain insult and include loss of the normal configuration of the alveoli, filling of air spaces with exudate and red blood cells, distension of the perivascular space, and marked stretching of the capillary endothelial cells with marked disruption of the entire capillary endothelium. These changes are quite dramatic and occur quickly after the brain injury. The resulting edema is primarily characterized as a permeability edema (high-protein edema) though low-protein edema has been noted as well. This may reflect a spectrum of injury to the pulmonary capillary endothelium. The theories proposed for the pathogenesis of this brain-lung injury accommodate this spectrum of pulmonary edema protein changes noted in cases of neurogenic pulmonary edema.

Blast Theory [1]

The underlying thread that connects all NPE pathogenesis theories is an acute, massive centrally mediated sympathetic neural discharge as a result of a central nervous system (brain) insult (listed above).

Most studies suggest that there usually is some type of hypothalamic injury that results in the catecholamine release. The massive sympathetic discharge may cause pulmonary edema by several mechanisms that are not mutually exclusive. High catecholamine concentrations can cause massive peripheral vasoconstriction and systemic hypertension. These sympathetic vasomotor reactions produce marked rises in aortic and vascular resistance with a resulting increase in arterial blood pressure. The marked increase in afterload can limit cardiac output, causing a backward generated increase in pulmonary venous pressure. Additionally, marked peripheral vasoconstriction causes increased venous return and direct effects of the sympathetic discharge reduce the pulmonary vascular capacitance, further increasing the pulmonary arterial and venous pressures. The volume and pressure load of the pulmonary vasculature cause a disruption in the pulmonary capillary endothelium, resulting in the histological changes noted above.

The sequence of events that occur based on the blast theory and the transient but very high hydrostatic pressure that occurs is as follows. The hydrostatic pressure increase initially causes a loss of fluid from the pulmonary capillaries into the interstitial tissue of the lung. This fluid is relatively lower in protein consistent with a hydrostatic pressure-induced pulmonary edema. With extremely high pulmonary capillary hydrostatic pressure, pore stretching and endothelial cell injury may occur, causing leakage of protein and even red blood cells into the pulmonary interstitium. The severe pressure changes may also progress to injury of the endothelial basement membrane as well as the alveolar basement membrane with epithelial disruption and flooding of the alveoli with high-protein fluid and red blood cells.

The blast theory explains the histological findings as well as the clinical findings of the spectrum of edema ranging from purely hydrostatic edema, to high-protein edema, to finally hemorrhagic edema.

Direct Pulmonary Vascular Effect

Neurogenic pulmonary edema has also been noted to occur in the absence of changes in systemic vascular pressure increases [2]. Endothelin I has been speculated to be a possible mediator in the genesis of the permeability edema [3]. It may play a role both centrally (brain) and locally (pulmonary vasculature). Vascular pressure-mediated pulmonary endothelium injury can result in release of endothelin I which is a potent vasoconstrictor and may contribute to the increase in pulmonary circulation pressure. Additionally, intrathecal injection of endothelin I into rats resulted in a 22-fold increase in pulmonary vascular permeability but intravenous injection does not produce this result. Pre-emptive injection of an endothelin 1 antagonist can prevent the increase in pulmonary permeability. Sympathectomy can prevent the increase in permeability in this model as well.

To summarize, there is speculation that endothelin 1 activates its receptors in the medulla which results in massive norepinephrine release. The norepinephrine binds to pulmonary alpha-receptors, causing intense pulmonary vasoconstriction and subsequent pulmonary hypertension.

Norepinephrine and neuropeptide Y have also been implicated in causing a direct increase in pulmonary vascular permeability [4]. Additionally, nitric oxide may play a protective role as experimental injection of a nitric oxide synthetase inhibitor in a rat model of traumatic brain injury potentiated the hypertension and increased mortality [5]. Numerous cytokines have been suggested as possible mediators within the brain and locally in the pulmonary circulation. Supraphysiological doses of catecholamines can cause an increase in IL-6 expression [6]. The sympathetic “storm” may initiate cytokine expression and release, causing pulmonary inflammation. Cytokines such as interleukin (IL)-1B, IL-6, and TNF-alpha may be involved in the inflammatory process [7].

Summary of Pathogenesis

Neurogenic pulmonary edema is a complex phenomenon not easily explained by one simple mechanism although common to all the proposed processes resulting in edema formation is the sympathetic storm subsequent to brain injury. Ischemic injury to the hypothalamic area of the brain results in a massive sympathetic discharge that is rapid but very short in duration. The circulating catecholamines have a multitude of effects on the cardiovascular system and the pulmonary circulatory system. The alpha-mediated systemic vasoconstriction results in a substantial cardiac afterload. This, combined with a catecholamine-induced decrease in ventricular compliance, causes a decrease in cardiac output and an acute onset of backward heart failure. Additionally, the alpha-mediated pulmonary venous

constriction also causes an increase in pulmonary capillary pressure. The constellation of the cardiovascular and pulmonary circulatory changes causes a massive, but transient, increase in pulmonary capillary pressure, resulting in an acute increase in pulmonary transcapillary fluid flux into the pulmonary interstitium. There may be pressure-related pulmonary capillary endothelial injury resulting in efflux of protein and red blood cells, creating a high-protein pulmonary edema. Additionally, the sympathetic system may have direct effects on the pulmonary capillaries themselves leading to a further increase in pulmonary capillary permeability. Finally, the substantial increase in transpulmonary pressure generated by inspiring against an upper airway obstruction is likely a major cause of pulmonary edema in this condition (see Chapter 32).

The ultimate result of this whole process can be massive pulmonary edema and inflammation. The clinical scenarios described in veterinary medicine seem to agree with the proposed theory as many of the animals have an acute onset of respiratory distress within minutes after the neurological insult. The pulmonary edema can be relatively mild to severe, possibly reflecting the spectrum of pulmonary capillary injury that can occur. Figure 39.1 summarizes the proposed pathophysiology.

Clinical Characteristics of Neurogenic Pulmonary Edema

The typical history of a small animal suffering from neurogenic pulmonary edema is a relatively sudden onset (usually minutes) of increased respiratory rate/effort after a CNS insult. The most common CNS insults in veterinary medicine include head trauma, upper airway obstruction, seizures, and electrocution. The severity of the respiratory distress may range from just mild tachypnea to extreme distress with pulmonary edema leaking from the nares. Head trauma and upper airway obstruction anecdotally appear to cause the most severe pulmonary injury. Other clinical signs include coughing and signs associated with the underlying cause (e.g. evidence of head trauma, oral burns from an electrical cord, etc.) [8].

Physical examination findings are not specific for neurogenic pulmonary edema. Evidence for head trauma, electrocution (oral burns), or upper airway obstruction may be present, but absence does not rule them out as potential causes. Thoracic auscultation findings may range from mild increase in lung sounds to fulminant, diffuse pulmonary crackles. If a persistent upper airway obstruction is present that caused the NPE, then upper airway sounds will be noted as well although transient upper airway obstructions can result in NPE and there will be no evidence of upper airway signs at presentation. Pulmonary auscultation abnormalities tend to be

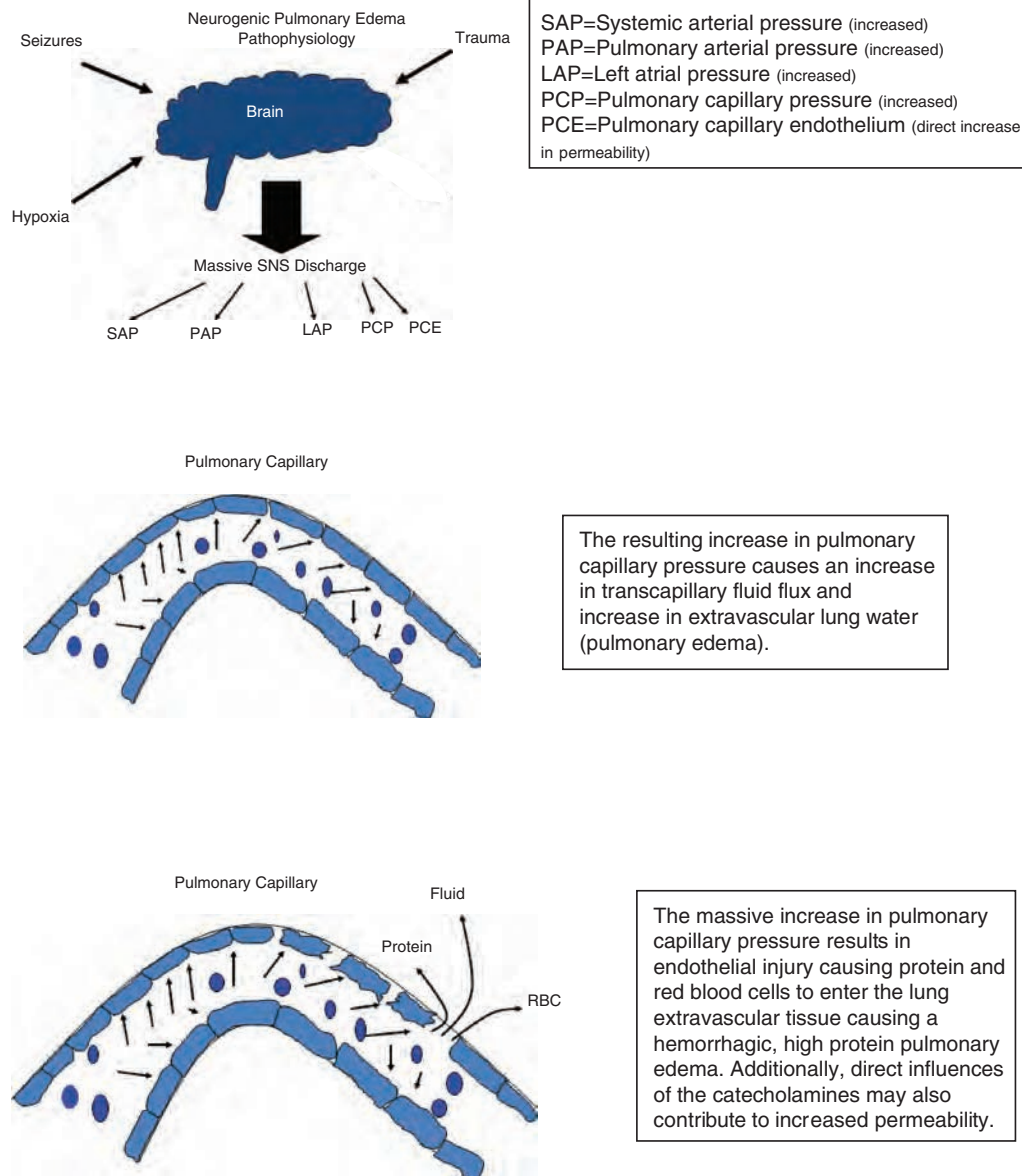


Figure 39.1 Proposed pathophysiology of neurogenic pulmonary edema.

symmetrical, although asymmetry can occur, with the right side being more severe. Cardiac arrhythmias have been noted with NPE (usually premature beats) and are associated with a worse prognosis.

Diagnosis

Neurogenic pulmonary edema is a reasonable differential diagnosis in any critical animal that is showing signs of respiratory distress. The form (cardiac or non-cardiac) of pulmonary edema is not always clear, and on rare occasions both cardiogenic and non-cardiogenic pulmonary edema may be present. Clinical acumen and experience are

essential to reaching a diagnosis as measurement of pulmonary capillary wedge pressure to rule out cardiogenic causes is very rarely applied in the veterinary emergency setting. A thorough history and physical examination provide the foundation for the diagnosis of NPE.

A history of acute onset of respiratory distress after one of four major inciting events (head trauma, upper airway obstruction, electrocution or seizures) is highly supportive of a diagnosis of NPE. The absence of the inciting events does not rule out NPE as many of these can be transient insults that the owner was not present to observe.

A thorough physical examination should include all organ systems to detect the presence of systemic disease.

There are no pathognomonic physical signs for NPE. Particular attention should be paid to the presence of cardiac abnormalities, such as a cardiac murmur, gallop, or arrhythmia, poor pulse quality, jugular pulse, and prolonged capillary refill time, as these may be signs of cardiac disease. However, secondary cardiac signs may occur from NPE or mediators from systemic inflammation (typically cardiac arrhythmias), confusing the physical determination of cardiogenic versus non-cardiogenic pulmonary edema. Unfortunately, when animals present with severe respiratory distress, restraint can be stressful and detrimental to the patient. Therefore, a thorough physical examination may not be possible until the animal has been stabilized.

Thoracic radiographs should be obtained once the patient is stable enough to tolerate them to determine the cause of the respiratory distress. tFAST can be performed on an emergent basis to evaluate the left atrial size and the pleural space if the patient is not stable enough for radiographs. Cardiogenic pulmonary edema is often located in the more compliant perihilar region, although it can be diffuse (especially in felines), and is seen concurrently with left-sided cardiomegaly and pulmonary venous distension (Figure 39.2). Full echocardiography may be required to rule out heart disease.

Initially, NPE will typically appear radiographically as an interstitial pulmonary edema, although by the time the patient is radiographed, the disease may have already resulted in a mixed interstitial-alveolar or alveolar pattern. The radiographic distribution of NPE is typically in the caudodorsal lung quadrant although diffuse involvement can also occur (Figure 39.3). The alveolar infiltrates are typically symmetrical though mild asymmetry can occur, with the right tending to be more severely affected than the left.

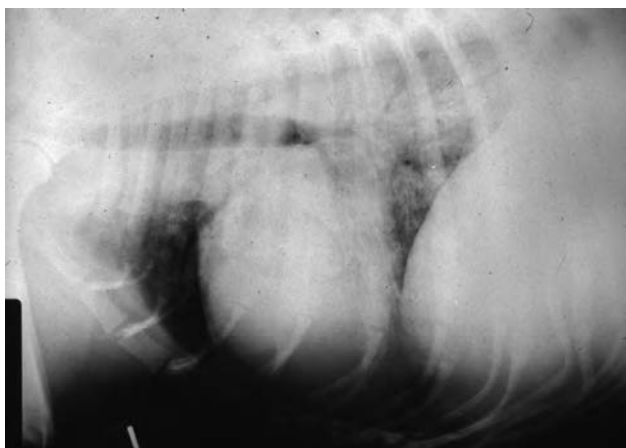


Figure 39.2 Lateral thoracic radiograph of a dog with congestive heart failure. Note the enlarged left atrium and perihilar distribution of pulmonary infiltrates.



Figure 39.3 Lateral thoracic radiograph of a dog with NPE due to a transient upper airway obstruction. Note diffuse pulmonary parenchymal infiltrates with the most severe changes in the caudodorsal lung fields.

Arterial blood gas changes are not diagnostic of NPE but reflect pulmonary function. Hypoxemia with NPE is most commonly due to ventilation:perfusion mismatch. The PaCO_2 initially is low, owing to hyperventilation in response to the pulmonary parenchymal disease and, if severe, hypoxemia. In the later stages, compromised pulmonary compliance can interfere with the animal's ability to ventilate, causing hypercapnia.

Similar to blood gases, general clinical pathology information (complete blood count, serum chemistry profile, and urinalysis) is not diagnostic for NPE but may reflect the underlying cause or the consequences of NPE. For example, severe liver functional changes may be found on the chemistry screen (decreased albumin, cholesterol, BUN, and glucose in animals with seizures due to hepatic encephalopathy; see Chapter 90). Hypoproteinaemia has been reported in dogs with acute respiratory distress syndrome, most likely due to the severe pulmonary injury and loss of protein into the pulmonary parenchyma. Very early in NPE, hyperglycemia may be present due to glycogenolysis from the massive sympathetic discharge [8].

In summary, diagnosis involves assessing a combination of the history, physical abnormalities, thoracic radiographs, echocardiogram, arterial blood gas measurements, and clinical laboratory test results. The measurement of pulmonary capillary wedge pressure is sometimes necessary for ruling out an increased hydrostatic cause of the pulmonary edema. However, such measurements are not yet routine in veterinary critical care.

Initial Approach and Management

Ideally, the identification and elimination of the inciting cause of NPE might result in dissipation of the pulmonary

edema. However, the inciting cause has often resolved by the time the animal is presented. Corticosteroids and blockers of the cyclo-oxygenase and leukotriene pathways have not been proved to resolve the pulmonary inflammatory process occurring in most patients with NPE. A variety of other therapies have been attempted but have also not shown consistent promise and some are even detrimental. These findings may reflect how this permeability edema varies over time within an animal, how it differs between animals, and how it sometimes varies even within the lungs of an affected animal. In lieu of specific therapies for the underlying disease process or resolution of the pulmonary endothelial inflammation, therapy for NPE is primarily supportive.

Immediate oxygen therapy by oxygen cage, nasal oxygen, or intubation and ventilation should be provided during the initial assessment and stabilization (see Chapter 181). Though rare, the severity of some cases of NPE is such that ventilation may be required for obtaining initial stabilization (see Chapter 188).

Cardiac function in animals with NPE can be adversely affected by hypovolemia, depressed myocardial contractility, and vasoconstriction. Low blood volume may be a result of massive fluid and protein loss into the pulmonary parenchyma. Fluid administration to increase blood volume, cardiac preload, and subsequent cardiac output helps improve tissue perfusion and oxygen delivery. The major concern with fluid infusion is that it may increase pulmonary edema in patients with NPE.

The choice of crystalloids versus colloids is a continuing controversy. The decrease in intravascular oncotic pressure and the increase in hydrostatic pressure associated with crystalloid infusion may promote pulmonary edema in patients with increased pulmonary capillary permeability. Alternatively, colloid solutions do not necessarily decrease the incidence of pulmonary edema, and may be hazardous in the setting of altered pulmonary capillary permeability. The loss of colloid particles into the pulmonary interstitium would result in increased interstitial oncotic pressure and a subsequent increase in extravascular lung water. The relative permeability of the pulmonary microvasculature with NPE cannot be predicted clinically. A test infusion of a colloidal solution and monitoring of the intravascular colloid osmotic pressure might provide insight into the vasculature's ability to retain the infused colloids. No improvement, or a rapid decrease in colloid osmotic pressure, suggests that the colloid is rapidly lost from the vasculature and its use in the patient should be restricted.

Existing data are thus contradictory on the comparative benefits of crystalloids and colloids with regard to pulmonary function in patients with NPE. Until more information is available, the choice of fluid therapy must

be made on a patient-by-patient basis and according to the clinician's preference and experience (see Section 5).

Diuretics and vasodilators may be used to decrease pulmonary microvascular hydrostatic pressure. In dogs, 2 mg/kg (1 mg/kg in cats) furosemide bolus intravenously (or intramuscularly if intravenous access is not available) can be administered. This dose is repeated every 1–2 hours depending on the response. If no improvement is noted after 2–3 doses, then it is unlikely this drug is going to be helpful. Continuous intravenous infusion of furosemide (0.1 mg/kg/h) has been demonstrated to have an improved diuretic response in critically ill patients [9]. A systemic vasodilator such as nitroprusside (1–10 µg/kg/min constant-rate infusion) can rapidly lower pulmonary capillary wedge pressure and possibly decrease pulmonary fluid accumulation, though expense and availability make this drug impractical. Systemic hypotension and decreased tissue oxygen delivery must be avoided if diuretics or vasodilators are being used as part of therapy.

Monitoring blood pressure is warranted, particularly when one uses vasodilators. Systemic hypotension (mean arterial pressure < 80 mmHg) in an animal with adequate blood volume indicates the need for either a positive inotrope or vasopressor. Both dopamine (5–10 µg/kg/min) and dobutamine (5–20 µg/kg/min) can be used to increase myocardial contractility and improve cardiac output, and may prevent the volume overloading associated with excessive fluid therapy. More recently, beta-adrenergic stimulation has been shown to enhance alveolar edema clearance in some animal models of lung injury [10]. More studies are necessary to determine if these drugs are useful in our clinical patients.

In the clinical patient with NPE, it may be impossible to predict the degree of pulmonary endothelial injury and the severity of the increased permeability. With severe permeability defects, it is unlikely that diuretics will result in significant improvement and fluid therapy may be detrimental. Unfortunately, their effects cannot be predicted without empirically administering them and their use will lie in the clinician's judgment until more objective clinical evidence is available.

Monitoring the Effectiveness of Therapy

Frequent assessment of mucous membrane color, capillary refill time, heart rate, pulse quality, thoracic auscultation, and respiratory rate and effort provides vital subjective information on the response to therapy. Serial pulse oximetry and arterial blood gas measurement provide more objective information about pulmonary function. The resolution of NPE on thoracic radiographs is characterized by a shift from an alveolar to a mixed alveolar-interstitial and finally an interstitial pattern.

Improvement of the radiographic pulmonary pattern lags behind the animal's clinical improvement.

Patients with NPE often have multiple organ problems and therefore warrant intensive monitoring of extrapulmonary organs, such as the cardiovascular, central nervous, gastrointestinal, and renal systems. Measurement of blood pressure, cardiac rhythm, and more extensive cardiovascular parameters such as central venous pressure, pulmonary capillary wedge pressure, cardiac output, systemic vascular resistance, oxygen delivery, and oxygen consumption provides more detailed information regarding the patient's cardiovascular status. Urine output, serial urinalyses, and serum creatinine and BUN provide assessment of renal function. In patients with systemic inflammation or sepsis, coagulation parameters should be serially evaluated for disseminated intravascular coagulation. The degree of monitoring should

reflect the severity of the disease process, with the more severely affected patients requiring the most intensive monitoring.

Prognosis

Animals with NPE due to upper airway obstruction and seizures appear to have worse outcomes (50% survival) compared to NPE secondary to head trauma or electrocution (79%). Animals that required mechanical ventilation had the worst survival rate (17%). Seventy-seven percent of animals with NPE die, are euthanized or are discharged within 48 hours of presentation. These retrospective data should be viewed with caution as they are based on small numbers of cases and are confounded by clinician biases, client financial constraints, and other variables [8].

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40

Submersion Injury

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Introduction

Drowning and submersion injuries are a public health problem in human medicine, being responsible for more than 500 000 deaths globally each year [1]. It is the leading cause of accidental death and injury in children 1–14 years old in the United States and represents more than 90 000 visits to emergency departments every year in Europe [2,3]. Most drowning events occur in fresh water, including lakes, rivers, and other natural bodies of water, followed by pools, bathtubs/buckets, and saltwater drowning [4]. Fatality rates are higher in males, in children between 0–4 years of age, and in freshwater locations [5,6].

To date, in veterinary medicine there have been four clinical reports concerning submersion injury. One case report described a gelding which had a drowning incident in a pool [7]. The gelding was treated with antibiotics, anti-inflammatory drugs, bronchodilators, diuretics, humidified oxygen and surfactant, and survived. The second study described the histopathological findings of two dogs and one cat suspected of dying by drowning and found that these were similar to those described in human victims [8]. The third study was retrospective and described three cats which had suffered from “inflicted submersion injury” in a population of dogs and cat victims of animal abuse in the UK [9]. Finally, Heffner et al. [10] described the clinical characteristics, treatments, and outcome of a population of 25 dogs and three cats with submersion injury. There was a 64% survival rate in dogs, and respiratory failure was the main cause of death. All cats in the study died.

Definitions

Drowning refers to a process resulting in primary impairment from submersion/immersion in a liquid [11]

regardless of the outcome (survival or death). *Immersion* is defined by the victim's body being immersed but maintaining the airway above the surface of water whereas *submersion* occurs when the airway is under water. Old terms such as “near drowning” or “primary or secondary drowning” have now been abandoned [12].

Precipitating Factors

In human medicine, several precipitating factors have been identified which increase the risk of drowning: epilepsy, cardiac dysrhythmias, hypertrophic obstructive cardiomyopathy, hyperventilation, hypoglycemia, hypothermia, and consumption of alcohol and illicit substances [2]. Some of these factors have also been identified in veterinary patients, including epilepsy and collapse, probably caused by ventricular arrhythmias [10].

Pathophysiology

Drowning is a continuous process which begins when the victim's airway lies below the liquid surface and which may culminate in the death of the patient [12]. At the initial moments of submersion, the “instinctive drowning response” is initiated, with the victim struggling to maintain the head above the surface and trying to breathe as much as possible [2,13]. This response lasts for 20–30 seconds for children and 60 seconds for adults [13]. The duration of this response in dogs and cats is unknown.

Immersion in liquid medium induces several physiological changes. In thermoneutral water, these are mainly caused by the hydrostatic pressure exerted upon the body and include an increase in venous return to the heart, a 32–66% increase in cardiac output and an increase in left-to-right shunting due to pulmonary pooling [14]. Cephalic

movement of the diaphragm and compression of the chest wall also occur, increasing the work of breathing [14]. Importantly, the increase in venous return and central shift of blood volume are sensed by the body as hypervolemia, resulting in increased diuresis, natriuresis and kaliuresis resulting in increased diuresis, natriuresis and kaliuresis.

When the victim submerges, water enters the oropharynx and is either spat out or swallowed. To avoid aspiration, the victim voluntarily tries to hold their breath. In humans, breath-hold time lasts approximately ≤ 1 minute [15]. When the victim can no longer hold the breath, gasping follows, leading to aspiration of small amounts of water into the airway. This triggers a coughing reflex, laryngospasm, and hypoxemia. As little as 1–2.2 mL/kg of water aspirated into the lungs can cause significant alterations in arterial oxygenation [16]. Due to the laryngospasm and water aspiration, hypoxemia, hypercapnia, and acidosis become prominent. When the arterial partial pressure of oxygen (PaO_2) reaches a critical level, laryngospasm abates and additional water is aspirated to the lungs and stomach [13]. If a significant amount of water is aspirated, death ensues, with the lethal dose being estimated as 22 mL/kg in humans and unknown in dogs and cats [17]. Hypoxemia leads to cerebral hypoxia, causing unconsciousness and apnea [16]. Cardiac deterioration follows, manifested by tachycardia, bradycardia, pulseless electrical activity, and finally asystole [2].

Hypothermia is common in drowning victims. It can occur with prolonged immersion in cold water, when wind and surface spray affect exposed body surfaces or when cold water is flushed in and out of the lungs and stomach [14]. Children and possibly dogs and cats are more prone to develop hypothermia due to their large body surface area to mass ratio [14]. Hypothermia induces a peripheral vasoconstrictive response which redirects blood to the central circulation, increasing right atrial pressure and aggravating the “pseudo-hypervolemia” sensed by the body [14]. Hypothermia also decreases antidiuretic hormone production and its function in the kidney. The resulting increased diuresis can contribute to the development of hypovolemia.

Hypothermia can also induce two types of autonomic responses: the cold-shock response and the diving response [18]. The former consists of a pattern of reflexes driven by cutaneous cold thermoreceptors and is characterized by sympathetically mediated tachycardia, a respiratory gasp, uncontrollable hyperventilation, peripheral vasoconstriction, and hypertension [19]. The cold-shock response has been suggested as one of the major causative factors of inability to swim in cold water [20]. The diving reflex is characterized by sinus bradycardia, expiratory apnea, and peripheral vasoconstriction. It is initiated by stimulation of the ophthalmic division of the trigeminal nerve on immersion of the face in cold

water. It is present in all marine and terrestrial vertebrates, especially pronounced in diving mammals, and particularly present in children. It decreases metabolism and increases cerebral perfusion and has the main role of conserving oxygen and extending underwater time [21]. The combination of hypothermia with the diving reflex has been suggested as one of the reasons why children submerged in very cold water ($< 5^\circ\text{C}$) had increased survival [14]. In some patients, cold water immersion seems to trigger both the cold-shock response and the diving response. This may cause an autonomic conflict, and increases the incidence of dysrhythmias [18].

Hypothermia reduces brain metabolism and is protective against cerebral ischemia, especially if present before the onset of ischemia. This mechanism can explain why victims of submersion in ice-cold water may survive without neurological deficits [22]. On the other hand, prolonged hypothermia affects enzymatic and most biological functions, which can induce major complications during hospitalization [23].

Complications of Submersion Injury

The main pathophysiological event of drowning is hypoxemia. Studies have shown that the lung is the organ most common affected by drowning in both humans and animals [10,24]. Hypoxemia mainly occurs due to intrapulmonary shunting of blood through poorly ventilated areas. The latter results from several mechanisms including bronchospasm, impaired alveolar-capillary gas exchange from aspirated fluid within the alveolar space, surfactant inactivation and washout, decreased surfactant production due to alveolar damage, and atelectasis.

Drowning is associated with development of lung injury and edema, which increases ventilation:perfusion mismatch and decreases lung compliance. Interestingly, no clinically important differences have been found in lung injury caused by freshwater versus saltwater drowning [1]. The development of pneumonia and/or aspiration pneumonitis due to aspiration of gastric contents and dirt/sand also contributes to further lung injury, especially in the first 24 hours post drowning [2]. All these injuries can culminate with the development of acute respiratory distress syndrome (ARDS) [1].

The neurological system is the second most affected body system. The lesions are mainly due to hypoxic-ischemic encephalopathy but the development of cerebral edema also contributes to further injury [2].

Hypoxemia, hypothermia, and acidosis combine to induce cardiac dysfunction and dysrhythmias which, combined with hypovolemia, can lead to decreased cardiac output [1]. Several arrhythmias can occur although

ventricular fibrillation is more often seen in severely hypothermic patients [14].

Less common complications include rhabdomyolysis and acute renal injury due to anoxia, shock, myoglobinuria, or hemoglobinuria [10,14]. Systemic inflammatory response syndrome, sepsis, and disseminated intravascular coagulation have also been reported, especially in the first 72 hours after resuscitation [1,10].

Metabolic acidosis is the most common and significant metabolic abnormality in the drowning victim [2]. It was previously believed that different electrolyte disturbances were due to freshwater or saltwater aspiration [16,25]. Clinical studies have shown that drowning victims rarely aspirate quantities of water able to cause these changes [2].

Diagnosis and Treatment

The diagnosis and treatment of submersion injury in human patients begin at the scene, with bystander rescue and immediate initiation of resuscitation considered fundamental to increase survival [26]. Ideally, the same approach should be applied in veterinary medicine. If the owner does not have knowledge of cardiopulmonary resuscitation (CPR), it is recommended to wrap the pet in a blanket, to perform mouth-to-nose breathing if respirations are not noted, and to bring the animal to a veterinary facility as quickly as possible [27].

At presentation, airway, breathing, and circulation should be immediately assessed and if there is cardiopulmonary arrest, CPR should be instituted according to the most recent guidelines [28]. Initial physical examination should also include body temperature, mentation, and pupil responsiveness. The secondary and more focused examination should then proceed, based on initial examination findings.

Minimum database should include measurement of arterial blood pressure, ECG, and a thoracic radiograph when the patient is stable (Figure 40.1). Pulse oximetry can be used to monitor hemoglobin oxygen saturation (SpO_2) although its feasibility can be decreased in victims of cold water submersion [29]. Bloodwork should include arterial blood gas analysis, complete blood count, chemistry profile including a coagulation panel, and creatine kinase if rhabdomyolysis is suspected.

Human drowning victims are classified in six groups, depending on initial clinical signs, and treated accordingly [30]. A similar scheme can be adapted to veterinary patients as well (Figure 40.2).

Oxygen should be administered to maintain $SpO_2 > 95\%$ and/or $PaO_2 > 80$ mmHg with the lowest FiO_2 possible, to avoid hyperoxia-associated lung and brain injury (Figure 40.3) (see Chapter 181). Apneic patients need

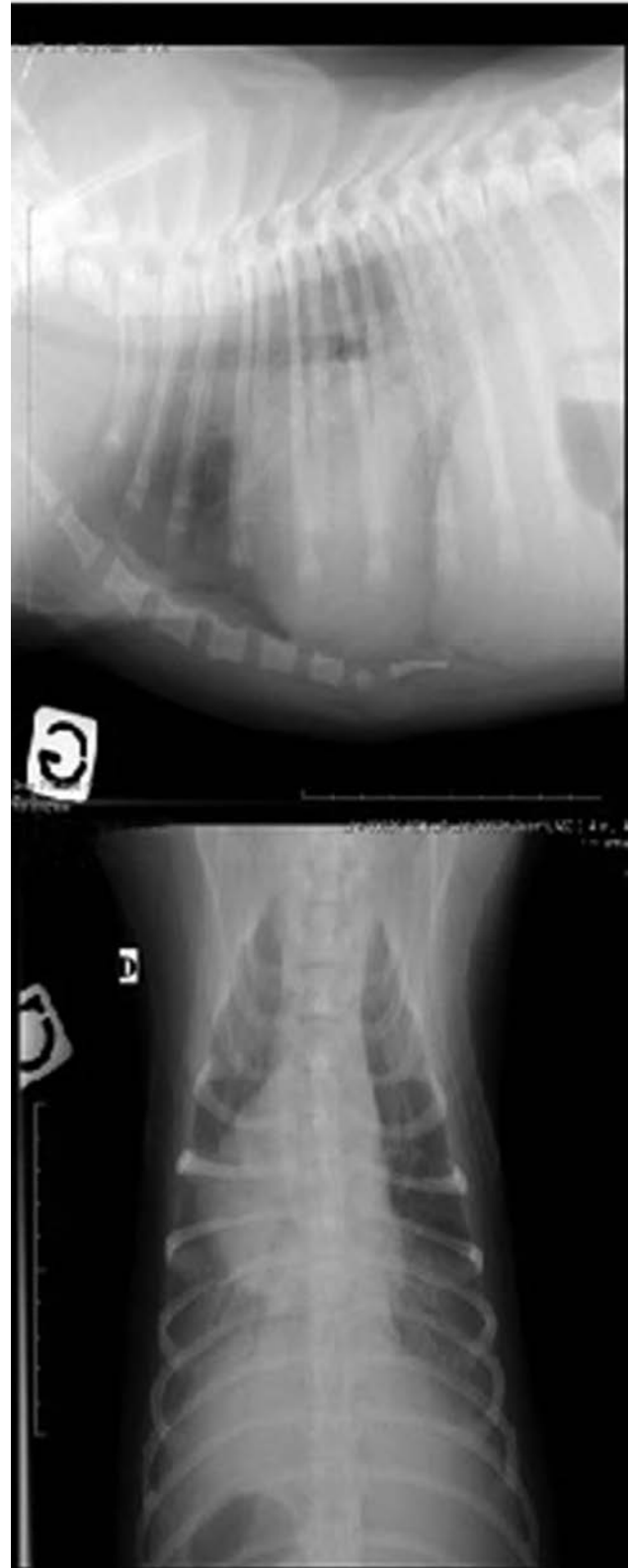


Figure 40.1 Thoracic radiograph of a dog which suffered from submersion injury. Note the presence of pulmonary infiltrates in the diaphragmatic lung lobes (caudodorsal lung fields).

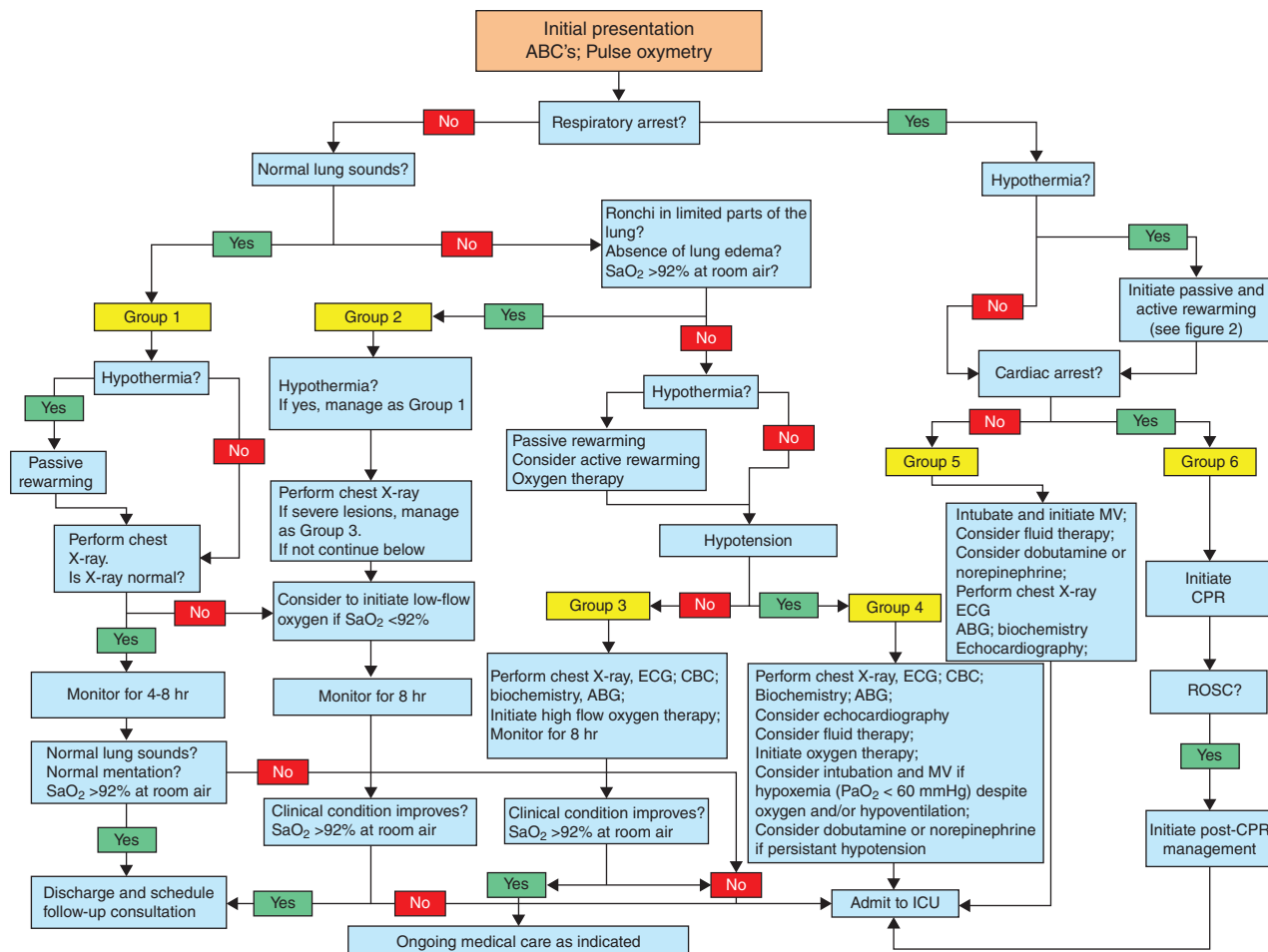


Figure 40.2 Management of patients with submersion injury at arrival to the emergency department. Patients are divided into six groups according to initial clinical findings at presentation. This approach is adapted from a scoring system described in humans where patients are allocated to one of six groups, with each group being associated with a specific percentage of survival [30]; patients belonging to groups 1, 2, 3, 4, 5, and 6 have 100%, 99%, 95%, 80%, 56% and 7% percentage of survival, respectively. ABG, arterial blood gas; CBC, complete blood count; CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; ICU, intensive care unit; MV, mechanical ventilation; ROSC, return of spontaneous circulation.

intubation and mechanical ventilation (MV). MV should also be performed in patients with $\text{PaO}_2 < 60 \text{ mmHg}$ or $\text{SpO}_2 < 90\%$ despite oxygen therapy, worsening hypercapnia and/or severe respiratory distress suggestive of impending respiratory failure. MV should be instituted using positive end-expiratory pressures [13] and following the “lung protective strategies” as suggested for ARDS (see Chapter 188) [1]. Corticosteroids are not recommended, except when bronchospasm refractory to bronchodilators occurs [16,31]. The prophylactic use of antibiotics to prevent secondary pneumonia is not recommended and can lead to selection of resistant and aggressive organisms [1]. A wait-and-see approach should be adopted, coupled with initiation of empirical therapy after collection and culture of samples by



Figure 40.3 The same dog as in Figure 40.1 receiving oxygen through a nasal catheter. Submersion injury victims frequently need oxygen supplementation to correct hypoxemia.

transtracheal or bronchoalveolar lavage at the minimal sign of infection. Exceptions to this policy include submersion in contaminated or polluted waters, and aspiration of gastric secretions or dirt/sand in a patient in an unstable condition [27].

In humans, when respiratory failure/hypoxemia becomes refractory to conventional ventilation, good results were obtained with extracorporeal membrane oxygenation (ECMO) [32]. Small studies have also shown improvement of refractory hypoxemia with exogenous surfactant therapy [33,34]. Inhaled nitric oxide and partial liquid ventilation with perfluorocarbons are also under investigation for this purpose [1]. Unfortunately, these techniques are rarely available to veterinary patients and are very expensive.

Hypothermia should be corrected in all drowning patients, according to its severity (Figure 40.4). The goals are to safely rewarm the patient while maintaining hemodynamic stability. The target core temperature for

rewarming is still controversial in humans and unknown in animals (see Chapter 148). Some authors suggest rewarming human patients to 35–36°C, and only after, with the patient stable, to initiate mild therapeutic hypothermia (MTH) for neuroprotection. In MTH, the patient is cooled and maintained at 32–34°C for 12–72 hours [1]. Other authors argue that to obtain most neuroprotective benefits, rewarming should be performed slowly and only to achieve a core temperature of 32–34°C [35].

The initial data about MTH in veterinary medicine came from studies in dogs [36]. The RECOVER initiative concluded that available data suggest a beneficial effect on neurologically intact survival of mild hypothermia (core temperature of $33 \pm 1^\circ\text{C}$) instituted as soon as possible after return of spontaneous circulation (ROSC) and maintained for >12 hours [37]. Clinical application of MTH after submersion needs to be studied in dogs and cats. Although no studies have shown an ideal rewarming rate, slower rewarming rates (1–2°C/h) are

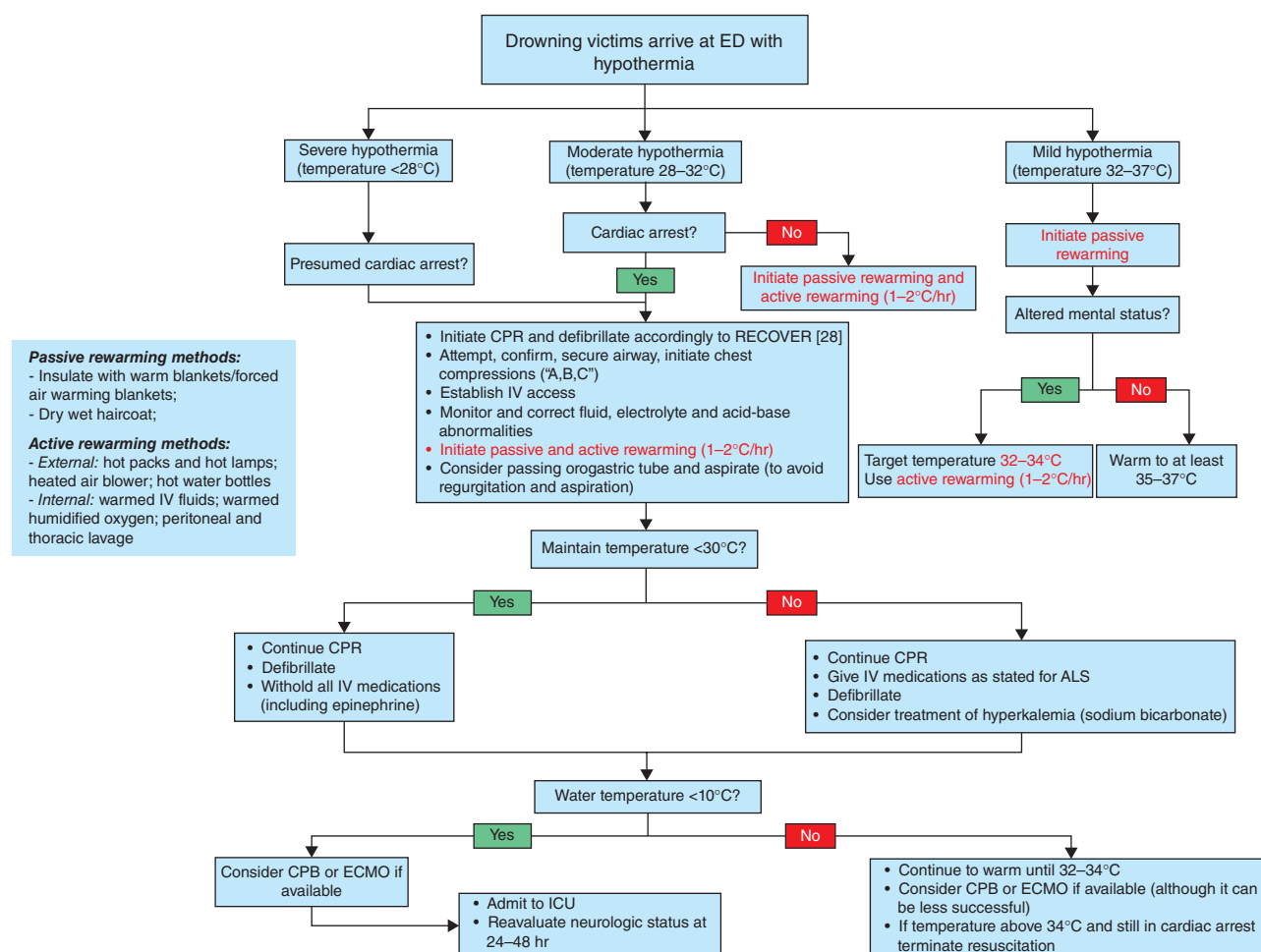


Figure 40.4 Management of patients with submersion injury according to the degree of hypothermia. ALS, Advanced Life Support; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ED, emergency department; ICU, intensive care unit; IV, intravenous.

preferred over faster ones. Warming until the animal is not shivering is recommended to avoid excessive oxygen utilization. Active rewarming should stop when core temperature reaches 37°C to prevent rebound pyrexia [38].

No evidence supports a specific type of fluid for treating hypovolemia in drowning victims [13] and most authors suggest a bolus of isotonic crystalloids (e.g. 20 mL/kg NaCl 0.9%) [2]. If cardiac output remains low despite fluid therapy, echocardiography can be used to decide if the patient needs inotropic (mainly dobutamine) or vasopressor (norepinephrine) drugs or both [13]. Metabolic acidosis normally resolves with correction of ventilation, oxygenation, and perfusion abnormalities and bicarbonate infusion is rarely needed.

The management of hypoxic encephalopathy is mainly supportive and includes prevention of hypoxemia/hyperoxia, hypertension/hypotension, hypoglycemia, hypercapnia, hyperthermia and seizure prophylaxis [35]. Besides MTH, no therapeutic measures, including mannitol, barbiturate coma and neuroprotective agents, have improved the prognosis of drowning patients with severe neurological damage [2,35].

Outcome

Several factors have been found to predict survival and/or recovery with good neurological function in humans after drowning (Box 40.1). The most important are submersion time, duration of CPR before ROSC, Glasgow Coma Score at admission, and time to return to neurological function [2]. However, no single factor or

Box 40.1 Prognosis of good neurological outcome in children [2]. PRISM is a score based on 14 physiological parameters and has been employed in pediatric intensive care since 1988 [23].

Factors of good prognosis:

- Arrival in the ED with a detectable heart rate
- Submersion time <10 minutes
- GCS >3

Factors of poor prognosis:

- GCS ≤3
- PRISM score >20–24
- Lack of neurological improvement after 48 h
- IF CPR is initiated >7 min post injury
- If ROSC with CPR occurs only after 10 minutes
- pH <7.0
- Presence of dilated unresponsive pupils at presentation
- Troponin and potassium levels

Factors which do not seem to predict prognosis or for which prognostic value varies:

- Water temperature
- Hypothermia at presentation

CPR, cardiopulmonary resuscitation; ED, emergency department; GCS, Glasgow Coma Score; PRISM, pediatric risk of mortality score; ROSC, return of spontaneous circulation.

combination of factors accurately predicts outcome. In a veterinary study, none of the studied variables, including level of consciousness, blood pH and presence of hypothermia, was found to have prognostic value [10].

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41

Pulmonary Hemorrhage

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Etiology and Pathogenesis

Pulmonary hemorrhage is not well defined in veterinary or human medicine. In people, the definition varies from the appearance of fresh blood in the trachea [1] to bleeding into the alveolar spaces [2]. Hemoptysis is defined as the expectoration of blood or bloody mucus from the respiratory tract at or below the larynx. Hemoptysis may or may not occur in cases of pulmonary hemorrhage (see Chapter 36). Bleeding from the upper airways can lead to blood-filled alveoli, so it is reasonable to classify pulmonary hemorrhage similar to hemoptysis as bleeding from any site at or below the level of the larynx.

Etiology

The prevalence of pulmonary hemorrhage in small animals is difficult to estimate given the scarcity of literature. There is evidence that exercise-induced pulmonary hemorrhage occurs in canine racing breeds such as greyhounds, although cases tend to be mild and subclinical. Histopathological examination of dogs with pulmonary hypertension has shown evidence of intra-alveolar hemorrhage, although the clinical relevance of alveolar hemorrhage in these cases is unclear [3]. Clinically significant pulmonary hemorrhage in small animals occurs secondary to underlying pathological processes.

Pulmonary contusions following blunt thoracic trauma are probably the most frequent secondary cause of pulmonary hemorrhage, reported in over a third of dogs and cats suffering thoracic injury [4]. Most pulmonary contusions are not life threatening (<10% mortality) and confirmation of pulmonary hemorrhage may be lacking in many cases [4,5].

In contrast to non-lethal and subclinical causes of pulmonary hemorrhage as described above, severe bleeding into the lungs is rare in dogs and cats. It has been reported at necropsy in dogs with leptospirosis infection,

pulmonary-renal syndrome, severe chest trauma, heartworm disease, neoplasia, thrombocytopenia, and coagulopathies including disseminated intravascular coagulation (DIC) [4–7].

Infectious outbreaks of fatal hemorrhagic pneumonia in housed dogs secondary to *Streptococcus zooepidemicus* [8,9] and *Escherichia coli* [10] have been reported. Although subclinical in most dogs, canine influenza virus has been isolated from greyhounds with hemorrhagic pneumonia in Florida [11,12]. The virus was subsequently detected in dogs in other parts of the USA but was mainly associated with milder respiratory disease. Lungworm infestation (*Angiostrongylus vasorum*) has also been reported to cause pulmonary hemorrhage via direct pulmonary vascular injury or secondary to coagulation disturbances. Severe fatal pulmonary hemorrhage secondary to grooming and other pet services has also been documented in postmortem forensic studies in dogs, although the exact cause leading to pulmonary hemorrhage was speculative [13].

A retrospective study of hemoptysis in dogs showed that all dogs with hemoptysis had concurrent evidence of pulmonary hemorrhage. The study reported underlying causes of hemoptysis including neoplasia, metastatic neoplasia, infections (bacterial, parasitic, fungal), foreign body aspiration, thoracic trauma, lung lobe torsion, heartworm disease, pulmonary thromboembolism, coagulopathies (immune-mediated thrombocytopenia, rodenticide poisoning), left-sided congestive heart failure, pulmonary hypertension, and iatrogenic, including fine needle biopsy of the lung [3].

Pulmonary hemorrhage in cats is very rarely reported in the literature and tends to be diagnosed based on the presence of hemosiderosis following transtracheal wash [14]. Bronchoalveolar lavage (BAL) in 11 cats with dyspnea revealed pulmonary hemorrhage in two cases, one with chronic bronchitis and the other with tracheal lymphoma [15]. Heart failure, trauma, infection,

pneumonia, foreign body migration, lung lobe torsion, pulmonary embolism or infarction, neoplasia, asthma, and bleeding diathesis have been associated with hemosiderophages/hemosiderosis on transtracheal wash specimens from cats [14]. Hemosiderophages have been thought to indicate pulmonary hypertension attributable to congestive heart failure. In cats with congestive heart failure, hemosiderophages are believed to result from increased erythrocyte transmigration or diapedesis secondary to vascular congestion, and not from overt hemorrhage [14]. Acute fatal pulmonary hemorrhage has been reported under isoflurane anesthesia in two Himalayan cats exposed to toxic black mold associated with flood damage [16].

Pathogenesis

Hemorrhage into the alveolar spaces is a common sequela of numerous pathological processes affecting the pulmonary system, so the pathogenesis varies depending on the underlying condition. In cases of diffuse pulmonary hemorrhage, there is often injury to the alveolar microcirculation [2]. Histopathologically, disruption of the alveolar-capillary basement membrane results in the accumulation of red blood cells in the alveoli (Figure 41.1). Hemosiderin-laden macrophages may collect in the affected portions of the lungs within 2–3 days (see Figure 41.1) [2]. Leptospirosis has received some attention as a cause of pulmonary hemorrhage in humans and dogs although the pathogenesis remains poorly understood. Vascular damage due to a leptospiral toxin,

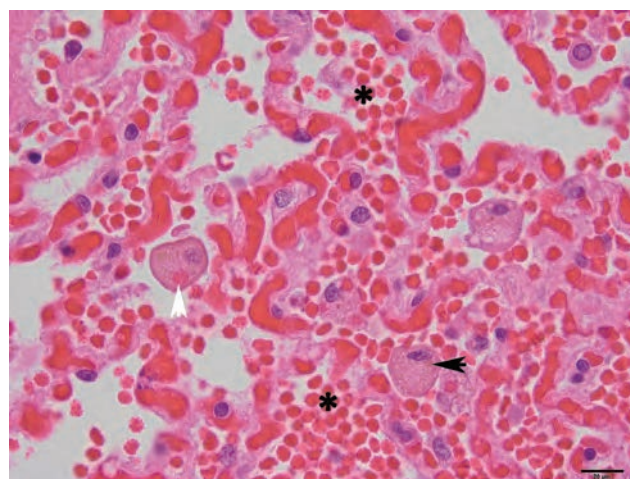


Figure 41.1 Photomicrograph of the lung. Free red blood cells in the alveolar spaces (*) consistent with pulmonary hemorrhage in a dog with metastatic hemangiosarcoma. Erythrophagocytosis (white arrow) and hemosiderin-laden macrophages (black arrow) indicate chronicity. Reproduced with permission of Jennifer Davis, Diagnostic Services Unit, University of Calgary.

immunological mechanisms, or a disseminated intravascular coagulopathy has been proposed as a potential pathological mechanism [7]. Hemoptysis has been reported in a dog with seizures, with a proposed pathophysiological mechanism being the presence of severe but transient pulmonary hypertension, leading to the rupture of pulmonary capillaries (see Chapter 39) [17].

Patient Evaluation

History and Physical Examination Findings

For patients presenting with hemoptysis or those in which pulmonary hemorrhage is suspected, it is important to consider the possibility of anticoagulant rodenticide exposure, travel history and heartworm preventives, recent contact with other dogs or multiple household pets showing similar symptoms (possible infectious causes), possibility of trauma, concurrent prothrombotic medications (e.g. glucocorticoids), and any history of underlying hypercoagulable conditions (e.g. hyperadrenocorticism, hypertrophic cardiomyopathy in cats, etc.). Hemophilia or other congenital clotting factor deficiencies should also be considered in puppies and kittens while von Willebrand's disease should be considered in Doberman pinschers.

When outbreaks of hemorrhagic pneumonia are seen in dogs, *S. equi* subsp. *zooepidemicus* and *E. coli* should be considered in the differential diagnoses. Bacterial outbreaks have been reported following transportation of racing dogs, in newly arrived densely housed research dogs, and in kennelled dogs [8]. It has been proposed that environmental stresses contribute to immunosuppression and consequently increased viral and/or bacterial susceptibility, particularly to more aggressive and opportunistic bacteria like *S. equi* subsp. *zooepidemicus*.

Clinical manifestations of respiratory distress are likely in cases of moderate-to-severe pulmonary hemorrhage. Underlying pulmonary pathology and extrapulmonary diseases may further influence the clinical presentation and contribute to non-respiratory clinical signs. For instance, coagulopathy-induced pulmonary hemorrhage may be associated with melena, petechia and ecchymosis, and patients with infectious hemorrhagic pneumonias may have hyperthermia [8].

Owners may report respiratory signs including, from most to least common, coughing with or without hemoptysis, dyspnea, tachypnea, exercise intolerance, and collapse [3]. Lethargy, weight loss, hematochezia, melena, hematuria, and pallor may also be reported, depending on the duration of illness and associated underlying cause [3]. A chronic insidious onset of cough is more likely to be associated with neoplasia, heartworm

disease, left-sided congestive heart failure, or chronic bronchitis. Acute onset of signs is more likely in cases of trauma and rodenticide toxicity.

Physical exam findings specific to pulmonary hemorrhage are associated with the respiratory system and may include tachypnea, dyspnea, spontaneous coughing, hemoptysis, crackles, wheezes, cyanosis, and diminished lung sounds [3]. Other physical exam findings vary with the underlying cause but may include hyperthermia (possible infection/immune processes), pallor, cardiac murmurs and arrhythmias (underlying cardiac condition), dehydration, evidence of trauma, petechia, ecchymosis, melena, hypothermia, palpable abdominal fluid wave, and peripheral edema [3].

Diagnosis

The presence of red blood cells and/or hemosiderosis on cytological samples from tracheal, bronchial, or bronchoalveolar washes identifies hemorrhage. Contamination or aspiration of bleeding from the airways above the larynx should be ruled out. Diagnostic testing for pulmonary hemorrhage varies depending on the suspected underlying pathology. Diagnostic tests specific to the lungs include thoracic radiography, computed tomography, lung ultrasound, endoscopic examination of the respiratory tract, fine needle aspiration and cytology of the lung, transtracheal wash (TTW), bronchoalveolar lavage (BAL), culture, histopathology of the lung, or a combination of the above [3]. Other diagnostic tests to consider in cases of hemoptysis/pulmonary hemorrhage include CBC, biochemistry panel, coagulation testing, heartworm antigen testing, Baermann fecal float, echocardiography, exploratory thoracotomy, and leptospiriosis antibody testing.

Radiography

Most dogs and cats with moderate-to-severe pulmonary hemorrhage will have abnormal thoracic radiographs. However, some cases may be occult on conventional radiography, depending on the severity of hemorrhage and underlying cause of the condition. One human study demonstrated thoracic radiographs as normal in 39% of patients with alveolar hemorrhage confirmed by bronchoalveolar lavage [18]. Furthermore, definitively differentiating pulmonary hemorrhage from primary pulmonary disease is not possible on thoracic radiographs [3].

When present, radiographic findings with pulmonary hemorrhage tend to be variable and non-specific in the absence of other pulmonary conditions [3]. Focal to diffuse interstitial to alveolar or mixed patterns are

most commonly identified [3]. Traumatic causes can be diffuse or may be localized to one lung lobe. Localized hemorrhage may obscure underlying focal neoplastic processes. Lung lobe consolidation and multifocal nodules have also been reported on thoracic radiographs in dogs with pulmonary hemorrhage [3]. If heart disease is the underlying cause of pulmonary hemorrhage, an enlarged cardiac silhouette and venous congestion may be evident.

Lung Ultrasound (see Chapter 182)

Lung ultrasound is rapidly becoming a popular cage-side emergency test to assess patients presenting with respiratory distress, with or without the presence of trauma [19]. In cases of pulmonary hemorrhage where bleeding extends to the periphery of the lungs, sonography may reveal an increased number of B lines. Underlying causes of pulmonary hemorrhage, such as nodules or consolidated lung regions, may also be detected with ultrasound if these lesions are located along the periphery of the lung. If lesions are visualized, ultrasound-guided centesis with cytopathology of obtained samples (with or without cultures) may prove helpful in diagnosis.

Computed Tomography

Thoracic computed tomography (CT) has been assessed in humans with diffuse pulmonary hemorrhage. Acute hemorrhage is described as having a patchy ground-glass opacity without significant interlobular septal thickening [2]. As the duration of pulmonary hemorrhage increases (typically within 48 hours), septal thickening may occur while the ground-glass opacities persist. In cases of chronic and/or recurrent pulmonary hemorrhage, pulmonary fibrosis develops. CT may also be helpful in identifying other conditions including masses, thromboembolism, and lung lobe torsions.

Echocardiography

Echocardiography may be helpful in identifying underlying causes of pulmonary hemorrhage such as heartworm disease, congestive heart failure, and pulmonary hypertension. Doppler echocardiography has been used as a non-invasive predictor for the presence of pulmonary hypertension in both human and canine studies [20,21].

Transtracheal Wash, Bronchoalveolar Lavage, Cytopathology, Histopathology, and Culture

The nature of the expectorated fluid from patients with pulmonary hemorrhage may vary from frothy and

pink-tinged (more common with congestive heart failure) to blood mixed with sputum (more common in bronchopneumonia) to bright red blood (suggestive of significant vascular hemorrhage).

Bronchoscopy is considered the diagnostic test of choice in humans with hemoptysis [2]. It allows visual examination of the respiratory tract to the level of the bronchi. It can diagnose (localize) and treat (retrieval) foreign bodies and is useful to diagnose infection via cytopathology and culture [3].

Cytopathology of TTW or BAL fluid that reveals cells with features of malignancy is suggestive of an underlying neoplastic process. Cytology that reveals the presence of erythrophagocytosis, hemosiderin-laden macrophages, or both is suggestive of chronic hemorrhage (see Figure 41.1) [3].

Culture is recommended in cases where infection is suspected, particularly with outbreaks. Ensure that patients are sufficiently stable to undergo BAL prior to inducing anaesthesia.

Histopathological examination of lung specimens obtained via lung biopsy or at the time of necropsy may be very helpful in determining the underlying cause. Antemortem lung biopsies from dogs with hemoptysis revealed primary or metastatic neoplasia, chronic lobar pneumonia, chronic bronchitis, lung lobe torsion, and traumatic lung injury as underlying causes. Pulmonary histopathology from dogs at necropsy revealed metastatic neoplasia (Figures 41.2 and 41.3), severe and diffuse pulmonary hemorrhage without apparent structural damage, and bacterial bronchopneumonia [3]. Necropsy has also identified spontaneous hemorrhage into the pulmonary parenchyma in a dog with DIC [3].

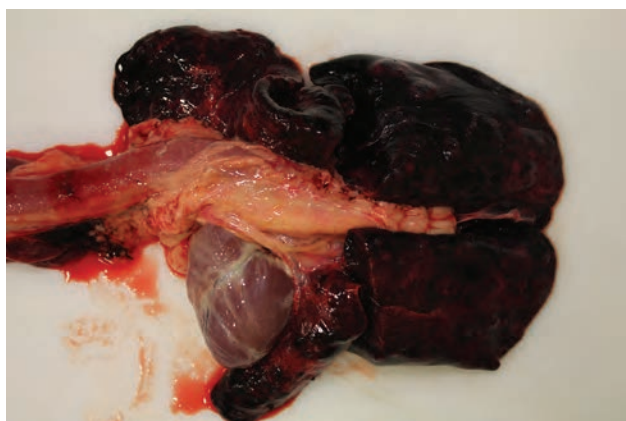


Figure 41.2 The lungs are diffusely dark red to black consistent with pulmonary hemorrhage in a dog with metastatic hemangiosarcoma. Reproduced with permission of Jennifer Davis, Diagnostic Services Unit, University of Calgary.



Figure 41.3 Tracheal bifurcation. Blood-tinged froth in the distal trachea and mainstem bronchi indicating pulmonary hemorrhage in a dog with metastatic hemangiosarcoma. Reproduced with permission of Jennifer Davis, Diagnostic Services Unit, University of Calgary.

Hematology: Complete Blood Count, Serum Chemistry, Coagulation Testing, and Other Laboratory Tests

Complete blood count, serum chemistry profile, and coagulation testing are often helpful in cases of pulmonary hemorrhage when an obvious underlying cause is not apparent. Anemia may or may not be present. In a retrospective study of dogs presenting with hemoptysis, almost a third of cases had anemia. Immune-mediated thrombocytopenia will result in platelet counts below $25\text{--}30 \times 10^3/\mu\text{L}$, values that are considered the cut-off for observation of spontaneous hemorrhage [3]. The presence of eosinophilia should prompt consideration of parasitic infection (e.g. lungworm).

Azotemia may be seen in cases of pulmonary renal syndrome or leptospirosis. Clotting profiles will be prolonged in patients with clotting deficiencies or rodenticide toxicity. Cases of thromboembolism may have increased D-dimers or hypercoagulable thromboelastography (TEG) tracings, although the role of TEG in diagnosing thromboembolism is unclear. Heartworm testing should be considered in endemic areas with appropriate history of exposure. Endemic areas of lungworm should have a Baermann fecal test performed to look for the presence of larvae.

Advanced Pulmonary Testing

A distinguishing feature of diffuse pulmonary hemorrhage in humans is the increased diffusion capacity of the lung for carbon monoxide and decreased level of exhaled nitric oxide in pulmonary function testing. These findings are attributed to the absorption of carbon monoxide and nitric oxide by the hemoglobin in alveolar blood [2].

Treatment

Therapy for pulmonary hemorrhage consists of treatment directed at stabilizing the patient, particularly the pulmonary system, and ultimately addressing the specific underlying cause. Supportive care of the respiratory system includes establishing a patent airway, anxiolytics, and oxygen therapy (see Chapter 181).

When indicated, fluid therapy including transfusions should be given to maintain adequate circulating volume and oxygen-carrying capacity. Transfusion for correction of coagulopathies may also be required (see Chapters 176 and 177). Caution should be exercised in patients that are euvoletic with concurrent pulmonary hemorrhage (e.g. pulmonary contusions), because aggressive fluid therapy in these patients can exacerbate respiratory distress.

Severe cases of pulmonary hemorrhage that remain hypoxemic despite oxygen therapy, have marked hypercarbia, or remain severely dyspneic with increased work of breathing may require positive pressure ventilation (see Chapter 188). Uncontrolled isolated pulmonary hemorrhage (e.g. secondary to tumor, lung lobe torsion, or a single lobe secondary to trauma) may benefit from surgery.

In outbreak situations or suspected cases of bacterial pneumonia where patients show respiratory disease and additional clinical signs such as pyrexia, anorexia, and depression, treatment with broad-spectrum antibiotics should be considered while cultures and sensitivity results are pending. Isolates of *S. zooepidemicus* have been shown to be susceptible to penicillin, ampicillin, amoxicillin, and enrofloxacin [22] but resistant to tetracycline and doxycycline [23,24].

Outcome

Overall, the short-term prognosis (discharge from hospital) in cases presenting with hemoptysis is good, with roughly 75% of cases being sufficiently stable to be discharged from the hospital. The long-term prognosis varies considerably with the underlying cause and the severity of pulmonary hemorrhage. For example, cases of pulmonary contusion, tracheal foreign bodies, and bronchial pneumonia generally have an excellent long-term prognosis if they survive to hospital discharge. Cases of neoplasia, congestive heart failure, pulmonary hypertension, and immune-mediated diseases have a guarded prognosis with higher risk of complications and euthanasia in relation to the underlying process.

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42

Pulmonary Thromboembolism

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Introduction

Pulmonary thromboembolism (PTE) is a complication of underlying venous or intracardiac thrombosis. Disease processes that lead to an overall hypercoagulable state are associated with thrombi formation that may translocate to the pulmonary vasculature, resulting in PTE.

Given the lack of gold standard diagnostic test for PTE, the prevalence of PTE in dogs and cats is unknown. Based on postmortem examination, the prevalence of PTE in dogs and cats was reported to be 0.9% and 0.06%, respectively. The actual prevalence is likely to be higher since not all animals with clinical suspicion of PTE had postmortem examinations. The subgroup prevalence of PTE varies greatly with underlying diseases. Previous studies reported a prevalence of 33–57% in dogs with immune-mediated hemolytic anemia (IMHA) and about 10% in dogs with sepsis [1–4]. PTE was reported in 35% and 41% of cats with neoplasia and cardiac diseases, respectively [5,6].

Risk Factors

According to the British Thoracic Society, patient-associated risk factors in humans include history of previous venous thrombosis, immobility, age, obesity, central venous catheterization, and congenital or acquired coagulopathies. Similar to human beings, co-morbid conditions are known risk factors for PTE in dogs and cats. Many disease processes such as IMHA are well documented to cause an overall hypercoagulable state inciting thrombosis (Box 42.1).

Pathophysiology

The key pathophysiological processes that occur during acute PTE lead to alterations in hemodynamics and

pulmonary functions. The extent of circulatory occlusion determines the magnitude of physiological consequences of PTE. Regardless of the location of vascular occlusion, pulmonary blood flow redistributes to the gravitationally

Box 42.1 Risk factors of pulmonary thromboembolism (PTE) in dogs and cats.

Diseases associated with PTE

- Babesiosis
- Blastomycosis
- Cardiomyopathy
- *Dirofilaria immitis*
- Disseminated intravascular coagulation (DIC)
- Endocarditis (tricuspid/pulmonic)
- Feline infectious peritonitis
- Hyperadrenocorticism
- Hypothyroidism
- Immune-mediated hemolytic anemia
- Neoplasia
- Nephrotic syndrome
- Pancreatitis
- Protein-losing nephropathy
- Protein-losing enteropathy
- Renal amyloidosis
- Sepsis
- Systemic inflammatory response syndrome (SIRS)
- Trauma

In-hospital risk factors

- Catheterization: central venous catheters, dialysis catheters
- Immobility/recumbency
- Surgeries

Other

- Corticosteroid administration

non-dependent regions via capillary recruitment. This redistribution of blood flow is also mediated by hypoxic pulmonary vasoconstriction in response to alveolar and blood partial pressures of oxygen. Platelets within thrombi are sources of thromboxane A_2 and serotonin, both of which are potent pulmonary vasoconstrictors. Other vasoconstrictive mediators include endothelin-1 and prostaglandin $F_{2\alpha}$.

These changes in pulmonary hemodynamics result in ventilation/perfusion (V/Q) mismatch with high or infinite V/Q values due to vascular occlusion or extremely low V/Q values in non-occluded regions [7]. Lung units with low V/Q ratios contribute greatly to arterial hypoxemia as poorly oxygenated blood enters the systemic circulation, resulting in venous admixture and physiological right-to-left shunting. Arterial hypoxemia is also exacerbated by loss of surfactant, atelectasis and bronchoconstriction mediated by thrombin-induced 5-hydroxytryptamine (serotonin) [8]. Regions of the lung that are completely depleted of Q become anatomical deadspace, thereby decreasing the efficiency of eliminating alveolar CO_2 [9].

Thromboembolic occlusion and pulmonary vasoconstriction via neural reflexes and humoral factors increase pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (mPAP) [7]. For that reason, PTE can sometimes result in pulmonary hypertension (PH). Approximately 25–55% of vascular occlusion can result in clinically detectable PH. Abrupt development of PH results in elevation of right ventricular (RV) afterload, RV dilation and dysfunction. High RV pressure also leads to decrease in coronary blood flow and subsequent myocardial infarction or ischemia. As RV dilation causes interventricular septal bulging and shifting into the left ventricle (LV) (ventricular interdependence), LV distensibility and filling decrease. This compromises CO and leads to systemic hypotension and cardiogenic shock [9].

Clinical Signs

Dogs and cats with PTE have a wide spectrum of clinical signs, depending on the extent of thromboembolic occlusion and underlying diseases. Animals with acute PTE may present with tachypnea, tachycardia, anxiety, cough, epistaxis, syncope, respiratory distress, cyanosis, and sudden death [3,6]. Thoracic auscultation in patients with respiratory signs may reveal increased adventitious lung sounds, pulmonary crackles, and cardiac murmurs. Chronic PTE may be presented with signs consistent with RV failure such as hepatomegaly, splenomegaly, ascites, pleural effusion, and jugular pulsation. It is important to recognize that clinical signs of

PTE can be indistinguishable from clinical signs of the underlying disorders.

Diagnosis

Diagnosing PTE is challenging in the veterinary emergency setting since there is no gold standard diagnostic test. For that reason, PTE diagnosis in small animals should be based on known risk factors, clinical signs, diagnostic imaging, point-of-care (POC) and laboratory tests. Acute onset of respiratory signs with a previous history of normal pulmonary and cardiac function should raise the suspicion of PTE. Figure 42.1 outlines the diagnostic algorithm that facilitates the diagnosis of PTE.

Coagulation Testing

Clotting times such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and activated clotting time (ACT) are not helpful in identifying hypercoagulable patients at risk of or with PTE. According to several retrospective studies, no differences in clotting times were found between dogs with and without PTE. However, prolongations of PT and aPTT are common in cats with PTE, which may be secondary to the underlying diseases [6].

Thromboelastography (TEG) provides a global assessment of the coagulation system, including the dynamics of clot formation, clot strength, and fibrinolysis. TEG can therefore be used to identify animals that are hypocoagulable, hypercoagulable or hyperfibrinolytic. Although no TEG variables are discriminant for PTE diagnosis, dogs with relative hypocoagulability are less likely to survive than those with hypercoagulable TEG tracings [1].

Thoracic Radiographs

Thoracic radiographs are useful in ruling out other causes of respiratory distress but not specific in diagnosing PTE. Lack of radiographic signs does not rule out PTE. Approximately 10–27% of dogs with PTE had normal thoracic radiographs [3].

Radiographic signs include pulmonary infiltrates and alveolar opacities that are due to pulmonary edema, hemorrhage or atelectasis. Alveolar opacities often have indistinct borders. Pulmonary infarct may appear as distinct pleural-based, wedge-shaped densities [10]. Pulmonary vascular changes such as uneven vessel diameter, enlargement of pulmonary arteries or loss of lobar veins may also be seen.

Regional oligemia or hypovascularity, known as Westermarck sign, is characterized by areas of hyperlucency

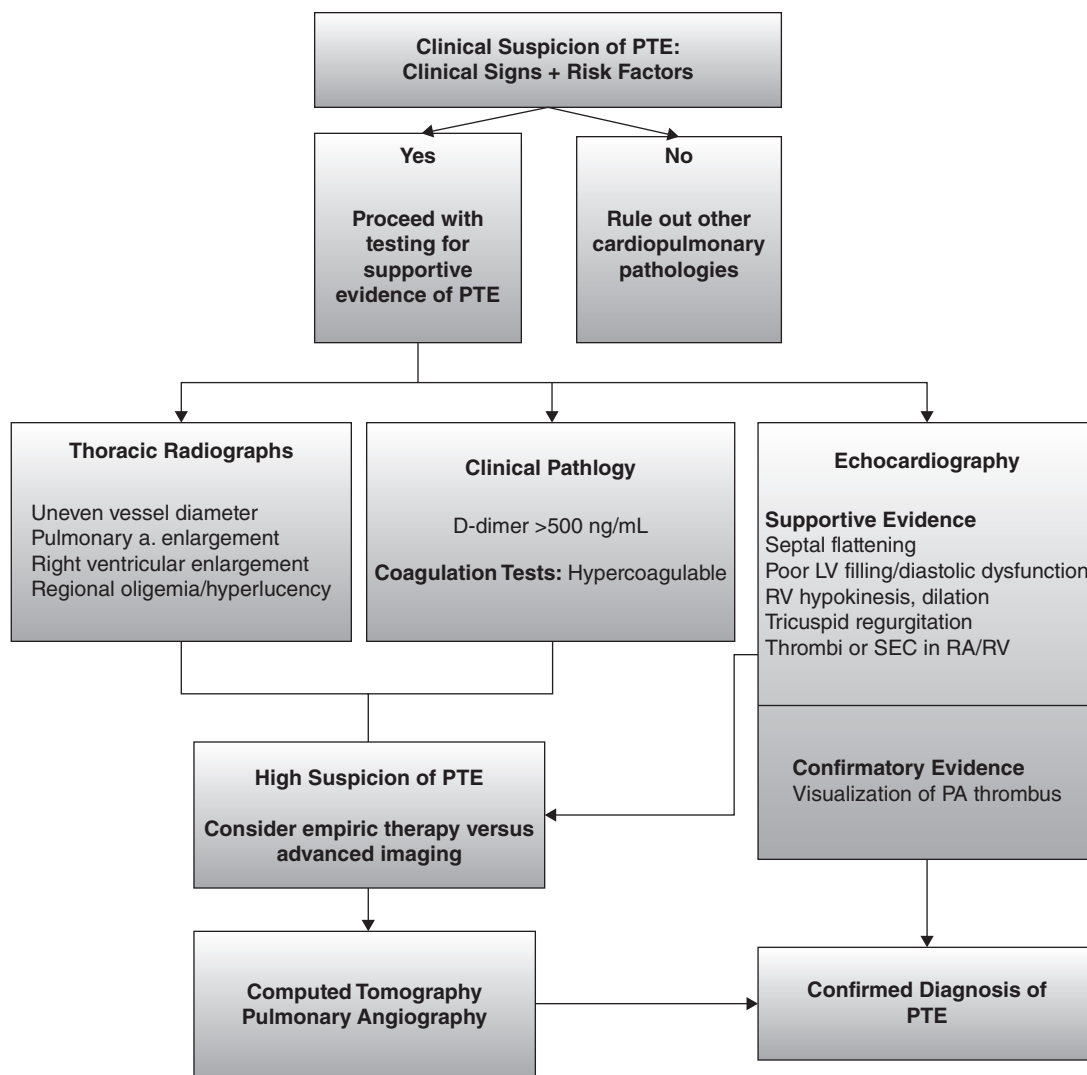


Figure 42.1 Diagnostic algorithm of pulmonary thromboembolism in dogs and cats.

due to reduced blood flow distal to the site of vascular occlusion (Figure 42.2). Mild-to-moderate pleural effusion may occasionally be seen.

Arterial Blood Gas

Arterial blood gas should be used to increase clinical suspicion of PTE and guide clinical stabilization. Common findings in dogs include low arterial partial pressures of oxygen (PaO_2), carbon dioxide (PaCO_2), elevated alveolar-arterial oxygen gradient $[\text{D(A-a)}\text{O}_2]$ and decreased ratio of PaO_2 to fractional inspired oxygen ($\text{PaO}_2:\text{FiO}_2 < 300$) [1,3]. In humans, results of arterial blood gas are used for enabling accurate risk stratification of PTE patients and guiding clinical decisions [11]. To date, there are no reports on arterial blood gas findings in cats with PTE.

Echocardiography

Transthoracic echocardiography is an important diagnostic tool in patients with suspected PTE. The most beneficial observation by echocardiography is the visualization of thrombi in the right atrium, RV, main pulmonary artery or proximal pulmonary artery branches. Spontaneous echocardiographic contrast in the right side of the heart may be supportive of a hypercoagulable state. Identifiable thrombi and/or spontaneous echocardiographic contrast are rare in patients with suspected PTE [12].

Acute RV pressure overload is frequently noted in patients with massive PTE. In a canine PTE model, obvious increase in RV chamber size (eccentric hypertrophy) and reduced RV systolic function was apparent [13]. Acute response to pressure overload on the RV leads to eccentric RV dilation due to the high compliance of the

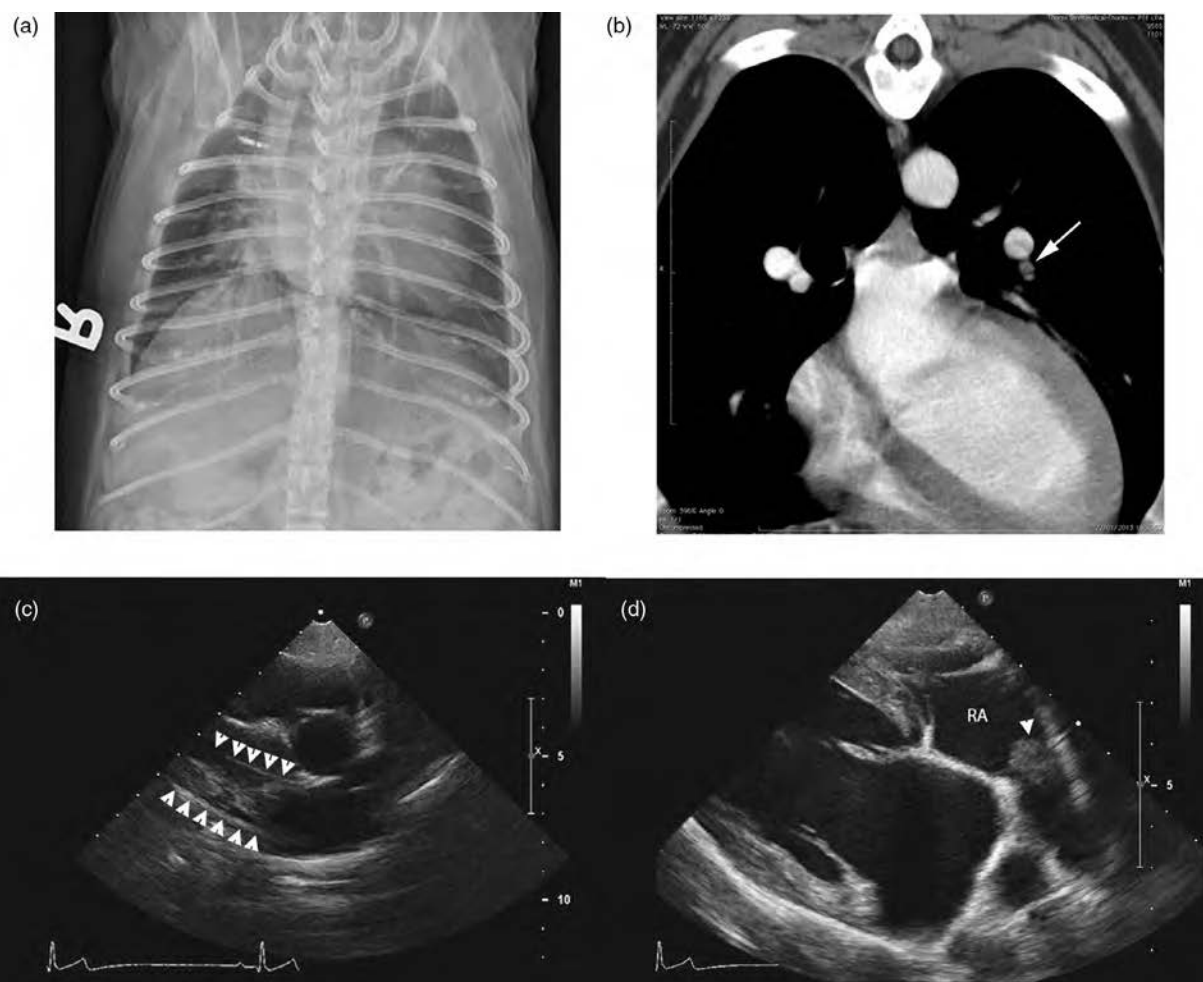


Figure 42.2 (a) Thoracic radiograph obtained from a dog with multiple pulmonary emboli. Note the hyperlucency (oligemia) of the left hemithorax while the vasculature of the right hemithorax remains normal. A mild, focal interstitial opacity is seen at the left 8th intercostal space. (b) Positive computed tomography pulmonary angiography (CPTA) study from a dog with IMHA demonstrating intraluminal filling defect in the left main pulmonary artery (*white arrow*). (c) Echocardiographic image (right parasternal short axis view) of the heart base from a dog. Large thrombus within the lumen of the right branch of the main pulmonary artery (*white arrowheads*). (d) Echocardiography (right parasternal four-chamber view) showing a thrombus at the cranial vena cava and right atrial (RA) junction.

RV. Chronic RV pressure overload could theoretically be encountered with chronic thromboembolic events and would result in concentric RV hypertrophy. Although RV functional assessments are in their infancy for dogs and cats, obvious RV systolic functional change or hypokinesis may be evident. As continued research defines the normal reference ranges for tests of RV systolic function, the quantitative assessment of these indices may prove useful in the evaluation and prognostication for canine and feline PTE patients [14].

Additionally, in severe RV pressure overload some patients will appear to have an underfilled left atrium and LV. Observation of this underfilling of the left side of the heart may represent a reasonable finding on emergency thoracic ultrasound that could support a differential diagnosis of PTE.

While echocardiography can provide supportive evidence in patients with suspected PTE, it is important to remember that the echocardiographic findings listed above are non-specific and could be seen with other conditions of both primary pulmonary or cardiac origin.

CT Pulmonary Angiography

In human medicine, spiral CT pulmonary angiography (CTPA) is a gold standard for antemortem diagnosis of PTE. The use of CPTA for diagnosing PTE in small animals is largely limited by its availability, requirement of general anesthesia, and availability of board-certified radiologists. One advantage of CTPA is the ability to image both thoracic and abdominal cavities for ruling out other potential pathologies. Recent studies have demonstrated

success in CTPA for the diagnosis of PTE in awake dogs and cats without sacrificing image quality [1,15,16]. As spiral CTPA becomes more accessible, its use for PTE diagnosis may gradually increase in veterinary medicine.

Biomarkers

D-dimers

D-dimer, an oligomer of fibrin, is a specific marker of fibrinolysis following thrombosis. The diagnostic sensitivity for PTE was 99.5% in human patients presented to the emergency room with suspected PE. This means that those without elevated D-dimer concentration were unlikely to have PTE, making D-dimer a good screening assay. However, controversy remains on the diagnostic accuracy among clinically relevant subgroups in humans. For example, D-dimer levels differ substantially between age groups in human patients [17]. To date, little is known regarding the variability of D-dimer levels among veterinary patients. Some diseases that are known to influence D-dimer levels include metastatic malignancies, liver disease, hemorrhage, IMHA, disseminated intravascular coagulation (DIC) and sepsis [18–21].

The diagnostic utility of D-dimer levels has been evaluated in dogs with PTE. Using postmortem diagnosis of PTE as a gold standard, a cut-off of 250 ng/mL had a sensitivity and specificity of 80% and 30%, respectively [4]. Another study reported a sensitivity of 100% and specificity of 70% for predicting thromboembolism in dogs with a cut-off of 500 ng/mL [22]. This discrepancy is likely due to the use of different assays, differences in disease severity, and inclusion of all thromboembolic dogs in the latter study. Nonetheless, both studies established the value of D-dimer as an appropriate screening test for dogs with clinical suspicion of PTE.

Troponin

Troponin is a marker of myocardial injury and has been extensively studied in human patients with severe PTE. Troponin I has been shown to correlate well with RV dilation and overload. A meta-analysis evaluating the prognostic value of troponins in acute PTE showed that elevated troponin was associated with increased short-term mortality [23]. The diagnostic value of troponin I was recently evaluated in a group of IMHA dogs. All dogs with elevated troponin I had CTPA findings that either confirmed or suggested the presence of PTE. However, 40% of those that did not have PTE also had elevated troponin I [1]. Larger prospective studies are needed to investigate the diagnostic utility of troponin I in dogs with PTE.

N-Terminal Prohormone BNP

N-terminal prohormone BNP (NT-proBNP) is secreted due to increased wall tension within the myocardium. In

people with acute PTE, RV enlargement, RV dysfunction, and mortality are associated with elevated NT-proBNP levels [24–26]. NT-proBNP is also a predictor of RV dysfunction and 30-day mortality [25,26]. NT-proBNP assays have been validated in cats and dogs for differentiating respiratory signs due to congestive heart failure from primary pulmonary diseases. One experimental study that utilized a canine model of embolic chronic PH found that NT-proBNP concentrations were positively correlated with pulmonary arterial pressures and echocardiographic findings consistent with PH [27]. To date, no clinical studies have evaluated the diagnostic utility of NT-proBNP in dogs and cats with PTE.

Management

Oxygen therapy (see Chapter 181) should be initiated in patients with respiratory distress and hypoxemia. Initial volume resuscitation with isotonic crystalloids is indicated in hypovolemic patients. In animals with clinicopathological evidence of cardiogenic shock or RV dilation, fluid therapy should be used judiciously since excessive fluid administration in these patients can exacerbate RV wall stress, RV ischemia, interventricular septal shift, and worsening of LV compliance and preload.

Clinical evidence supporting the use of vasopressors and inotropes in small animals with PTE-associated shock is lacking. Based on canine experimental studies, norepinephrine (NE) resulted in improved survival, RV function, RV blood flow, cardiac output (CO), and myocardial oxygen demand compared to volume expansion, suggesting that NE may augment coronary blood flow in dogs [28–30]. Dobutamine, which has more potent beta-1 and beta-2 adrenergic stimulation, increased CO and decreased PVR more effectively than dopamine in dogs with induced PTE [31]. Based on the available data, NE may be used in hypotensive dogs due to acute PTE and dobutamine may be used in PTE dogs with evidence of RV dysfunction.

Mechanical Ventilation

Mechanical ventilation (MV) is indicated in animals with respiratory failure, severe hypoxemia or respiratory distress despite oxygen therapy (see Chapter 188). However, clinicians should be mindful of the compromising effects of positive pressure ventilation on hemodynamics.

Anticoagulants and Thrombolytics

The objective of early parenteral anticoagulants in acute PTE patients is to prevent thrombus propagation and additional thromboembolic events. Unfractionated

heparin (UFH) is widely available and can prevent further fibrin generation and thrombin activation by potentiating antithrombin. Due to its variable anticoagulant effects, doses should be adjusted based on either aPTT (1.5–2.5 × baseline) or anti-Xa levels (0.35–0.75 U/mL) in order to sustain therapeutic targets and prevent bleeding complications. Monitoring UFH therapy using aPTT can be challenging as aPTT prolongation is variable in critically ill dogs and cats [32].

Low molecular weight heparin (LMWH) is superior to UFH due to its consistent anticoagulant effects and pharmacokinetics. Approximately 10% of critically ill IMHA dogs developed PTE while receiving dalteparin and enoxaparin despite achieving the recommended therapeutic anti-Xa activity (0.5–1.0 U/mL) [33,34]. Based on the incidence of PTE in IMHA dogs (32–80%), LMWH may be helpful in preventing PTE in IMHA dogs. LMWH pharmacokinetics is less predictable in cats, which require more frequent dosing to achieve therapeutic anti-Xa range.

Antiplatelet therapy is warranted once patients are able to tolerate oral medications. A retrospective study in IMHA dogs showed that aspirin therapy was associated with higher survival rates [35]. Combining aspirin

and clopidogrel does not seem to prevent PTE compared to clopidogrel or aspirin alone in dogs with IMHA [36]. However, clopidogrel administration alone significantly reduced the recurrence of aortic thromboembolism (ATE) compared to aspirin in cats with cardiomyopathy [37].

Anticoagulants and management of their complications are detailed in Chapter 71.

The use of thrombolytic agents for PTE in small animals is controversial. Evidence regarding their efficacy and safety is lacking in veterinary medicine. Recombinant tissue plasminogen activators (tPA) such as alteplase and reteplase are fibrin specific and therefore are safer and more effective than streptokinase. A prospective study evaluating tPA administration in cats with ATE reported a complication rate of 100%. Adverse effects included azotemia, hyperkalemia, hemorrhage, neurological signs, and cardiopulmonary arrest [38].

The clinical benefits of thrombolytics in human PTE patients without hemodynamic compromise at presentation remain controversial. For that reason, tPA may be considered in small animals with RV dysfunction and cardiogenic shock due to acute PTE. However, clinicians should weigh the risks and benefits of tPA therapy in each individual patient.

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Primary and Metastatic Pulmonary Neoplasia

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Introduction

Patients with primary or metastatic lung tumors may exhibit such clinical signs as coughing, exercise intolerance, increased respiratory rate, or dyspnea. Primary lung tumors may also be detected as an incidental finding in patients with no clinical signs undergoing chest radiographs for an unrelated reason. Patients with metastatic pulmonary disease may also have weight loss and non-specific signs, such as decreased appetite or lethargy. Weight loss, lethargy, and dyspnea were the most common clinical signs reported in one study of 86 cats with primary lung tumors [1]. Patients with neoplastic pleural effusion may present with dyspnea, tachypnea, lethargy, weakness, decreased appetite, or collapse.

Similar to clinical signs, patients with primary and even metastatic lung tumors may have no significant physical exam abnormalities. Physical exam abnormalities that may be detected include increased or decreased lung sounds, tachypnea, dyspnea, coughing, and weight loss. Patients with neoplastic pleural effusion may have decreased lung sounds, muffled heart sounds, tachypnea and dyspnea, as well as decreased chest compliance in cats.

Hypertrophic osteopathy (HO) is a condition that is reported in dogs with primary and metastatic pulmonary neoplasia, and dogs with this condition may present on an emergent basis for limb swelling or lameness [2,3]. The pathophysiology is not well understood. A recent retrospective study reported on 30 dogs diagnosed with HO related to pulmonary neoplasia [2]. The most common breeds were large-breed dogs, and the median body weight was 31.1 kg. The most common clinical signs were limb swelling, lameness, ocular discharge, episcleral injection, and lethargy. Most dogs with limb swelling had swelling of all their limbs. Interestingly, owners reported coughing in less than one-third of the dogs. Anemia, neutrophilia, and elevated alkaline

phosphatase were the most commonly occurring laboratory abnormalities. The majority of dogs in the study (25) had metastatic pulmonary nodules as opposed to a solitary pulmonary mass.

A case series of four dogs with HO from metastatic osteosarcoma who underwent metastatectomy reported that clinical signs of HO resolved within 24 hours of surgery in all dogs, and only one of three dogs went on to develop recurrent HO with additional pulmonary metastatic disease [3]. Chest radiographs may therefore be warranted in older, large-breed dogs who present for swelling and/or lameness of one or more limbs to determine if they may have pulmonary lesions that may be causing HO.

Cats with lung tumors may also present for lameness due to metastasis of primary pulmonary tumors to one or more digits. Two retrospective studies have described this condition in cats [4,5]. All cats in both studies were presented for lameness with no cat having a presenting complaint related to their pulmonary neoplasia. Swelling, skin ulceration, and missing nails were the most common digit abnormalities noted. A small number of cats in both studies had radiographs performed of their digits, and these radiographs often revealed bony lysis of the distal phalanx with or without lysis of the second phalanx. Unfortunately, often multiple digits are affected at diagnosis, or additional digits become affected, so digit amputation is generally not recommended. The second study found that the majority (87.5%) of digit tumors diagnosed in cats were metastatic, not primary, lesions [5].

A more recent study examining the histological diagnosis of amputated feline digits reported that just 20.6% of cats had suspected digit metastasis from pulmonary carcinoma, and the median survival time reported for those cats was still poor, at 104 days [6]. Although lung tumors are uncommon in cats, it is reasonable to

recommend chest radiographs in an older cat who presents for lameness and in whom swelling or ulceration of the digit is found, particularly if more than one digit is affected.

Diagnostic Tests

Imaging

Most primary lung tumors are initially detected via thoracic radiographs. Even though a solitary lung mass is unlikely to represent metastatic disease, the recommended work-up for such a patient includes a thorough physical examination and abdominal ultrasound examination to look for any primary tumors that may have metastasized. This work-up includes asking the owner and/or referring veterinarian about the patient's history, paying particular attention to any history of mass removals and evaluating all available biopsy or cytology reports. If this work-up reveals no other primary tumor, then the rest of the work-up is focused on determining the type of primary lung tumor, assessing the feasibility of surgical resection, and evaluating for the presence of gross metastatic disease.

If the tumor is located on the periphery of the lung field, it may be amenable to fine needle aspiration, depending on the body size and condition score of the patient. Consulting with a radiologist is recommended to determine the feasibility and level of risk of obtaining a fine needle aspirate sample. The recommended treatment for almost all primary lung tumors is surgical resection; therefore, if the clinical suspicion is low for a non-neoplastic lesion, such as a fungal granuloma, it is also reasonable to proceed with the latter two parts of the work-up without obtaining a cytological diagnosis.

Computed tomography (CT) is most commonly used to evaluate intrathoracic lymph nodes and the other lung fields for metastatic lesions from the primary lung tumor that were not visible on radiographs. CT has been shown to have superior sensitivity and specificity for identifying tracheobronchial lymph node status compared to radiographs [7]. Specific features identified on CT, such as lymph node size and contrast enhancement pattern, have been associated with a higher likelihood of metastasis as well [8]. Performing a CT scan prior to surgery can also help with surgical planning and estimating the likelihood of complete surgical removal of the mass. After surgical removal, the mass is submitted for histopathology to find out the type (if not known prior to surgery), and grade of the tumor.

Computed tomography is also a helpful screening tool for metastasis in patients with non-pulmonary

tumors. Several studies have documented the increased sensitivity of CT versus plain radiographs for detecting metastatic lesions [9–11]. Thoracic CT results in detection of an increased number of pulmonary nodules, and nodules of smaller size being detected compared to digital or film radiographs. It is important to realize that although more lesions may be detected when performing a CT scan, the scan will not necessarily distinguish between neoplastic and benign lesions. Only one of the above studies included histopathological confirmation of pulmonary metastatic disease [10]. CT-guided aspirates may be considered for some suspicious lesions, particularly if the results will change the owner's decision for the patient.

The impact of metastatic nodules that are visualized by CT and not radiographs remains unknown. If a patient has no detectable lesions on CT or radiographs, then it is reasonably concluded that the patient has no visible metastatic disease. In contrast, if a patient has one or more pulmonary nodules detected on CT only, the degree to which that finding should alter the treatment recommendations and expected prognosis remains unclear.

Laboratory Tests

Routine laboratory testing is recommended for cats and dogs with pulmonary neoplasia, either as a preanesthesia screen in patients with primary lung tumors and/or an assessment of general health and candidacy for medications such as non-steroidal anti-inflammatory medications. There is currently no blood test that can determine if a pulmonary mass is neoplastic or not so fine needle aspiration or biopsy of the primary tumor is necessary to make a definitive diagnosis. In patients with a prior history or current diagnosis of a cancer that is known to metastasize to the lungs who develop multiple pulmonary nodules or masses, sampling of these lesions is typically not recommended.

Patients with primary or metastatic pulmonary or pleural tumors may present with pleural effusion. If the source of the neoplastic effusion is not lymphoma (or another round cell tumor such as mast cell tumor), then obtaining a definitive diagnosis can be challenging. Additional differential diagnoses for dogs and cats with neoplastic effusions include carcinomatosis and mesothelioma. Distinguishing between these two differentials can be challenging, as normal mesothelial cells will proliferate and exhibit dystrophic changes when exposed to effusion [12]. Therefore, it is often not possible to determine if any abnormal cells seen are reactive or neoplastic mesothelial cells based on cytological evaluation of fluid alone. If fluid analysis does not yield a diagnosis and masses are visualized with imaging, then the next step is to sample those lesions via biopsy or fine needle

aspiration, depending on the location of the masses, the index of suspicion for lymphoma versus another disease, and the status of the patient.

Prior to pursuing thoracic surgery in a cat or dog suspected to have neoplastic effusion, a CT scan can be helpful to better delineate the presence of pleural masses and to evaluate the lungs for the presence of a primary mass and/or metastatic lesions depending on the amount of effusion present at the time of the CT scan [13]. Thoracoscopy has been offered as an alternative to open chest surgery and has been shown to provide excellent visualization of the pleura and biopsy samples of adequate quality for diagnostic histopathological evaluation [14].

Treatment and Prognosis

Pulmonary Carcinoma

Surgical resection is the mainstay of treatment for primary lung tumors in dogs and cats. Factors to be considered when determining whether to recommend surgical removal include the severity of the patient's clinical signs, the location and size of the mass, and whether or not results of imaging studies are suspicious for metastatic disease. Specific negative prognostic factors for dogs with primary lung tumors include increasing tumor size (larger than 100 cm³), presence of clinical signs, and presence of lymph node metastasis or multiple pulmonary tumors [15–19]. If surgery is not pursued, supportive care measures include antitussives, non-steroidal anti-inflammatory drugs, and pain management. Pain management is an essential part of the treatment plan for patients with HO. Overall, the expected survival following surgery for dogs with primary lung tumors is varied (ranging from months to years after surgery) and depends on the presence or absence of the above prognostic factors.

Even more limited information is available regarding primary lung tumors in cats. Historically, only tumor grade has been shown to be a prognostic factor but a more recent study found that additional factors, such as presence of clinical signs, presence of pleural effusion, and tumor stage higher than T1N0M0, were also negative prognostic factors, as well as tumor grade [20,21]. Outcome following surgery for cats with primary lung tumors is quite variable, with median survival times ranging from days to years depending on these prognostic factors. The prognosis for cats with primary lung tumors with digit metastasis is extremely poor (median survival times of 28 and 67 days reported), and treatment beyond palliative care and eventual euthanasia is rarely recommended [4,5].

Metastatic Pulmonary Nodules

Treatment for patients with pulmonary metastatic disease is purely palliative, aimed at alleviating clinical signs, if possible. Some tumor types may respond to palliative cytotoxic therapy. A clinical benefit (partial response or stable disease) was found in 11 of 23 dogs with osteosarcoma metastasis treated with toceranib phosphate [22]. Median duration of treatment in those dogs was 24 weeks, which is longer than the expected survival for dogs with osteosarcoma pulmonary metastasis.

Mesothelioma and Carcinomatosis

Mesothelioma is a rare cancer in both cats and dogs. Carcinomatosis results from pleural metastasis, most commonly from carcinomas, such as mammary carcinoma. No definitive therapy is currently available for dogs or cats with mesothelioma. All treatments are aimed at palliating the clinical signs associated with the pleural effusion, which is typically what is making the patients feel poorly. Intracavitary chemotherapy with cisplatin was reported in six dogs, four of which had pleural effusion [23]. Resolution of the effusion was noted in all dogs, and the response duration ranged from 129 to greater than 306 days.

A more recent study reported on the outcome of using intracavitary mitoxantrone and carboplatin with or without intravenous doxorubicin in dogs with mesothelioma and carcinomatosis, and in one dog with sarcomatosis [24]. The outcome of these patients was compared to a group of dogs with carcinomatosis who did not receive chemotherapy treatment. Overall, the median survival time was significantly longer for treated versus untreated dogs (332 versus 25 days, $P = 0.001$). Only half of the dogs had thoracic involvement, and all of them had pleural effusion. There were too few dogs with pleural effusion to make statistical comparisons between treated (four) and untreated (two) dogs, and the survival times of the two untreated dogs were not available. The survival times for the four treated dogs ranged from 18 to 299 days.

The use of chemotherapy to decrease the amount of effusion for cats with neoplastic effusions has been published in individual reports, and just one of those reports describes a cat with neoplastic pleural effusion [25,26]. That cat with suspected pleural mesothelioma treated with intracavitary carboplatin died of progressive disease after 4 months [26].

Additional treatment for patients with neoplastic effusions involves glucocorticoids or non-steroidal anti-inflammatory medications, thoracocentesis, and analgesics. The prognosis for these patients depends on the extent of their disease and how much it is affecting their quality of life, as well as their clinical response to treatment.

Conclusion

Primary lung tumors are uncommon in both cats and dogs. Although some patients may have no clinical signs or physical exam abnormalities, others may present on an emergent basis. Such emergent presentations include dyspnea, pain of the limbs or digit, and coughing. Similar emergent presentations may occur in patients with

metastatic pulmonary disease. Initial treatment and diagnostic steps include oxygen supplementation, thoracocentesis (see Chapter 183) in patients with neoplastic effusion, and thoracic radiographs. The prognosis is varied for patients with primary lung tumors and depends on patient status and tumor stage and grade. The prognosis for patients with metastatic lung tumors is uniformly poor, although some palliative cytotoxic therapies are available.

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44

Pneumothorax

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Anatomy

In health, the pleural space is a potential space between two layers of pleura. The visceral pleura line the surface of the lungs and at the root of each lung the pleurae reflect to line the mediastinum, the inside of the thoracic wall, and the diaphragm as the parietal pleurae. The pleurae are serous membranes that secrete a small amount of fluid that allows frictionless sliding of the lungs past the thoracic wall during respiration.

The left and right lungs delineate the left and right sides of the thorax, between which lies the mediastinum. The mediastinum is another potential space wherein lies the heart, the great vessels, the esophagus, trachea, and thymus. The mediastinum is contiguous with the fascial planes of the neck cranially and the retroperitoneal space caudally. Unlike other species, the mediastinum in dogs and cats is fenestrated [1]. If the mediastinal tissue is healthy, fluid and air should equilibrate across the hemithoraces. If there is disease that causes thickening of the pleura, such as mesothelioma or pleuritis, or there are large amounts of fibrin within the pleural cavity, such as which occurs with pyothorax, air and fluid can become trapped within pockets and lateralize.

The presence of a pneumomediastinum or pneumoretroperitoneum almost always means that the source of the air leak is a mediastinal structure. Small leaks of air from the trachea and esophagus tend to remain confined to the mediastinal space, the fascial planes of the neck, and the retroperitoneal space. Only with very large leaks does a pneumothorax develop.

Pathogenesis

Traumatic Pneumothorax

Trauma is thought to be the most common cause of pneumothorax in dogs and cats [1,2]. Both blunt and

penetrating trauma can cause pneumothorax. Examples of blunt trauma include motor vehicle accidents, falls from a height, and being shaken. Blunt trauma causes a closed pneumothorax, meaning the thoracic wall is intact. It is thought that the energy absorbed by the thoracic wall at the time of impact (the trauma) is transmitted to the lungs, resulting in rapid compression of air, a transient increase in airway pressure, and rupture of alveoli [3].

Penetrating trauma to the chest wall such as bite wounds causes an open pneumothorax. Air enters the chest from the outside but there may also be leakage of air internally from damaged alveoli.

Iatrogenic Pneumothorax

Pneumothorax is a potential complication of any medical or surgical procedure involving the airways or thoracic wall. It can occur due to laceration of the alveoli with a needle or scalpel, or rupture of alveoli due to barotrauma such as during general anaesthesia if the pop-off valve is closed. A very common cause of iatrogenic pneumothorax is thoracocentesis. The risk is particularly high if the pleura is thick due to chronic irritation by a long-standing effusion and fails to seal the hole or if the system used during thoracocentesis is not airtight (see Chapter 183).

Spontaneous Pneumothorax

Spontaneous pneumothorax occurs when air enters the pleural space in the absence of a traumatic event. *Primary* spontaneous pneumothorax occurs in seemingly normal lungs, without the presence of underlying pulmonary parenchymal disease. *Secondary* spontaneous pneumothorax occurs when lung tissue

is weakened by underlying disease, causing alveoli to rupture.

Primary Spontaneous Pneumothorax

This type of pneumothorax has not been reported in cats but is the most common cause of spontaneous pneumothorax in dogs [4–6]. It is caused by rupture of air-filled pulmonary blebs or bullae. Blebs are blister-like lesions within the layers of the visceral pleura, usually located at the lung apices. It is thought that they form when air escapes from within the lung parenchyma and travels to the surface of the lung. They can range in size up to several centimeters in diameter. Bullae are pockets of air that result from the destruction and confluence of adjacent alveoli. They can occur in any location within the lung parenchyma and vary in size from very small (involving only a few alveoli) to involving a majority of a lung lobe.

It is unclear why pulmonary blebs and bullae form. In humans, they typically occur in young males with an ectomorphic (tall, thin) body type [7]. Similarly, in dogs the typical patient is a young to middle-aged large-breed or deep-chested dog. Siberian huskies were overrepresented in one study [5]. No sex predilection has been found.

There is a growing body of evidence that blebs and bullae may be caused by microscopic lung diseases previously unknown to the medical community. Dysfunctions of enzymes such as alpha-1 antitrypsin, which prevents protease-induced destruction of the alveoli, have been suggested as a cause [8] but this has not been proven in humans or dogs.

Secondary Spontaneous Pneumothorax

There is no typical patient that develops secondary spontaneous pneumothorax. Rather, there are patients that commonly develop the underlying pulmonary diseases that lead to the pneumothorax. In dogs, some reported underlying diseases include neoplasia [5,9], pulmonary abscess [10], mycotic granulomas [11], heartworm disease [12,13], and pulmonary thromboembolism [14]. In cats, the most commonly reported underlying disease is lower airway disease [15–18] (asthma) followed by neoplasia [17,18].

A full list of all reported causes of pneumothorax in dogs and cats is provided in Table 44.1.

Table 44.1 Causes of pneumothorax.

Category	Species	Underlying causes
Primary spontaneous	Dogs	Pulmonary blebs
		Pulmonary bullae
	Cats	Not reported

Category	Species	Underlying causes
Secondary spontaneous	Dogs	Neoplasia
		Bacterial pneumonia
		Mycotic granuloma
		Parasitic granuloma
		Heartworm
		Pulmonary abscess
		Pulmonary thromboembolism
		Congenital lobar emphysema
		Reactive bronchopneumopathy
		Uremic pneumonitis
	Cats	Lower airway disease
		Neoplasia
		Heartworm
		Pulmonary abscess
		Lungworm
		Bronchopulmonary dysplasia
		Bacterial pneumonia
		Pulmonary thromboembolism
Traumatic	Dogs and cats	Blunt trauma:
		motor vehicle accident
		falls from a height (including “high-rise” syndrome)
		kicking
		shaking
		Penetrating trauma:
		bite wounds
		gunshot wounds
		stabbing
		impalement
Iatrogenic	Dogs and cats	migrating foreign body
		Thoracocentesis
		Post lung fine needle aspirate or biopsy
		Leakage from alveoli or bronchi following partial or full lung lobectomy
		Leakage around thoracostomy tubes
		Traumatic intubation (cats)
		Jugular venepuncture
		Barotrauma – positive pressure ventilation or closed pop-off valve
		Bronchoscopy
		Feeding tube misplacement
		Intervertebral disk fenestration
		Gastropexy (circumcostal)

Clinical Consequences of Pneumothorax

The degree of respiratory compromise following development of pneumothorax depends on the volume of air and the patient's innate pulmonary reserve. When air enters the pleural space, the negative intrapleural pressure which keeps alveoli open is lost and the result is atelectasis. The larger the volume of air, the greater number of alveoli affected and the less the gas exchange capability. Severe atelectasis leads to the development of pulmonary shunt and severe hypoxemia.

Patients with pneumothorax compensate for the loss of functional pulmonary volume by breathing at a faster rate to maintain minute ventilation and prevent hypoxemia. A patient with concurrent pulmonary disease such as pulmonary contusions will become clinical for a pneumothorax at smaller volumes of air than a patient with healthy lungs as they have fewer healthy alveoli to start with.

Pneumothorax also has cardiovascular consequences via its effect on intrapleural (intrathoracic) pressure). As the volume of pneumothorax increases, the intrapleural pressure rises (become less negative or even positive) and this pressure is exerted onto the intrathoracic vessels, reducing their volume capacity and subsequently, venous return. *Tension* pneumothorax is the most severe type of pneumothorax. Though various definitions exist, it is generally regarded to be the point at which intrapleural pressure exceeds central venous and pulmonary artery pressures, causing cardiogenic shock as well as severe hypoxemia [19]. Tension pneumothorax can occur immediately after injury with very large, rapid accumulations of air, or over time if the air leak acts like a valve, opening on inspiration to allow air into the plural space but closing on expiration so the air can't get out. Tension pneumothorax is a true medical emergency and without rapid decompression, it is fatal.

Physical Examination

The classic clinical findings in a patient with pneumothorax are tachypnea or dyspnea with soft or absent lung sounds. Quiet lung sounds are particularly significant in tachypneic patients, as lung sounds should get louder with increasing respiratory rate due to increasing turbulence of air within the airways. Patients with pneumothorax often also exhibit paradoxical abdominal motion. This is an abnormal respiratory pattern in which the thorax and abdomen move in opposite directions and indicates a very high level of work of breathing. For patients with paradoxical abdominal motion, during inspiration, the diaphragm is pulled cranially,

causing the abdomen to get smaller while the thorax expands. During expiration, the diaphragm moves caudally causing the abdomen to expand while the thorax gets smaller.

Air travels "up," so the location of the majority of air will depend on the recumbency of the patient. If standing or in sternal recumbency, the air will be in the dorsal aspect of the chest. If in lateral recumbency, it will lie mostly in the non-dependent hemithorax. Patients with pleural space disease often appear to have abdominal pain. This may be because abdominal palpation further reduces thoracic volume and causes the patient to breathe faster, which can be interpreted as a pain response.

Other clinical signs may be present if there is concurrent disease. Patients who have experienced trauma are likely to have other thoracic injuries such as pulmonary contusions and rib fractures [20–22]. They may also have injuries to other parts of the body. Patients with pulmonary neoplasia may be thin or have a palpable primary abdominal tumour.

Diagnosis

Thoracocentesis

Unless confirmed beforehand on ultrasound or a radiograph, one can never be sure that a pneumothorax performed after thoracocentesis was not iatrogenic. However, it is preferable to perform "blind" thoracocentesis on a dyspneic patient suspected of having a pneumothorax rather than delay life-saving treatment. In these cases, thoracocentesis is both therapeutic and diagnostic. If aspiration of air from the pleural space eases the patient's tachypnea or dyspnea, you can be fairly certain they had pneumothorax.

Ultrasound (see Chapter 182)

While harder to interpret than radiographs, thoracic ultrasound has the benefit of being bedside, limiting time to diagnosis and stress on the patient. The use of ultrasound as a diagnostic tool in thoracic trauma is known as thoracic focused assessment with sonography for trauma (TFAST). In a normal thorax, the parietal and visceral pleura can be visualized as two hyperechoic lines sliding past each other during normal respiration. This is called the "glide sign." Pneumothorax is diagnosed if the glide sign is absent [23]. Ultrasound can also be used to diagnose concurrent intrathoracic conditions such as pleural effusion/hemothorax, pericardial effusion, and alveolar fluid.

Radiography

Radiographs remain the primary modality for diagnosing pneumothorax. Care must be taken not to precipitate respiratory crisis when moving and restraining dyspneic animals in radiology. Sedation and oxygen supplementation should be provided, or the clinician should consider performing thoracocentesis if the likelihood of pneumothorax is high. One or two views of the thorax is usually sufficient to make a diagnosis. Pneumothorax is visualized as a radiolucent area adjacent to the chest wall or diaphragm where no pulmonary tissue can be seen. This can be difficult to appreciate in patients with concurrent subcutaneous emphysema. With large pneumothoraces, the heart can appear to become elevated off the sternum on the lateral view.

Computed Tomography

Computed tomography (CT) can detect much smaller volumes of air than radiography and, as such, is the gold standard test for diagnosing pneumothorax. It is generally not used in patients who are clinical for pneumothorax as obtaining good images requires general anesthesia and breath-holding techniques which can worsen alveolar air leak.

Determining the Underlying Cause of Pneumothorax

Atelectasis hinders the radiographic assessment of the pulmonary parenchyma by causing an alveolar pattern, which can persist after thoracocentesis and is easily confused with mass lesions. CT is better at differentiating atelectasis from mass lesions, particularly if intravenous (IV) contrast is used. CT is more sensitive than radiology in the detection of pulmonary blebs and bullae [4] but overall sensitivity is low, around 50% [24]. If the underlying cause for spontaneous pneumothorax is not evident on imaging, or imaging is declined by the pet owner, surgical explore is the next step.

The presence of concurrent thoracic injuries such as pulmonary contusions and rib fractures is supportive of trauma as a cause of pneumothorax although non-traumatic rib fractures have been reported in cats associated with pulmonary disease, chronic renal failure, and neoplasia of the ribs [25]. Non-traumatic rib fractures tend to occur in the midbody of the rib, whereas traumatic fractures tend to occur closer to the vertebrae [25].

The presence of pneumomediastinum or pneumoretroperitoneum is a clue that the source of air leak is a mediastinal structure.

All patients with suspected secondary spontaneous pneumothorax should undergo testing for pulmonary parasites. Fine needle aspirates can be taken of mass

lesions for cytology, but the risk of pneumothorax must be weighed against the benefits of proceeding directly to surgery for excisional biopsy in such cases.

Treatment

Patients who are clinical for their pneumothorax need to have the air evacuated. Clinical signs will develop at lower volumes of air in patients with concurrent lung disease compared to those with healthy lungs. Thoracocentesis is the first-line treatment, followed by thoracostomy tubes and continuous suction if needed (see Chapter 183).

Patients who present with a severe tension pneumothorax can alternatively be intubated and placed on 100% oxygen and have a hole (stab with scalpel blade) made in the chest wall to evacuate air rapidly. If this occurs, the clinician must remember to provide the patient with positive pressure ventilation as the thorax is now open and negative intrapleural pressure has been lost. Thoracostomy tubes should then be placed. Patients with pneumothorax who have arrested must have open chest CPR performed (see Chapter 150).

Supplemental oxygen delivered via nasal lines, oxygen hood, or oxygen cage is required in patients who remain hypoxemic (see Chapter 181). This can be due to persistent pneumothorax, atelectasis, or concurrent pulmonary disease. It has long been thought that supplemental oxygen may also speed resolution of remaining pneumothorax by encouraging nitrogen (which makes up almost 80% of atmospheric air) to travel down its concentration gradient from the pleural space to peripheral blood. However, a recent study in infants failed to show any benefit [26].

Further pulmonary work-up for patients with traumatic pneumothorax is generally not required. Patients with spontaneous pneumothorax should have further work-up for the underlying cause as well as specific therapy for the underlying condition to prevent recurrence. Lung lobectomy to remove blebs, bullae, and other pulmonary lesions is recommended in dogs with spontaneous pneumothorax, whereas medical therapy may be the best approach in cats.

Patients with persistent pneumothoraces can benefit from (more) surgery to remove or repair the leaking tissue, pleurodesis, or a relatively new technique called blood patching.

Thoracostomy Tubes

Thoracostomy tubes allow for repeated drainage of air without the need for repetitive needle punctures, and for the continuous suction of air. They can also be used for pleurodesis and blood-patching procedures.

Thoracostomy tubes should be placed in patients with large or continuous air leaks. The general criteria for placement of thoracostomy tubes in cases of pneumothorax are:

- presence of tension pneumothorax (indicative of a large air leak)
- need for >2 thoracocenteses per hour (indicative of continuous air leak)
- post thoracotomy.

There are two main types of thoracostomy tubes: large-bore tubes and smaller tubes placed via the Seldinger technique. Large tubes are preferred for large dogs, for use in continuous suction, and for the removal of fluid but they require general anesthesia and are more uncomfortable than smaller tubes, which can be placed using sedation and local block. It is possible to manage a patient on continuous suction with a small-bore tube. Please refer to Chapter 184 for instruction on how to place thoracostomy tubes.

Thoracostomy tubes must be well secured to the patient to prevent their inadvertent removal and the patient should wear an Elizabethan collar so they cannot chew on the tubes. Thoracostomy tubes cause the patient discomfort so analgesia must be provided. Some patients will require sedation to be safely managed while thoracostomy tubes are in place.

Continuous Suction

Continuous suction of air from the thorax is an option in patients which are producing too much air to be managed safely by intermittent drainage. The patient's thoracostomy tubes are attached to a commercial suction unit. The unit ensures that no more than 20 cmH₂O negative pressure is applied to the chest, as anything greater than this may injure lung tissue and prevent the leak from healing.

Pleurodesis and Blood Patching

Pleurodesis is a procedure that causes adherence of the parietal and visceral pleurae, obliterating the pleural space. It is achieved by the instillation of irritating substances such as talcum powder into the pleural space, or mechanical abrasion of the pleural surface (such as with dry gauze sponges) to cause pleuritis and the formation of adhesions between the two layers. These techniques are employed in cases of persistent pneumothorax in people, including post lung lobectomy. The use of both methods has been described in veterinary medicine but they are not commonly performed [27].

In blood patching, autologous, non-anticoagulated whole blood is instilled into the pleural space with the intention of sealing an air leak. It is theorized that the seal occurs when fibrin, which forms as the blood coag-

ulates, adheres to the leaking tissue and plugs the defect [28]. As such, blood patching is not "true" pleurodesis. There are reports of the successful use of blood patching in dogs [28,29]. The success rate in humans following single or multiple blood patches is 75–85% [30–33]. In some reports, the seal was achieved immediately.

Blood patching is a relatively simple procedure. The patient needs to have a thoracostomy tube or a needle/catheter in the pleural space and a large IV catheter from which peripheral blood can be drawn, ideally in the jugular vein. Blood is removed via the IV catheter in 20–50 mL increments then immediately injected through the thoracostomy tube. The tube is then flushed with plain saline to prevent clogging. This is repeated until the desired amount of blood is used (5–10 mL/kg). Both unilateral and bilateral blood patching have been described. If unilateral, the patient should be placed in various recumbencies to encourage the movement of blood across the mediastinum so it comes in contact with as much pleura as possible. The thoracostomy tubes should not be aspirated for a few hours to give the blood time to make a seal.

Reported complications of blood patching include fever, pleural effusion, and pyothorax [34]. Infection can be limited by employing sterile techniques. Sometimes multiple blood patches are required to achieve a complete seal.

Lung Lobectomy

Surgery is rarely required in traumatic pneumothorax but has a role in spontaneous pneumothorax. The goal of surgery is to remove the leaking pulmonary tissue but there is also a diagnostic benefit through histopathology. Surgery may be curative, depending on the underlying cause of the pneumothorax.

Dogs with spontaneous pneumothorax tend to have disease isolated to a single or small number of lung lobes that can be removed in their entirety without affecting ventilation. For this reason, surgery has been associated with lower recurrence and mortality rates than medical treatment alone and is the treatment of choice in dogs [5,34]. This differs from cats which tend to have widespread disease and surgery has been associated with poor outcomes [17,18].

In cases of multiple pulmonary lesions, it may not always be apparent which lesion is leaking air, particularly if the leak has since sealed. This is especially common in dogs with pulmonary blebs and bullae and is a cause of persistent air leak postoperatively.

Medical Therapy for Secondary Spontaneous Pneumothorax

For patients with widespread lung disease or for which surgery is otherwise not possible, treatment is limited to

pneumothorax management, blood patching, and other therapies for underlying lung disease, if present. For example, for cats with lower airway disease, this may include bronchodilators and corticosteroids. Supplemental oxygen may be used in the short term to alleviate hypoxemia or

hasten resorption of remaining pneumothorax. Prognosis for these cases is variable and depends on the underlying disease. Cats with lower airway disease appear to have a good chance of surviving to hospital discharge, although little long-term follow-up has been reported on these cases.

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Pleural Effusion*Lori Waddell, DVM, DACVECC**School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA, USA***Introduction**

A wide variety of diseases result in accumulation of fluid in the pleural space, which causes respiratory compromise as the expansion of the lungs is inhibited. Pleural effusions are classified based on the gross appearance, protein content, specific gravity, total nucleated cell count, and cytological characteristics of the cells. Samples should be evaluated based on the total nucleated cell count and protein levels, as well as aerobic and anaerobic cultures, if indicated. Analysis of biochemical parameters such as triglyceride and cholesterol levels is indicated if the effusion is suspected to be chylous, and should be compared to serum levels. By identifying which type of effusion is present, the possible causes of the effusion may be determined and will guide the diagnostic work-up for individual patients.

In dogs, common disease processes that cause pleural effusion include pyothorax, pericardial effusion, a cranial mediastinal mass, chylothorax, metastatic neoplasia in the pulmonary parenchyma, dilated cardiomyopathy, and right-sided heart failure [1]. In cats, the most common underlying diseases associated with pleural effusions are pyothorax, mediastinal lymphoma, heart disease, and feline infectious peritonitis (FIP) [2].

Bilateral pleural effusion is much more common in dogs and cats than unilateral pleural effusion, suggesting that the mediastinum is easily disrupted or functionally incomplete. Drainage of one hemithorax often provides drainage of the other side, but not always.

Clinical Signs

The respiratory signs caused by pleural effusion are all secondary to reduced lung expansion (and tidal volume), which initially results in rapid, shallow breathing. Dyspnea may also be characterized by increased

abdominal effort. Ultimately, the animal may exhibit an orthopedic position with the elbows abducted and neck extended to minimize any resistance to breathing. A paradoxical breathing pattern has been strongly associated with pleural space disease in cats [3]. If hypoxia becomes severe, the mucous membrane may become pale or even cyanotic.

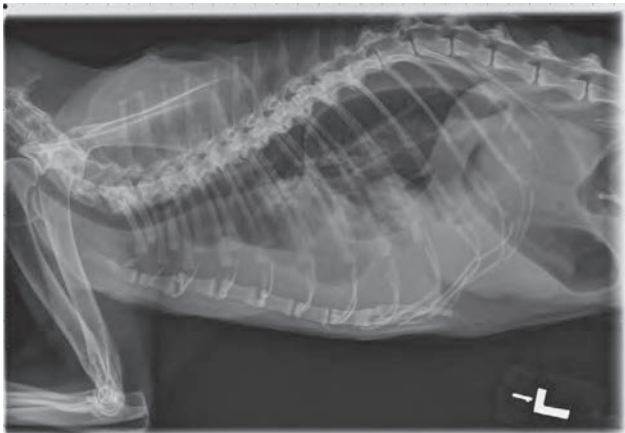
Thoracic auscultation reveals dull lung and heart sounds ventrally but they are often still present dorsally. The degree of respiratory compromise is typically proportional to the volume of fluid within the pleural cavity and the rate of accumulation. Fluid that accumulates gradually may reach a larger volume before producing clinical signs. Once a certain volume is exceeded, which has been reported to be 30–60 mL/kg in dogs and 20 mL/kg in cats, critical respiratory compromise exists and rapid decompensation can occur [4,5]. Other signs that may be present, depending on the etiology of the pleural effusion, include coughing, pyrexia, depression, anorexia, weight loss, arrhythmias, murmurs, ascites, and signs of hypovolemic shock.

Initial Treatment

Immediate recognition of the patient in respiratory distress is essential. Oxygen supplementation should be provided while the physical examination is performed (see Chapter 181). If tolerated by the patient, an IV catheter should be placed to allow for sedation if needed and vascular access if the patient arrests during handling. If pleural effusion is strongly suspected based on auscultation of the chest, thoracocentesis should be performed for both diagnostic and therapeutic reasons (see Chapter 183). If available, a quick ultrasonographic scan of the chest can confirm the presence and location of the effusion to facilitate thoracocentesis (see Chapter 182). Thoracocentesis will help stabilize the patient and



(a)



(b)

Figure 45.1 Ventral-dorsal and left lateral radiographs from a 12-year-old MC DSH who presented for difficulty breathing. On auscultation, his lung and heart sounds were muffled and a gallop rhythm was heard. Thoracocentesis removed 105 mL of a red-tinged fluid that on cytology was classified as a neoplastic effusion with carcinoma cells present. On radiographs taken after thoracocentesis (not pictured), a moderate pleural effusion was still present bilaterally, and a mineralized pulmonary mass could be seen in the right middle or ventral part of the right caudal lobe.

provide a sample of the fluid for diagnostic evaluation. Thoracic radiographs are not necessary if there is a strong clinical suspicion of pleural effusion or effusion can be confirmed by ultrasound, and radiography may pose a

significant risk to a patient in severe respiratory distress. Radiographs after thoracocentesis may show an underlying cause that would have been obscured by the presence of fluid and collapse of the lung lobes (Figure 45.1). If an animal remains dyspneic or hypoxemic after successful aspiration of pleural fluid, concurrent heart or lung disease should be suspected.

The patient's cardiovascular system should also be assessed to determine if any treatment is necessary to stabilize cardiovascular parameters. This may include the need for a bolus of IV fluids if hypovolemic or septic shock is present, or diuretics if the patient is suffering from volume overload or pulmonary edema secondary to congestive heart failure.

Types of Effusions

Transudates

Transudates are the result of a disturbance in the balance of capillary hydrostatic pressure, intravascular oncotic pressure, and vascular endothelial permeability that are responsible for the formation of pleural fluid and the rate of pleural fluid absorption. Decreased absorption can occur secondary to inflammation of the pleura, obstruction of the pleural lymphatics with neoplasia or emboli, or lymphatic hypertension.

A pure transudate (Table 45.1) can be seen with severe hypoalbuminemia caused by a protein-losing enteropathy or nephropathy, hepatic disease or marked loss of inflammatory fluid through a wound or into a body cavity. Typically, the albumin level must be <1.5 g/dL for effusion to occur [6]. Animals with hypoalbuminemia may also have ascites or peripheral edema.

Cardiac disease can affect the formation and absorption of fluid in the pleural space by increasing pulmonary and systemic capillary hydrostatic pressures. Dogs typically develop pleural effusion with right-sided or bilateral congestive heart failure while cats may develop pleural effusion with right- or left-sided congestive heart failure. The fluid that is seen with heart disease is typically a modified transudate (slightly higher protein level than a pure transudate; see Table 45.1).

Table 45.1 Characterization of pleural effusions.

Fluid type	Total protein	Total nucleated cell count
Pure transudate	<2.5 mg/dL	$<1500/\mu\text{L}$
Modified transudate	$2.5\text{--}7.5$ mg/dL	$1000\text{--}7000/\mu\text{L}$
Exudate	>3.0 mg/dL	$>7000/\mu\text{L}$

Lung lobe torsion or a diaphragmatic rupture can obstruct venous and lymphatic drainage, resulting in leakage of fluid through the organ capsule into the pleural space, causing a modified transudate. Chylous and hemorrhagic effusions may also be seen with lung lobe torsions. Afghan hounds and pugs appear to be predisposed to lung lobe torsions [7,8]. Lung lobe torsion may occur as a primary entity, particularly in deep-chested dogs, but may also occur secondary to pleural effusion in any breed. This can make it difficult to determine whether the pleural effusion or the lung lobe torsion occurred first. Underlying causes for pleural effusion should be ruled out. Lung lobe torsion has been associated with trauma, chylothorax, pulmonary neoplasia, respiratory disease, and thoracic surgery. The right middle lung lobe and right cranial lung lobe are most frequently affected. Thoracic radiographs after pleural drainage often show diffuse consolidation of a lung lobe and altered orientation or abrupt termination of the lobar bronchi. Lung lobe torsion requires immediate surgical treatment to remove the affected lobe.

Neoplasia that does not exfoliate may result in a modified transudate by obstruction of lymphatic drainage. Systemic inflammatory response syndrome (SIRS) can cause a modified transudate from increased endothelial permeability.

Hemorrhagic Effusion

A hemorrhagic effusion will appear grossly bloody, will not clot, and will have a packed cell volume (PCV) of at least 10%. Typically, the PCV of the effusion will be within 10% of the patient's peripheral PCV.

The most common cause of hemorrhage into the pleural cavity is thoracic trauma, such as fractured ribs or pulmonary parenchymal lacerations. A small amount of hemorrhage is common after thoracic surgery and this may be marked if an intercostal vessel has been lacerated. An intrathoracic tumor or a coagulopathy (e.g. anticoagulant rodenticide toxicity) may result in spontaneous hemorrhage into the pleural cavity. Other reported causes of a hemothorax include diaphragmatic hernia, hiatal hernia, pulmonary thromboembolism, *Spirocerca lupi*, and dirofilariasis as well as iatrogenic hemorrhage from jugular venepuncture or catheter placement, thoracocentesis, and fine needle aspirates or biopsy of intrathoracic structures.

Patients with hemothorax often require supportive treatment with fluid therapy and blood products as they usually have significant signs of cardiovascular shock in addition to respiratory compromise. If the bleeding is secondary to anticoagulant rodenticide toxicity, treatment with vitamin K1 and active clotting factors from fresh whole blood or fresh frozen plasma must also be provided (see Chapter 70).

Neoplastic Effusion

Primary and metastatic thoracic neoplasia may produce variable types of pleural effusion by causing inflammation of the pleura, hemorrhage, and/or obstruction of lymphatic drainage. These effusions may be classified as a transudate, exudate, or hemorrhagic. Not all tumors will exfoliate readily into the effusion so the absence of neoplastic cells on cytology does not rule out neoplastic disease. Mediastinal lymphosarcoma may exfoliate lymphoblasts into pleural fluid. Pulmonary or metastatic carcinoma can sometimes be diagnosed on cytology. Mesothelioma (neoplasia of the pleura) is usually characterized by a severe pleural effusion and may also affect the pericardium, causing a pericardial effusion. It is particularly difficult to differentiate reactive mesothelial cells from malignant cells on cytology. Biopsy of the pleura is indicated in these cases. A modified transudate may be seen with neoplasia, which can make diagnosis of the cause of effusion challenging, and may require imaging of the chest, including thoracic radiographs, ultrasound, and CT with contrast. Fine needle aspirates and/or biopsy are often required to definitively diagnose intrathoracic neoplasia.

Intracavitary chemotherapy, thoracic omentization, or placement of a pleural-peritoneal shunt may provide palliative therapy for some patients with diffuse disease in which primary surgical intervention is unlikely to be curative.

Exudates

These effusions are characterized by a high protein level and high nucleated cell count, with or without the presence of bacteria (see Table 45.1). Pyothorax, which causes a septic exudate, often contains predominantly degenerative neutrophils, typically with intra- and extracellular bacteria. It occurs in both dogs and cats but is more common in cats. Mixed populations of bacteria are often cultured from both species (see Chapter 46).

In non-septic exudates, the predominant cell type may include non-degenerative neutrophils (inflammation), small lymphocytes (chylothorax), or neoplastic cells, depending on the underlying cause. A major cause of non-septic exudates in cats is FIP, and both pleural and peritoneal effusions often occur with this disease. Effusions caused by FIP typically have a protein concentration of greater than 4.0 g/L and a total nucleated cell count of $2.0\text{--}6.0 \times 10^9/\text{L}$ [9]. Serum hyperproteinemia, with or without hypoalbuminemia, is also a common finding. FIP can also cause a modified transudate pleural effusion.

It has been suggested that cat pleural effusions be categorized into transudates or exudates based on additional

criteria, eliminating the traditional categorization into pure transudates, modified transudates, and exudates [10]. The pleural fluid lactate dehydrogenase level and the pleural fluid protein to total protein ratio were found to be the most reliable measures to distinguish between transudates and exudates [10].

Chylous Effusions

Chylothorax is the accumulation of lymphatic fluid in the pleural space that leaks from the thoracic duct system. Thoracic duct fluid has three main sources: lymph of hepatic origin, from the hindlimbs, and from the intestines. Chyle is lymphatic fluid drained from the intestines and has a high fat content, giving chylous fluid its milky appearance. This fat is mainly in the form of chylomicrons, which are aggregates of triglycerides, phospholipid, lipoprotein, and cholesterol. In addition to chylomicrons, thoracic duct lymph contains fluid and proteins similar to that of plasma. The thoracic duct system provides the major pathway for the return of fluid and protein from the interstitial space to the circulation.

Chylothorax can affect any breed of dog or cat but Afghan hound and shiba inu dogs and Oriental breeds of cats such as Himalayan and Siamese may be predisposed [11,12]. A fluid analysis (including cell count) should be performed and fluid triglyceride levels determined. Chylous effusions are generally either white or pink. The specific gravity of chylous effusions can range from 1.022 to 1.027 in dogs and from 1.019 to 1.050 in cats. Total protein concentrations can range from 2.5 to 6.2 g/dL in dogs and 2.6 to 10 g/dL in cats. The total nucleated cell count is usually less than 10000 WBC/ μ L in both species and is predominantly the small lymphocyte [11,12]. Chylothorax is diagnosed by evaluation of a pleural fluid triglyceride level. The concentration of pleural fluid triglycerides will be higher than that of serum triglycerides. In one study, all dogs with pleural fluid triglycerides > 100 mg/dL had chylothorax [13]. This difference is usually marked (10-fold difference or greater) unless the affected animal is anorexic, in which case pleural triglyceride levels can drop towards those of serum levels.

Chylothorax remains difficult to treat because of lack of identification of the underlying cause. Congenital cases have been described but are rare. In the majority of dogs and cats, chylothorax is associated with dilation of ("lymphangiectasia") and leakage from the thoracic duct lymphatic system. Experimentally, thoracic duct system lymphangiectasia and leakage can be produced by ligating the cranial vena cava close to the right atrium, so conditions that increase pressure in the cranial vena cava have the potential to cause chylothorax [14]. Thoracic duct system lymphangiectasia and leakage can also occur secondary to physical obstruction caused by neoplasia.

Chylothorax has been associated with heart disease (including congenital conditions, heart base tumors, and cardiomyopathies), pericardial disease, thoracic duct obstruction (neoplasia or granuloma), mediastinal lymphosarcoma or thymoma, foreign body or fungal granulomas, heartworm disease, lung lobe torsion, diaphragmatic hernia or peritoneopericardial hernia, transvenous pacemaker implantation in cats, and cranial vena caval thrombosis [15]. Chylothorax can also occur associated with more generalized lymphatic abnormalities such as intestinal lymphangiectasia and lymphangioma. Previously, many cases of chylothorax were thought to be traumatic in origin, with chylous fluid leaking from a ruptured thoracic duct system. However, many cases had no history of trauma, and experimentally the thoracic duct system in normal dogs heals rapidly after deliberate transection [16].

If an underlying condition causing the chylothorax is not identified, it is classified as idiopathic. Some of these cases may eventually reveal an underlying cause, such as microscopic neoplasia obstructing the thoracic duct system that is undetectable without a surgical or post-mortem biopsy.

Treatment should be aimed at any identifiable disease causing chylothorax. If no cause is identified, general medical management may include intermittent thoracentesis, a reduced-fat diet, increased intake of medium-chain triglycerides, and the use of benzopyrones. Benzopyrones (rutin) are used to theoretically increase chyle reabsorption from the pleural space [17]. Although chylothorax resolves in some treated animals, it is not clear if this is as a result of the benzopyrone treatment or represents spontaneous resolution of the disease. Rutin has been recommended at doses ranging from 50 to 100 mg/kg orally three times daily.

Surgery is indicated to obtain biopsy samples to confirm underlying disease, to remove non-lymphomatous mediastinal masses or lung lobe torsions, and to treat cases that are idiopathic and have not responded to conservative therapy. Thoracic duct ligation has been the mainstay of surgical chylothorax treatment for many years. After thoracic duct ligation, many new lymphatic-to-venous anastomoses form in the abdominal cavity to transport lymph to the venous system, bypassing the thoracic duct system. Successful thoracic duct ligation resolves the chylothorax completely; however, in 20–50% of dogs and 50–80% of cats, either chylothorax or a serosanguineous pleural effusion persists after surgery [18]. Reasons for failure of surgical treatment include branches of the thoracic duct system not visualized or ligated during surgery, and persistence of the underlying disease.

Placing the omentum into the thoracic cavity and removing the pericardium are procedures that were

initially used when thoracic duct ligation failed to resolve chylothorax. Both of these procedures are now being used as primary surgical treatments for chylothorax, either together or combined with thoracic duct ligation [19,20]. The omentum has a substantial blood and lymphatic supply and is thought to either act as a physiological drain when placed into the thoracic cavity or assist in sealing the leaking thoracic duct system. Primary pericardial disease or pericardial thickening in response to chronic chylous effusion is thought to potentially elevate caval pressure and contribute to chylothorax in some cases. Thoroscopic techniques have been developed to try to reduce morbidity and patient recovery time [21]. Ablation of the cisterna chyli can also be performed as an adjunctive treatment to decrease lymphatic flow to the thoracic duct and is often combined with these other procedures [22].

Pleuroperitoneal shunting has been used to treat chylothorax when thoracic duct ligation has failed. In this technique, a commercially available shunt catheter is implanted and the owner pumps pleural fluid into the peritoneal cavity [23]. Potential complications include dislodgment and flipping of the pump chamber and obstruction of the pump chamber with fibrin.

Conclusion

Pleural effusion causing respiratory distress is a common cause of both dogs and cats presenting to an emergency room. Rapid recognition and appropriate therapy, including thoracocentesis, are essential for these patients. Fluid analysis and cytology are a vital part of the diagnostic work-up.

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Pyothorax

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Introduction

Pyothorax, or thoracic empyema, is an accumulation of purulent fluid in the pleural cavity resulting from the presence of an infectious agent. The overall incidence of pyothorax in dogs and cats has not been established [1]. One study looking at 81 cases of canine pleural and mediastinal effusions determined that the most common type of effusion was pyothorax, diagnosed in 16% of cases [2], while a review of pleural effusion in 82 cats documented pyothorax in 14.5% of cases [3]. Retrospective studies have demonstrated that pyothorax in small animals can be unilateral or bilateral, though the majority of cases involve bilateral effusions [4–11].

Etiology

In small animals, identification of an underlying cause for pyothorax is often undetermined. A definitive etiology in dogs has been reported in 4–22% of cases [4–6], while an underlying cause was found in 35–67% of cases reported in cats [3,8,9,12].

In dogs, reported causes include foreign body migration, penetrating thoracic trauma, hematogenous or lymphatic spread, esophageal perforation, parasitic migration, progression of discospondylitis, parapneumonic spread, neoplasia, ruptured lung abscesses, and iatrogenic causes (thoracic surgery or thoracocentesis) [1,4–7,10,11,13–19]. When identified, the most common documented cause is a migrating grass awn or plant material, though the incidence of inhaled foreign material will likely vary based on region, climate, vegetation, and prevalence of working-type breeds [1,13,14].

In cats, reported etiologies include parapneumonic extension, penetrating thoracic wounds, foreign body migration, parasitic migration, and hematogenous

spread [1,3,6,8,9,13,14,20–25]. While the leading cause in cats is currently unknown, a common belief exists that direct inoculation by cat bites may be a predominant cause. This is supported by studies showing that bacterial organisms isolated from pleural infections are similar to those found in cat-bite abscesses [9,26–28]. Additionally, cats with pyothorax are 3.8 times more likely to live in multicat households [9] and a higher incidence of pyothorax occurs in late summer and fall, when outdoor activities such as fighting and mating may be increased [9,25]. Nonetheless, no significant increase in risk for pyothorax has been established in outdoor or male cats, and recent histories of wounds have only been documented in a minority of cases [1,3,6,8,9,21,25]. A recent review demonstrated that only 15.6% of feline pyothorax cases described in the literature (20 out of 128 total cases) resulted from bite wounds [1].

An alternative explanation for increased incidence of pyothorax in multicat households could stem from the additional risk for development of upper respiratory tract infections, which could predispose cats to colonization of the lower respiratory tract by normal oropharyngeal flora [1,8,14,21]. Multiple studies have demonstrated pneumonia or pulmonary abscessation in association with pyothorax and have suggested that parapneumonic spread may be a more common mechanism to cause pyothorax [1,3,8,12,20,21,29].

Microbiology

A high prevalence of polymicrobial infections is documented in dogs and cats, with commonly cultured organisms including obligate anaerobes or a mixture of obligate anaerobes with facultative aerobic bacteria [4–11,20,27,28]. The oral cavity and upper respiratory tract appear to be common sources of these organisms

and represent the typical microflora found. Fungal organisms are rarely reported but include *Cryptococcus* spp., *Candida albicans*, and *Blastomyces dermatitidis* [8,21,30]. Geographic differences likely exist, as grass awns are regionally prevalent and are associated with *Actinomyces* [5–7,15,28].

Signalment

While pyothorax can occur in any animal, it tends to be a disease of younger dogs and cats, typically 3–6 years [1,3–9,13,14]. However, case reports have described pyothorax in a 1- and 4-month-old kitten [23,31] and a neonatal boxer [32]. No sex or breed predilections have reached statistical significance, though some groups are more reported in the literature. Male dogs and cats appear overrepresented in multiple studies [5,6,8,9]. Amongst dogs, medium and large breeds are more commonly reported, with hunting breeds overrepresented [5–7,10]. Amongst cats, domestic shorthairs and domestic longhairs are most often described but are not overrepresented compared to local populations [3,6,9].

Clinical Signs and Physical Examination Findings

Clinical signs of pyothorax are often non-specific, can be acute or chronic, and may be related to pleural effusion or pulmonary abscessation. Common presenting signs include tachypnea, cough, anorexia, lethargy, and weight loss or signs referable to pleural effusion. As 50% or fewer of cats may present with fever, a normal body temperature should not rule out pyothorax [6,8,9]. Additional signs may be consistent with systemic inflammatory response syndrome or sepsis. In a study of 80 cats with pyothorax, 40% fit the clinical criteria for sepsis [9]. In a retrospective study of 29 cats with severe sepsis, pyothorax was found to be the most common underlying disease [29]. The occurrence of sepsis in dogs with pyothorax is unknown.

Diagnosis

Pyothorax, or at least pleural effusion, may be suspected based on history and physical examination findings. Thoracic imaging is utilized to identify pleural effusion, but definitive diagnosis of pyothorax requires thoracocentesis with cytological examination of pleural fluid. Aerobic and anaerobic culture and susceptibility are recommended, but multiple studies document a <100% culture positive rate. Grossly, the fluid may appear turbid

or opaque, may have flocculent material, and can have a malodorous smell if an anaerobic infection is present.

Clinicopathological Findings

The most frequent hematological abnormalities are anemia and a neutrophilic leukocytosis with or without a left shift [5–9,18,19]. In a study of degenerative left shifts in cats, pyothorax was found in 17% of cases [33]. The most common biochemical abnormalities reported include hypoproteinemia (generally hypoalbuminemia), hypoglycemia or hyperglycemia, electrolyte abnormalities, and mild elevations in liver enzyme activities [5,6,9,19].

Thoracic Imaging

Portable thoracic ultrasonography has become increasingly available and is a valuable tool for the rapid bedside diagnosis of pleural effusion in critical patients in respiratory distress (see Chapter 182). This technique can be used to evaluate the approximate amount of effusion, visualize its echogenicity and location, and potentially determine the presence of masses, abscesses, or foreign material [3,21,34–37]. Ultrasound can be utilized to guide thoracocentesis, chest tube placement, and sampling of focal lesions.

Thoracic radiographs can also be performed as an alternative to diagnose pleural effusion. For patients in respiratory distress, therapeutic thoracocentesis may need to be performed prior to radiographs. Radiographs are recommended after thoracocentesis is performed to further characterize the pulmonary parenchyma and thoracic cavity for abnormalities.

Studies have shown that, compared with thoracic radiographs, computed tomography (CT) has improved sensitivity in the detection of small pleural effusion and has provided additional information regarding anatomic localization and extent of pathology [38,39]. In one study involving dogs and cats with migrating intrathoracic grass awns, CT permitted correct detection of more abnormal sites and enabled improved tracing of the path of the foreign body compared to radiographs [34]. CT may be a useful tool to help identify lesions such as abscesses or foreign bodies that could require surgical intervention, and it may help to detect lesions that would otherwise go unnoticed at surgery [40]. While CT findings were similar to surgical findings in this study, additional findings at surgery did suggest the need for an appropriate thoracic exploratory surgery.

The use of bronchoscopy in patients with the suspicion of a migrating foreign body has been shown to increase the documentation and removal of them [34,41]. Thus, bronchoscopy may also be of therapeutic benefit for

migrating foreign bodies before considering exploratory thoracotomy.

Treatment

Treatment for pyothorax has traditionally been classified into medical or surgical management, but evidence-based guidelines for optimal care have not been established. The generally accepted foundation of treatment involves systemic antimicrobial therapy, supportive care, and thoracic drainage. Medical management typically involves thoracic drainage via thoracocentesis

or thoracostomy tube placement, while surgical management involves an exploratory thoracotomy.

Table 46.1 compares the varied outcomes related to different treatment options in dogs and cats since the year 2000. While medical therapy may offer successful outcomes and tends to be less invasive and expensive, surgical intervention provides the potential benefit of allowing complete exploration of the thoracic cavity and removal of a nidus of infection, which may be particularly important in regions prone to migrating grass awns. Thoracoscopy may offer a less invasive alternative to median sternotomy, but currently only one veterinary study has investigated its use [42].

Table 46.1 Summary of outcome with various treatments in canine and feline pyothorax studies since 2000.

Author, year (reference)	Species	Geographic region	Treatment	Survival to discharge	Recurrence
Crawford et al, 2011 [20] [*]	Feline	United Kingdom	Surgery (pneumonectomy)	4/4 (100%)	0/4 (0%)
Boothe et al, 2010 [4] [†]	Canine	United States	Thoracocentesis	2/7 (29%)	0/2 (0%)
			Thoracostomy tube	20/26 (77%)	3/20 (15%)
			Surgery	12/13 (92%)	4/12 (33%)
Johnson and Martin, 2007 [10] [§]	Canine	United Kingdom	Single unilateral thoracocentesis	15/15 (100%)	0/15 (0%)
Barrs et al, 2005 [8] [‡]	Feline	Australia	Thoracocentesis	2/2 (100%)	2/14 (14%)
			Thoracostomy tube	18/18 (100%)	
			Surgery	1/1 (100%)	
Mellanby et al, 2002 [2] ^{**}	Canine	United Kingdom	Thoracostomy tube	6/8 (75%)	0/7 (0%)
			Surgery	2/3 (67%)	
Demetriou et al, 2002 [6]	Canine, feline	United Kingdom, Ireland	Dogs:		0/36 (0%)
			Thoracostomy tube	25/29 (86%)	
			Surgery	6/7 (86%)	1/14 (7%)
			Cats:		
Waddell et al, 2002 [9] ^{††}	Feline	United States	Thoracostomy tube	10/11 (91%)	1/17 (6%)
			Surgery	3/3 (100%)	
			Thoracocentesis	3/9 (33%)	
Rooney and Monnet, 2002 [5] ^{§§}	Canine	United States	Thoracostomy tube only	31/45 (69%)	3/22 (14%)
			Surgery	5/5 (100%)	
			Thoracocentesis	6/7 (86%)	
Piek and Robben, 2000 [11] ^{††}	Canine	The Netherlands	Thoracostomy tube	16/19 (84%)	0/8 (0%)
			Surgery	9/9 (100%)	

^{*} All cats had evidence of consolidation, abscess, or mass.

[†] While survival to discharge was 29%, 77%, and 92% in the thoracocentesis, thoracostomy tube, and surgery groups respectively, long-term survival was 29%, 71%, and 70% given recurrence of disease in seven dogs, five of which were euthanized.

[§] One dog was diagnosed with a mass suspected to be an abscess and was referred for surgery. All other dogs that received thoracocentesis showed no evidence of pulmonary masses, consolidation, or granular pleural effusion.

[‡] Six cats died or were euthanized prior to treatment. The one patient requiring surgical treatment failed initial treatment with thoracostomy tube; this cat also experienced recurrence of disease a week after discharge.

^{**} Two dogs were euthanized without treatment.

^{††} Twenty-one cats were euthanized without treatment. The majority of medically managed cases involved thoracostomy tube placement.

^{§§} The proportion of disease-free patients 1 year after treatment was 25% in medically treated dogs and 78% in surgically treated dogs.

^{††} No evidence of migrating foreign material in any dogs.

Antimicrobial Therapy

Given the variety of potential pathogens, initial antimicrobial therapy should involve broad-spectrum coverage of aerobic and anaerobic organisms. Once culture and susceptibility results are available, final therapy can be altered appropriately if needed. Cytological evaluation is also critical, as some organisms such as *Actinomyces* spp. can be difficult to isolate. Empiric antimicrobial therapy often involves a beta-lactam with beta-lactamase inhibitor (e.g. ampicillin/sulbactam), as this is efficacious for *Actinomyces* spp. (important for dogs), most anaerobes, and *Pasteurella* spp. (important for cats and dogs); the addition of a fluoroquinolone such as enrofloxacin will improve gram-negative coverage and can be considered [1,5,13,14].

The ideal route and duration of antimicrobial therapy are not known due to a lack of evidence-based guidelines in veterinary medicine. Antimicrobials should be administered intravenously initially [43,44] and transitioned to an oral route when patients are clinically stable and willing to eat. There is also no consensus on the duration of oral treatment, but the British Thoracic Society recommends an additional 1–4 weeks of antibiotics to be given at discharge for children [44] and at least 3 weeks in adults, with discontinuation based on clinical, biochemical, and radiological response [43]. Although intrapleural antimicrobial infusions have not been critically evaluated in veterinary medicine, their use is not currently recommended in humans [43].

Thoracic Drainage

Antimicrobial therapy alone typically will not result in resolution of pyothorax, and so some form of thoracic drainage is essential. Thoracocentesis can be performed as a diagnostic and therapeutic tool, and it may be essential for patients which present in respiratory distress. While thoracocentesis has been documented to cause successful resolution of pyothorax in some dogs and cats, success rates are often low and outcomes are typically improved with thoracostomy tube or surgery as opposed to thoracocentesis alone [4,8,9]. However, one study reported successful treatment of 15 out of 16 dogs with thoracocentesis, but in these patients there was no evidence of pulmonary masses or consolidation [10].

If the decision is made to place an indwelling thoracostomy tube, there is additional debate regarding ideal number, size, and dwell time. Placement of unilateral versus bilateral tubes is typically made on an individual basis, depending on the distribution and volume of effusion. Generally, large-bore (14–28 Fr) trocar catheters have been recommended for improved drainage and to avoid obstruction by fibrin and thick exudate. Complications

associated with these tubes may include inadequate drainage, pneumothorax, lung laceration, hemorrhage, pain, arrhythmias, subcutaneous fluid leakage, infection, and anesthetic complications during placement [4–6,8,9,11,45]. Small-bore (14 Fr) wire-guided chest tubes placed via a modified Seldinger technique have also been shown to provide effective drainage with only mild complications in a small study of dogs and cats [45]. These tubes are being used increasingly in humans given the lack of direct evidence that large-bore chest drains are more efficacious. Possible benefits of small-bore chest tubes include the ability to place them under sedation rather than anesthesia, as well as potentially a lower complication rate (reduced trauma, increased comfort). However, the risk for obstruction and inadequate drainage are concerns.

Subsequent drainage can be accomplished intermittently (every 4–6 h) or via continuous suction. While no large prospective studies have compared the two, continuous suction is more expensive and labor intensive and has generally not been shown to be necessary for more effective drainage [1,6,8,9,13,18,46].

The reported median duration of tube placement is 4–8 days in dogs and cats [4,6,8,9,25]. Indwelling chest tubes are typically removed when fluid production has decreased to 2–5 mL/kg/day and there is clinical, radiographic, and cytological improvement [1,13,46]. Radiographs or ultrasound can confirm minimal effusion prior to removal, and cytology should show non-degenerate neutrophils and no evidence of infectious organisms.

Thoracic Lavage

Thoracic lavage is a technique that has been attempted to assist removal of pleural fluid [4,6,8,25,46]. Purported benefits include facilitation of drainage, minimization of bacteria and inflammatory mediators in the pleural space, reduction in viscosity of the fluid, prevention of thoracostomy tube obstruction, and breakdown of adhesions. However, there have been no prospective studies comparing thoracostomy tube placement with and without lavage, and there are no evidence-based veterinary guidelines regarding optimal lavage solution, dwell time, frequency, or duration of lavage. Retrospective veterinary studies have associated a benefit to this practice, [4,6] but routine pleural lavage is not included in human protocols [43,44]. As fluid overload is a risk, close monitoring of ins and outs is recommended. Retrieval of less than 75% of the volume infused should prompt additional investigation [46].

If pleural lavage is undertaken, infusion is typically performed slowly via the thoracostomy tube with warm sterile isotonic saline (10–20 mL/kg), though buffered balanced crystalloid solutions have been described

[4,6,8,13,14,46]. Fluid can be left in the pleural space for 10–15 minutes before withdrawal, and suction and lavage can occur 2–3 times daily or more frequently as needed. The appearance and volume of the aspirated fluid are often used to guide frequency of lavage, as well as when to pull thoracostomy tubes.

Additions to physiological lavage solutions have also been investigated. The use of fibrinolytics, such as tissue plasminogen activator or urokinase, to help improve pleural fluid drainage has been controversial. Observational studies and small randomized trials have shown improved pleural fluid drainage. However, a large randomized trial in humans showed that intrapleural fibrinolytics did not reduce mortality, frequency of surgery, or length of hospital stay but were associated with more adverse events (such as fever, pain, and hypersensitivity reactions) [47]. Additionally, the British Thoracic Society meta-analysis concluded that there is no indication for their routine use in adults [43].

The use of fibrinolytics has been described in the veterinary literature, but there has not been critical evaluation of their efficacy or safety in canine and feline patients [46]. At this time, their routine use cannot be recommended for these species [1,13].

The use of the intrapleural anticoagulant heparin was evaluated in one retrospective canine study which found that heparin (10 U/mL) added to the lavage fluid improved survival to discharge, but not long-term outcome [4], discouraging routine use of heparin in dogs and cats.

Surgical Management

To date, there have been no large clinical trials in the human or veterinary literature comparing the outcomes of surgical versus medical management, and no definitive criteria exist that dictate ideal therapy. Rooney and Monnet reported a better long-term outcome with

surgical management (78% of dogs were disease free at 1 year) compared to medical management (25% of dogs were disease free) [5]. Boothe showed that dogs treated with thoracotomy had improved short-term survival rates compared to dogs with thoracostomy tube, but long-term survival rates were similar between the two groups [4]. Waddell demonstrated improved short-term survival in cats with surgical therapy (100%) compared to cats treated with medical management (62.9%) [9]. The five cats that underwent thoracotomy and survived had failed to respond to medical management.

Generally accepted indications for surgical management include failure of medical therapy, diagnostic imaging consistent with pulmonary or mediastinal migrating foreign material or abscessation, and potentially the presence of *Actinomyces* spp. in areas where migrating grass awns are endemic [1,5,6,8,9,13,14,20,46]. Failure of medical therapy might include persistent effusion or infection despite appropriate thoracostomy drainage and antimicrobial therapy or failure of clinical improvement in 3 or more days. British Thoracic Society guidelines for adults and children recommend surgical intervention if patients are showing continued signs of sepsis after 5–7 days of appropriate thoracic drainage and antimicrobials [43,44].

Prognosis

With appropriate treatment and owner financial commitment, the prognosis for pyothorax in small animals can be good. Table 46.1 summarizes outcomes related to survival and recurrence in dogs and cats treated with a variety of techniques. Ultimate prognosis will depend on many factors, including underlying etiology for pyothorax, severity of clinical signs, and type of treatment elected. Overall survival in dogs is 83% and in cats is 62% [13].

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Diaphragmatic Hernia

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Anatomy

The diaphragm is a musculotendinous structure separating the thoracic and abdominal cavities. The Y-shaped tendinous portion is located at the center. The muscular portion surrounds the central tendon from which its fibers radiate to attachments on the lumbar vertebrae, ribs, and sternum. The muscular portion is weaker than the tendinous portion and is therefore where the majority of tears or ruptures occur [1–3].

The diaphragm contracts during inspiration. It aids in maintaining negative intrapleural pressure by preventing excursion of abdominal contents during inspiration. When the diaphragm has been compromised, the inspiratory functions are compensated for, and maintained by, the intercostal, scalenus, and serratus dorsalis muscles, provided the thoracic and abdominal cavities are not also compromised [4].

Types of Hernias

A hernia is a protrusion of an organ(s) through a rent in the structure in which it is contained. Diaphragmatic hernias (DH) may be either congenital or acquired [4–6]. Pleuroperitoneal, peritoneal pericardial, and hiatal are the reported types of congenital DH in dogs and cats. Trauma is the most common cause of acquired diaphragmatic hernias in small animal patients [7–28].

Congenital

Pleuroperitoneal DH is a rare but reported condition in both cats and dogs [3,7]. These are thought to occur due to a failure of fusion of the pleuroperitoneal membrane across the pleuroperitoneal canal during embryological development. The abdominal organs such as the liver, spleen, and stomach can herniate into the thoracic

cavity, causing compression of the lungs and possible compromise of the organs herniated [3,7].

Peritoneal pericardial diaphragmatic hernia (PPDH) is an uncommon anatomic abnormality reported in about 5–10% of canine and feline patients with diaphragmatic hernias [29–34]. The improper development of the transverse septum allows abdominal structures to herniate into the pericardial sac while maintaining an intact pleural space. This may result in compromise of the organs herniated as well as compression of the heart [3–6].

Hiatal DH is the herniation of abdominal contents (most commonly the stomach) through the esophageal hiatus in the diaphragm into the thorax. A “sliding” hiatal hernia is one in which the diaphragm migrates up and down the esophagus, resulting in the esophagogastric junction intermittently residing within the thorax. A “rolling” hiatal hernia is one in which the stomach migrates cranially, adjacent to the esophagus so that a portion of the stomach resides within the thorax. The herniated contents may be compromised and/or cause compression of the lungs [3–6,35].

Acquired

Approximately 85% of DHs in small animal patients are due to trauma [7–22]. However, often, it is of unknown etiology. Traumatic diaphragmatic hernias (TDH) result from a blunt force trauma sustained most often by motor vehicle accidents, although other sources of injury such as falls, kicks, and bite wounds/fights have been reported [7–28]. TDH can be acute or chronic in nature. TDH is considered chronic if a known trauma occurred and/or clinical signs relating to DH are present for greater than 2 weeks, or if signs consistent with chronicity are noted at surgery [25,26].

The pathophysiology of TDH is thought to be due to an acute transdiaphragmatic pressure gradient. The energy from the blunt trauma causes an increase in

intra-abdominal pressure, with subsequent dissipation of the energy cranially toward the diaphragm. With the glottis closed, the lungs remain filled with air and provide an intrathoracic counterforce. However, as the glottis opens, air is expelled from the lungs, with loss of the counterforce, resulting in a rupture of the diaphragm. The location of the rupture is dependent upon the position of the animal, the location of force/trauma, and the location of the abdominal contents. The tear in the diaphragm may be right-sided, left-sided or both, in addition to circumferential, radial or both [3,7–22].

Clinical Signs

Clinical signs of DH are most commonly associated with the respiratory and/or gastrointestinal tracts. The predominating clinical signs are related to the type and chronicity of the DH [7–22,29–37].

Congenital

Animals presenting with pleuroperitoneal hernia are typically young, but there have been some reports of older animals with few or no previous symptoms. These patients typically present for dyspnea. Death can occur shortly after birth due to respiratory compromise in severely affected animals [3,7,13].

The most commonly reported clinical signs in patients with PPDH are tachypnea, dyspnea, vomiting, anorexia, exercise intolerance, and cough [29–34].

Clinical signs most commonly displayed by patients with hiatal hernia are regurgitation, vomiting, hypersalivation, dysphagia, respiratory distress, anorexia, and/or weight loss [3–6,35].

Acquired

Dyspnea and tachypnea are the most common clinical signs in cats and dogs presenting with acute TDH. As these patients are typically presented following a traumatic event, the majority may be in various stages of shock (see Chapters 8 and 160). As such, these patients may display one or more of the following clinical signs: pale or cyanotic mucous membranes, tachycardia, head/neck outstretched, abducted elbows, difficulty lying down, decreased peripheral circulation, oliguria, depression, mental inappropriateness, and/or obtundation [7–22].

The most commonly reported clinical signs in patients with chronic TDH are dyspnea and vomiting. They may also present with non-specific clinical signs that either developed acutely or may be more insidious, chronic, and intermittent in nature (e.g. anorexia, lethargy, and weight loss) [36,37].

Diagnosis

Physical Examination

An accurate history is critical for accurately diagnosing DH. In any patient with a known history of trauma, a DH should be suspected (acute or chronic).

As the majority of these patients are presenting in respiratory distress, stress to the patient should be minimized while a complete and thorough physical examination is performed (see Chapter 4). Mucous membranes may be normal, pale, cyanotic or icteric. Thoracic auscultation may reveal a heart murmur, arrhythmias, decreased lung sounds, and/or borborygmus. Heart sounds may be muffled or increased (on the side opposite the hernia). Thoracic percussion may be hyporesonant (consistent with pleural effusion) or hyperresonant (consistent with gastric tympany). In patients with acute TDH, other injuries consistent with trauma such as soft tissue wounds and/or fractures may be noted [7–28].

Additional physical exam findings in patients with PPDH are umbilical hernia, supraumbilical hernia, cleft palate, and cryptorchidism. Weimaraners and domestic long-haired cats are the breeds most commonly affected [29–34].

Diagnostic Imaging

Radiography is the imaging modality of choice for the diagnosis of DH [38–42]. Ideally, lateral and ventrodorsal (VD) or dorsoventral (DV) views should be obtained. For patients in respiratory distress, a DV view is preferred over VD to minimize stress to the patient. The VD or DV projection should first be obtained to identify the side of the hernia. Once the side of the hernia is determined, the lateral projection may then be obtained with the side of the hernia facing down. Placing the patient in lateral recumbency with the hernia side up can cause a mediastinal shift in thoracic structures, resulting in further respiratory compromise [7–16]. A lateral projection may also be obtained using a horizontal beam with the patient standing or in sternal recumbency.

Thoracic radiographic findings in patients with PPDH include a rounded cardiac silhouette and a loss of distinction between the heart and the diaphragm [31,43]. Gas-filled small intestinal loops may also be noted within the pericardium (Figure 47.1).

The stomach may be cranially displaced on thoracic radiographs in patients with hiatal hernia. Gas-filled viscera and a small soft tissue mass in the caudal thorax, adjacent to the diaphragm, may also be visualized.

Radiographic findings in patients with TDH are dependent upon the side and size of the hernia. The most common findings are loss of the cupula, masking



Figure 47.1 Ventrodorsal radiographic view of the thorax of a dog with a peritoneal pericardial diaphragmatic hernia (PPDH). Gas-filled intestinal loops can be visualized superimposed over an enlarged cardiac silhouette.

of the cardiac shadow, increased intrathoracic density, and mediastinal shift. The loss of the diaphragmatic crura is more easily detected on the lateral projection [38–42]. Pleural effusion has also been reported. This may obscure structures in the thorax so thoracocentesis may be required to improve visualization. Atelectic lung lobes and rib fractures may also be noted [3,7–16,25]. Radiographic findings that may be suggestive of DH include dorsal displacement of the tracheal and bronchial segments, a cranioventrally directed gastric axis, and abdominal gas shadows within the thorax [38–41]. Abdominal structures noted within the thorax are in accordance with the location (right- or left-sided) of the DH. The liver is the most commonly reported herniated organ, followed by the small intestine, stomach, spleen, omentum, pancreas, colon, cecum, and kidney. Other reported herniated structures are the gall bladder and mummified fetus [7–22,44–46].

Ultrasonography may also be utilized for the diagnosis of DH. One study reported an accuracy of 93% in confirming a DH by noting abnormal borders or positioning of abdominal structures. This modality can be used to evaluate both the abdomen and thorax and can be quite useful when pleural effusion is present [46].

Contrast studies such as an upper GI series, pneumoperitoneography, positive-contrast pleurography,

positive-contrast peritoneography, portography, cholecystography, and angiography have all been reported for use in the diagnosis of DH [47–49]. These are rarely indicated given the high rate of diagnostic success with radiography and ultrasonography.

Laboratory Assessment

A complete blood count and serum biochemistry should be performed. If possible, urinalysis and blood gas should also be performed.

Results will be consistent with the degree of respiratory compromise, severity of trauma, and chronicity. Anemia, elevations in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and respiratory acidosis have all been reported [7–22,29–34].

Treatment

Initial treatment of patients with DH is based on the severity of clinical signs. The goal of therapy is to stabilize the patient and determine if emergency surgery is indicated. Animals displaying signs of respiratory distress should receive oxygen therapy via mask, flow-by, oxygen cage or nasal cannula (see Chapter 181).

An intravenous catheter should be placed and fluid resuscitation initiated. Debilitated patients and those with TDH may present in hypovolemic shock with concomitant injuries such as pulmonary contusions, atelectasis, and organ entrapment/compression which may predispose them to pulmonary edema [7–22]. Isotonic crystalloids, synthetic colloids, hypertonic saline or combinations thereof may be administered. Administration of blood products may also be indicated (see Section 5).

Thoracocentesis may be required if pleural effusion or pneumothorax is suspected based on physical exam or noted on imaging (Chapter 183). Samples of fluid should be submitted for laboratory analysis, especially when noted to be chylous or purulent. Pleural effusions may confirm a hemothorax, potentially due to a lacerated intercostal vessel as a result of a rib fracture or laceration of abdominal viscera.

Gastric decompression may be necessary if the stomach is trapped within the thoracic cavity. Pain management should be initiated using opioids (see Chapter 190). Alleviating pain may aid in improving chest excursions during respiration, especially when rib fractures are present.

Surgical Intervention

In most cases of DH, surgical intervention is required, but the timing of surgery is dependent upon the patient's stability. Early studies of TDH suggested that early



Figure 47.2 Ventrodorsal radiographic view of the thorax of a dog with a traumatic diaphragmatic hernia. The food-filled stomach can be visualized in the left hemithorax.

intervention (<24h) resulted in higher mortality rates [7–14]. However, more recent studies suggest that surgical intervention within 24 hours of TDH may not have an adverse effect [15,16,50,51].

Surgical procedures that may be performed to correct the DH include laparotomy, median sternotomy, lateral thoracotomy or a combination thereof [3–6,52–55].

Emergency surgical intervention is indicated if:

- the stomach is located in the thoracic cavity (Figure 47.2); gastric distension can lead to cardiovascular compromise
- the patient cannot be stabilized due to suspected continual hemorrhage
- abdominal pain is refractory to appropriate pain management.

Prior to induction, patients should be preoxygenated and premedicated using benzodiazepines and opioids.

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A quick-acting IV induction using etomidate, alfaxalone or propofol should be employed to facilitate a smooth induction and rapid endotracheal intubation. Nitrous oxide should not be used as it will diffuse into any hollow viscous or gas space and may exacerbate a pneumothorax or gastric dilation [56–59].

Reperfusion pulmonary edema is a life-threatening complication in these patients. Intermittent positive pressure ventilation is required for the duration of the surgical procedure and should not exceed 15–20 cm H₂O. The atelectic lung lobes should not be forcibly expanded, but should rather be allowed to slowly expand on their own. A thoracostomy tube is placed at surgery and air evacuated from the thoracic cavity until the patient is ventilating well. The residual pneumothorax can be gradually alleviated over the next 8–12 hours [60–65].

Postoperative Care

Patients recovering from surgical repair of a DH require intensive care and monitoring. Supportive care with IV fluids and analgesia should be provided. Oxygen supplementation may be required in the immediate postoperative period. The thoracostomy tube should be evacuated and monitored for continued pneumothorax or pleural effusion [38–50].

Complications and Prognosis

Based on published reports, approximately 15% of patients presenting for TDH will not survive to surgery [7–22,50–54]. This is due to several reasons including shock, multiorgan failure, hypoventilation, restraint for examination, poor anesthetic management, and inadequate ventilation.

Complications occur in approximately 50% of patients. Reported life-threatening postoperative complications include pneumothorax, pleural effusion, pulmonary edema, cardiac dysrhythmias, hemothorax, shock, cardiac arrest, and gastrointestinal rupture/strangulation or cause unrelated to the hernia. Other potential complications include ascites, hiatal hernia, esophagitis, and gastric ulceration [7–22,66,67].

Postoperative survival rates have significantly improved from 52% to 82–89% in more recent reports [16,50].

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Penetrating Thoracic Trauma

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Introduction

Penetrating thoracic trauma (PTT) is defined as any wound that extends from the outside of the thoracic wall through the pleural lining, and is differentiated from perforating trauma in which the injury passes completely through the body cavity [1]. The most common type of penetrating injuries in veterinary medicine are bite wounds from other animals [2,3]. Other documented causes of PTT include gunshot wounds (GSW), in both companion and working dogs, and impalement injuries [3,4]. In addition to thoracic wall trauma, PTT can cause damage to the respiratory tree, lung parenchyma, cardiovascular structures, and esophagus.

For patients presenting with an impalement injury, it is essential not to remove the object. The patient should be stabilized, appropriate diagnostic testing performed and the object removed as part of a planned surgical procedure.

Etiology

The incidence of penetrating trauma in veterinary patients varies; in one multi-institutional study of 315 canine trauma patients, 107 (34%) presented with penetrating wounds [2]. In a retrospective study of 16 dogs and cats with penetrating wounds, 50% involved solely the thorax and 17% involved the abdomen and thorax [3]. In a larger retrospective study of dog bite wounds, 64 of 196 (33%) involved the thorax [5]. Finally, although dog bite wounds are common in veterinary medicine, in a study of 65 dogs and cats thoracic bite wounds only eight had an injury penetrating the thoracic cavity [6].

The causes of PTT vary with certain dog breeds or body weight. Small-breed dogs (<15kg) appear to be more at risk for penetrating dog bite injuries [3,5,6]. Conversely large-breed dogs (e.g. German shepherds

and pit bull terriers) are more likely to sustain GSW when in an urban setting [7]. Male dogs appear to be more likely to have bite wounds and GSW according to several studies [3,5–7].

Physical Examination and Diagnostics

A physical examination in the acute trauma patient, regardless of the cause of the trauma, should be performed in a tiered manner, with the complete physical examination occurring after initial patient stabilization (see Chapter 2). Initial assessment of the respiratory and cardiovascular systems is essential for PTT patients as both of these may be either directly or indirectly injured. It is well described with both bite wounds and GSW that the amount of tissue damage deep to the skin is of greater magnitude than that evident at the site of penetration. This is due to a combination of the crushing and avulsion capabilities of these injuries, the amount of dead-space created, and bacterial inoculation. With GSW, the destruction the bullet causes is associated with the type of bullet used and the caliber and muzzle velocity but generally has more internal ramifications than the entrance wound may suggest [8].

Initial bloodwork including packed cell volume and total protein should be promptly acquired at presentation. When possible, an arterial blood gas should also be acquired to evaluate the patient's ability to oxygenate; if an arterial sample is not feasible, pulse oximetry is indicated. Additional bloodwork such as a complete blood count and serum chemistry panel may be indicated, depending on the patient's status, age, and co-morbidities. Finally, severely injured patients might present with trauma-associated coagulopathy (see Chapter 163) [9]. Some animals might therefore benefit from coagulation testing soon after presentation.

Use of electrocardiogram (ECG) evaluation in PTT patients is indicated as myocardial ischemia and subsequent changes to cardiac electrical activity have been documented in human trauma patients [10]. Likewise, dysrhythmias including ventricular and supraventricular extrasystoles, atrial fibrillation and flutter, supraventricular and ventricular paroxysmal tachycardias, and ventricular fibrillation have been documented in human and veterinary patients following thoracic trauma [11–13].

The use of point-of-care ultrasound for thoracic and abdominal evaluation has become commonplace in veterinary medicine (see Chapter 182). These techniques rapidly identify pleural, peritoneal, and pericardial effusion or air in the emergency room setting. Fluid sampling and analysis should be performed whenever possible.

Thoracic radiographs can be acquired once the patient is stabilized and can be very useful in PTT patients to assess for pleural effusion, pneumothorax, pulmonary contusions, rib fractures, and diaphragmatic and/or thoracic wall hernia. In a study of 50 dogs and cats with thoracic bite wounds in which radiographs were acquired, 68% showed at least one thoracic radiographic lesion although the number of thoracic radiographic lesions was not significantly associated with mortality [6]. Caution should be exercised when prognosticating based on radiographs as studies have shown that thoracic radiographs underestimate the amount of intercostal damage and thoracic wall defects when compared to surgical exploration of wounds [3].

In cases of suspected diaphragmatic hernia or in patients with concurrent abdominal trauma, a complete abdominal ultrasound may be indicated. Advanced imaging such as computed tomography or magnetic resonance imaging may be considered in a subset of the population based on the clinician's assessment. In certain PTT patients, endoscopic evaluation may be performed to evaluate the integrity of the esophagus and the respiratory tree, especially in those cases in which a pneumomediastinum is documented on thoracic radiographs.

Treatment

Supplemental oxygen therapy should be initiated immediately in all patients during the stabilization period (see Chapter 181). Ongoing oxygen therapy should be guided by the patient's pulse oximetry, arterial blood gas values, and/or clinical signs. Rapid assessment of perfusion should be performed while intravenous access is obtained. Many patients with PTT will require shock resuscitation (see Chapter 153).

Fluid and Blood Products

Animals with PTT commonly present with clinical signs of hypovolemic shock. Patients can initially be resuscitated with fluid boluses (see Chapter 153). A subset of patients might benefit from more complex volume resuscitation strategies that include blood products. This should be considered in animals with significant blood loss and lack of response to conventional therapy resulting in severe anemia, thrombocytopenia, and/or secondary coagulopathy (see Chapter 170). A ratio of packed red blood cell to plasma to platelets transfusion of 1:1:1 has been suggested in human medicine [8]. Seriously traumatized patients might present with trauma-associated coagulopathy and therefore suffer from hyperfibrinolysis. While it has not been evaluated in veterinary trauma patients, tranexamic acid has been used successfully in human patients with severe trauma (see Chapter 68) [14,15].

Respiratory Stabilization

In patients in which fluid or air accumulation in the pleural space is noted on ultrasound or thoracic radiographs, thoracocentesis may be indicated (see Chapter 183). Following PTT, air accumulation likely occurs secondary to the influx of air from the environment due to subatmospheric pressure in the thoracic cavity or from trauma of the respiratory tract or esophagus [2,16–18]. In a retrospective study of 32 thoracic GSW in dogs and cats, nine required a single thoracocentesis for hemothorax or pneumothorax [7]. Thoracocentesis is both a diagnostic and therapeutic procedure, and in cases of severe respiratory compromise, a thoracocentesis may be performed even without confirmed pleural space disease (see Chapter 183).

Penetrating thoracic trauma can result in an open pneumothorax ("sucking chest wound"). Emergency room stabilization requires re-establishment of subatmospheric pressure in the pleural space. In the patient that appears to be near arrest, immediate anesthesia, orotracheal intubation, and manual or mechanical ventilation are indicated (see Chapter 188). The open chest wound needs to be kept open to allow air to escape the pleural space during positive pressure ventilation. Surgical exploration, debridement, and reconstruction of the chest wall should be performed as soon as possible. In animals with open chest wounds that appear more stable, evacuation of the pleural space, (thoracostomy tube placement is recommended, see Chapter 184) in conjunction with sealing the open chest wound to prevent air entry, which should improve respiratory function in the short term. Surgical management should be performed once the patient is fully assessed and stabilized.

Rib fractures are common in patients with PTT and rarely need surgical fixation. Multiple rib fractures can cause a flail chest segment. A flail chest is defined as multiple fractures of three or more adjacent ribs. The flail segment moves independently from the thoracic wall and has paradoxical motion with breathing. The flail segment moves inward during inspiration and outward during expiration. Patients with significant disruption of the intercostal musculature can have a thoracic wall injury that can create a similar paradoxical movement of a segment of chest wall as a flail chest, commonly known as a “pseudo-flail chest.” Flail chest and pseudo-flail chest injuries indicate that pleural space disease and/or pulmonary contusions are highly likely. Life-saving interventions should be focused on these concerns initially. The flail chest itself rarely needs specific therapy during the stabilization period. Treatment is largely based on limiting the motion of the flail segment. In the initial stabilization period, this may be achieved by placing the animal in a position with the flail segment dependent. Once stabilized, bandaging the thorax may be beneficial in reducing motion of the flail segment and increasing the comfort of the patient.

Rib fractures and flail segments should be further assessed at the time of surgery and some may require surgical intervention to stabilize the chest wall. All animals with rib fractures require appropriate analgesic therapy (see below).

Pulmonary contusions are common in patients with PTT as a result of direct injury to the pulmonary parenchyma. Tissue disruption and associated hemorrhage impair gas exchange and decrease pulmonary compliance. Management of pulmonary contusions involves monitoring oxygenation and supplemental oxygen therapy to prevent hypoxemia and reduce respiratory effort. Mechanical ventilation may be required if severe hypoxemia or severe respiratory distress persists despite oxygen therapy (see Chapter 181).

Pain Management

Analgesia is a major concern for the PTT patient (see Section 7). Prompt pain assessment should be performed in all trauma patients and analgesia initiated as early as possible; full mu opioid agonists are generally the drugs of choice as these result in minimal cardiovascular depression, have potent analgesic properties, and are reversible. Non-steroidal anti-inflammatory drugs should be avoided in the acutely and severely injured PTT patient due to the potential for adverse effects. Local-regional anesthetic blocks along with dedicated nursing care (e.g. icing, recumbency change) can be considered in the analgesic plan (see Section 7).

Antibiotics

Bite wounds are considered contaminated by the oral bacteria of the biting animal, and all PTT wounds, including bite wounds, are potentially contaminated with the resident skin flora of the patient or soil organisms [5]. In a retrospective study of GSW, 78% of the cultures performed were positive for at least one bacterial isolate [7]. Likewise, in studies of dog bite wounds, 67–96% of the wounds in which bacterial cultures were performed were positive for bacterial growth, most commonly with aerobic bacteria [19,20].

Based on these studies, it is recommended that all PTT patients should be administered broad-spectrum antibiotics at the time of presentation. The most commonly reported aerobic bacteria isolated in penetrating wounds are *Pasteurella* spp, *Staphylococcus intermedius*, *Enterococcus* spp, *Staphylococcus coagulase negative*, and *Escherichia coli* [7,19,20]. The most common anaerobic isolates are *Bacillus* spp, *Clostridium* spp, and *Corynebacterium* spp [19]. A deep tissue culture and susceptibility testing should be submitted following clipping and lavage of the wounds or following surgical exploration to allow for tailored antibiotic therapy once results are available.

Surgical Indications and Procedures

Patients with bite wound injuries penetrating the thoracic wall may benefit from surgical exploration, debridement, and/or reconstruction [3,6]. In a retrospective study of 65 thoracic bite wounds in dogs and cats, all penetrating injuries and the identification of more than three radiographic lesions (lung contusions, rib fractures, pneumothorax, or pleural effusion) were suggestive of the need for explorative thoracotomy [6]. However, in this same study, damage to internal organs was uncommon (17%). In another larger retrospective study of dog bite wounds, performing an exploratory thoracotomy did not alter outcome [5].

In the authors' opinion, exploratory thoracotomy is mandated in cases in which gross contamination is a concern and in which patient comfort and cardiovascular or respiratory stability cannot be adequately controlled with medical management alone. Surgical thoracic exploration following a GSW is recommended in the human literature [21,22], and in the authors' opinion is standard of care in veterinary medicine when the clinical picture warrants surgery, given the relatively higher incidence of damage to internal organs with GSW as opposed to other forms of penetrating trauma [3]. Although there are no reports in veterinary medicine, resuscitative thoracotomy and damage control thoracotomy (see Chapter 189) have been advocated in humans with seriously compromised cardiorespiratory function despite initial resuscitation efforts [23,24].

Anesthetic Considerations

Prior to inducing anesthesia, appropriate cardiorespiratory resuscitation should be performed, including evacuating air or fluid from the thoracic cavity via thoracocentesis or thoracostomy tube. The anesthetist should be prepared to mechanically ventilate the patient as soon as anesthesia is induced. Low tidal volumes should be used when possible to minimize lung injury.

Surgical Management

Debridement, lavage, and establishment of drainage are the mainstay of PTT wound management. The integrity of the thoracic wall must be re-established to maintain sub-atmospheric pressure within the pleural space. This may be accomplished with reconstruction of the musculature, the use of muscular flaps or with a polypropylene mesh implant. When a synthetic implant is used, owners should be cautioned about the chance of implant-associated infections, particularly in contaminated PTT wounds. Drainage of the pleural space is best accomplished via placement of a thoracostomy tube at the time of surgery. Additionally, drainage of subcutaneous wounds may be facilitated by an active or passive drain.

Prognosis

Generally, outcome of PTT is considered fair to good but varies considerably with origin of the wound and owner-directed decisions concerning treatment. In one PTT study of 11 dogs, all dogs survived to discharge from the hospital [3]. In a separate study in dogs with penetrating dog bite wounds, the overall mortality was low (11%) but 77% of the dogs that died had PTT [5]. In another study evaluating dogs and cats with thoracic bite wounds, mortality, excluding cases of euthanasia, was 7.7% and the depth of the wound, ranging from superficial to penetrating, was not statistically associated with survival [6]. Conversely, dogs that suffer high-caliber, high-velocity GSW to the thorax may have a more grave prognosis, with survival rates of 31–54%; however, this study included dogs that died prior to arrival at a veterinary treatment facility [4]. In two other retrospective studies of GSW patients, injuries to the thorax were not associated with a worse survival, with 86–91% surviving to discharge [7,25].

Unfortunately there are few veterinary studies evaluating long-term survival following PTT; however, a favorable prognosis is generally assumed if the patient survives to discharge from the hospital.

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Blunt Thoracic Trauma

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Introduction

Blunt thoracic trauma (BTT) occurs secondary to a high-velocity impact to the chest wall without penetration into the thoracic cavity. The energy created by the impact is transmitted throughout intrathoracic viscera, potentially leading to life-threatening injuries.

Etiology

In a recent multicenter prospective evaluation of canine trauma, blunt trauma was the most common form reported, affecting 55% of dogs [1]. Another study in dogs with severe blunt trauma reported that 72% of patients had thoracic involvement [2]. Blunt thoracic trauma can be the result of various events including motor vehicular accidents, falls from a height [2], abuse [3], thoracic compression during cardiopulmonary resuscitation [4], gunshot trauma from non-lethal ammunition such as rubber bullets [5], or non-penetrating bites [6]. In animals experiencing a high-rise fall 34–90% of cats [7,8] and 63% of dogs [9] suffered trauma to the chest.

Pathophysiology

Following BTT, various thoracic organs can be damaged [10]. Reported frequencies of various injuries are presented in Table 49.1.

Lung contusion is the major cause of death in adult human BTT patients and severe contusions may result in the need for mechanical ventilation. Chest wall impact can cause shearing or bursting injury to the lung. The result is hemorrhage and fluid exudation within the parenchyma of the lung. This can lead to alveolar flooding, impairing gas exchange and decreasing pulmonary

compliance. The severity of lung contusions can worsen over the first 24–48 hours following injury before improvement is noted [11].

Trauma is recognized as a cause of acute respiratory distress syndrome (ARDS) through several possible mechanisms, including hemorrhagic shock and massive tissue damage. Pulmonary contusions can be a direct cause of ARDS. Following the initial pulmonary injury, there is infiltration of the pulmonary tissue with monocytes and neutrophils. Accumulation of fibrin, cell debris, and white blood cells will contribute to the pulmonary dysfunction and triggers a strong inflammatory response. This can lead to generalized pulmonary inflammation and ARDS in some patients [12–14]. While 3% of dogs with severe blunt trauma developed ARDS [2], 6% of cats with acute lung injury (ALI) or ARDS had sustained major trauma (unknown whether blunt or penetrating) [15].

Transmission of energy throughout the respiratory tract following an impact can lead to tissue disruption. The trachea and bronchi can rupture [16,17]. Tracheal avulsion can have a delayed presentation (days to weeks) due to short-term maintenance of the airway by surrounding soft tissue structures; this “pseudo-trachea” has been reported in cats [18]. Ribs can also be damaged following BTT, and 52% of cats that sustained various traumatic injuries had rib fractures; however, it is unknown how many of these patients had suffered blunt or penetrating injury [19]. Rib fractures were frequently associated with other injuries such as pulmonary contusions (82%), subcutaneous emphysema (47%), pneumothorax (41%), and pleural effusion (35%). Similarly, 26% of cats with a known cause of pneumomediastinum had sustained BTT [20].

A flail chest segment is the result of both dorsal and ventral fractures of several adjacent ribs. This will produce a segment of freely moving thoracic wall that is displaced paradoxically during inspiration and expiration [21]. Patients with significant disruption of the

Table 49.1 Reported incidence of various thoracic injuries following blunt thoracic trauma in dogs and cats.

Type of trauma	Species	Origin	Incidence	References	
Respiratory tract					
Pulmonary contusion	Dog	Severe blunt trauma	58%	2	
		High-rise	37%	9	
		Vehicular accident, high-rise	39%	12	
		Vehicular accident	17%	11	
	Cat	High-rise	13–61%	7, 8	
		Vehicular accident, high-rise	46%	12	
Hemothorax	Dog	Severe blunt trauma	18%	2	
	Cat	High-rise	8%	8	
Pneumothorax	Dog	Severe blunt trauma	47%	2	
		High-rise	25%	9	
		Vehicular accident, high-rise	24%	12	
		Vehicular accident (concurrent with pulmonary contusions)	46%	11	
	Cat	High-rise	20–57%	7, 8	
		Vehicular accident, high-rise	33%	12	
	Pneumomediastinum	Dog	Severe blunt trauma	8%	2
			Vehicular accident (concurrent with pulmonary contusions)	8%	11
Bullae	Dog	Severe blunt trauma	2%	2	
		Vehicular accident (concurrent with pulmonary contusions)	10%	11	
Diaphragmatic hernia	Dog	Severe blunt trauma	6%	2	
	Cat	High-rise	2%	8	
Flail chest	Dog	Severe blunt trauma	2%	2	
Rib fracture	Dog	Severe blunt trauma	14%	2	
		Vehicular accident (concurrent with pulmonary contusions)	13%	11	
Heart					
Pneumopericardium	Dog	Vehicular accident (concurrent with pulmonary contusions)	1%	11	
Abnormal electrocardiogram	Dog	Severe blunt trauma	22%	2	
		Vehicular accident	10–97%	11, 28	

intercostal musculature can have thoracic wall injury that creates a paradoxical movement similar to a flail chest. This is known as a “pseudo-flail” chest. Rib fractures, flail chest, and pseudo-flail injuries will be a source of pain and are often associated with other thoracic trauma such as pulmonary contusions, hemothorax, and/or pneumothorax. Hemothorax can occur as a result of rupture of intercostal vessels, pulmonary vessels, great veins, the aorta or the heart itself. Massive

hemothorax can be associated with hemorrhagic shock and respiratory compromise.

Cardiac injury is another serious complication of BTT and can manifest as structural or electrical defects. Mechanical damage can occur due to acceleration-deceleration events. Complete cardiac avulsion, large vessel laceration, and myocardial tears have frequently been reported in humans [22–24]. Cardiac injuries following BTT in dogs include trauma-induced communication

between the left ventricle and right atrium (Gerbode defect), atrial septal defect, and right atrial tear [25,26]. Electrical abnormalities can include premature ventricular complexes (PVCs), commotio cordis (i.e. sudden cardiac arrest following BTT without cardiac morphological changes), sinus tachycardia, atrioventricular block, and ventricular fibrillation [27] (see Chapter 61).

Patients which sustained serious trauma are also at risk for developing acute traumatic coagulopathy. This hypocoagulable, hyperfibrinolytic state is associated with worse outcomes [28] (see Chapter 163).

Physical Examination and Diagnostics

Initial triage examination should assess for airway patency, respiratory distress, and hypoperfusion (see Chapter 2). Following initial stabilization, a full physical examination is essential. Thoracic wall palpation is important to uncover possible abnormalities such as rib fractures, flail chest or “pseudo-flail” chest.

A diagnostic worksheet for the BTT patient is presented in Table 49.2. Oxygenation function should be investigated as early as possible via pulse oximetry or, ideally, arterial blood gas analysis. Unfortunately, it may not always be feasible or safe to obtain an arterial sample. The need for antiarrhythmic therapies should be established after prompt electrocardiogram analysis. In a canine report of naturally occurring BTT, while only 30% of patients had significant electrocardiographic abnormalities, 54% had elevation in serum troponin I concentration, suggesting the potential for subclinical myocardial injury following BTT [29]. The use of troponin I measurement in order to rule out myocardial damage following BTT has also been advocated in humans [30]. The utility of this test remains to be determined in veterinary medicine.

Initial emergency room bloodwork should include packed cell volume, total protein concentration, blood gas and lactate measurement when possible. Venous blood

samples can be submitted at the clinician’s discretion for a complete blood count, chemistry panel, and electrolyte quantification. In severely injured animals, the presence of acute traumatic coagulopathy can be investigated by submitting prothrombin time, activated partial thromboplastin time and possibly viscoelastic testing.

Imaging is another important aspect of evaluation of the trauma patient. In BTT patients, thoracic radiographs should be performed when patient stability allows. In one retrospective study, 78% of dogs and 72% of cats had abnormal thoracic radiographs following BTT [31]. In a separate study, 53% of cats that had sustained trauma had thoracic abnormalities noted on whole-body radiographs [32].

Emergency room ultrasonography has become more commonplace in veterinary medicine (see Chapter 182). Trauma patients should undergo abbreviated thoracic and abdominal ultrasonography such as abdominal (aFAST), thoracic (tFAST) focused assessment with sonography for trauma, or veterinary bedside lung ultrasound exam (vetBLUE). These techniques help to identify pleural, peritoneal, and pericardial effusion as well as pneumothorax and pulmonary parenchymal damage. Pleural fluid sampling and analysis should be considered whenever possible. Upon stabilization, further thoracic assessment can be obtained via computed tomography or magnetic resonance imaging. In a subset of patients, endoscopic evaluation might prove helpful to evaluate the integrity of the esophagus or respiratory tree.

Treatment

Patients with obstructed or damaged airways may require anesthesia for orotracheal intubation or emergency tracheotomy. In a feline report, 21% of tracheotomies were performed following trauma [33]. Those patients with signs of shock, respiratory distress, or hypoxemia should be immediately placed on supplemental oxygen.

Table 49.2 Diagnostic worksheet for the blunt thoracic trauma patient.

First tier	Triage examination	Pulse oximetry	Electrocardiogram	Packed cell volume Total protein
Second tier	Physical examination	aFAST, tFAST, vetBLUE	Blood gases Electrolyte quantification Lactate	Arterial blood pressure
Third tier	Complete blood count Chemistry panel Coagulation panel Troponin	Echocardiography	Fluid analysis	Thoracic radiographs
Fourth tier	Computed tomography scan	Magnetic resonance imaging	Bronchoscopy	Esophagoscopy

aFAST, abdominal focused assessment with sonography for trauma; tFAST, thoracic focused assessment with sonography for trauma.

Thoracocentesis should be performed in patients with suspected or confirmed pleural space disease (see Chapter 183). Following BTT, air accumulation likely occurs secondary to the influx of air from the environment due to subatmospheric pressure in the thoracic cavity or from trauma of the respiratory tract or esophagus, and hemothorax is the most likely cause of fluid accumulation [1,2,7,8]. A much less likely, but reported, cause of fluid accumulation is chyle secondary to trauma to the thoracic duct [34,35]. Diaphragmatic hernia is another potential cause of pleural space disease in the BTT patient (see Chapter 47).

Animals with severe hypoxemia or respiratory fatigue despite supplemental oxygenation and resolution of pleural space disease may require mechanical ventilation (see Chapter 188). Mechanical ventilation is required in 2–4% of dogs with severe blunt trauma [2,36]. Furthermore, 5% of an ICU population undergoing mechanical ventilation consisted of traumatized dogs [37]. The reported survival rate of dogs undergoing mechanical ventilation following BTT-induced pulmonary contusions is 30% [36,38].

Presence of a flail chest should be taken as an indication of severe BTT and it should be assumed that it is accompanied by pneumothorax, hemothorax, and pulmonary contusions, until proven otherwise. Movement of the flail segment should be minimized to reduce the impact on the underlying lung and to improve patient comfort. In the initial triage period, placing the patient in lateral recumbency with the flail segment down may be beneficial to minimize the pain associated with movement of the fractured ribs. Long-term management usually includes a circumferential chest wrap. Analgesia is clearly indicated in these patients. Evaluation and management of intercostal muscle trauma (pseudo-flail) is similar to that for flail chest injuries.

In cases of pneumothorax that require multiple thoracocenteses for stabilization, placement of a thoracostomy tube is indicated (see Chapters 183 and 184). The need for a thoracostomy tube is relatively uncommon in blunt force trauma patients. In one retrospective study, only 34 of 235 dogs with severe BTT required the placement of a thoracostomy tube [2]. In a retrospective study of 119 cats with blunt force trauma from high-rise syndrome, only one cat required placement of a thoracostomy tube despite the fact that 53 cats in that study required a thoracocentesis [1].

Patients with altered perfusion parameters will require fluid resuscitation. While many patients can be resuscitated with isotonic crystalloids, hypertonic saline or colloids, the best resuscitation approach to patients with pulmonary contusions has been a source of controversy. Balancing the need to restore circulating volume with minimizing pulmonary fluid accumulation has led to conjecture that small-volume resuscitation with fluids

such as hypertonic saline would be superior to isotonic crystalloids. This has not been supported by the literature where many studies have found no difference between the fluid type used and the resultant degree of lung injury and extravascular lung water, although the results of these investigations have been contradictory [39].

Animals with severe hemorrhage will require blood products as part of the resuscitation protocol (see Chapter 176). The current human literature supports the administration of a 1:1:1 ratio of units of packed red blood cells:fresh frozen plasma:platelets. This approach is not feasible in most veterinary facilities and the focus is on using whatever blood products are readily available and within the owner's financial capability to provide adequate red blood cell mass. There is evidence to support the early use of fibrinolysis inhibitors after trauma as part of severe hemorrhage management (see Chapter 68) [40–42]. Traumatized animals may also require blood product administration during anesthesia for hemodynamic support [43]. Some patients may demonstrate clinical signs of vasodilatory shock, manifested as persistent hypotension despite fluid therapy. The use of vasopressors is then indicated in order to maintain acceptable mean arterial pressure and overall tissue perfusion. In animal models, vasopressin has shown promising results as a first-line vasopressor for the treatment of hemorrhagic shock refractory to fluid resuscitation (see Chapter 170) [44,45].

Electrocardiogram findings should guide antiarrhythmic therapy (see Chapter 53). Proper pain assessment should be attempted in any trauma patient and analgesia initiated as early as possible. Full mu-opioid agonists can be used as these result in minimal cardiovascular depression and have good analgesic properties. Non-steroidal anti-inflammatory drugs are not recommended in acutely and severely injured BTT patients due to potential hypoperfusion leading to gastrointestinal derangements and acute kidney injury.

Antibiotic therapy is generally not indicated in BTT patients; in one study with a relatively small BTT subgroup, antibiotic prophylaxis after blunt thoracic injury had no effect on patients with chest drains [46]. When present, wounds should be clipped, cleaned, and covered with non-adhesive dressing, as soon as possible. Antibiotic therapy may be indicated in heavily contaminated wounds.

Surgical Indications

Possible indications for surgery following BTT include rib fractures (usually severely displaced), soft tissue injuries requiring reconstruction of the thoracic wall, persistent pneumothorax, persistent hemorrhage, the presence of a diaphragmatic hernia, and a flail chest. Most of these injuries can be managed medically but surgery may be

indicated if there is severe respiratory compromise or medical management is unsuccessful. The presence of a traumatic chylothorax is not an indication for surgery; in one canine study, experimentally induced chylothorax proved to be self-limiting within 10 days [47].

If surgical repair is indicated, a lateral thoracotomy or median sternotomy is performed. If the injuries are presumed to be unilateral, a lateral thoracotomy is often preferred, especially if resection of a lung lobe is required due to ease of access to the pulmonary hilus. A diaphragmatic hernia can be reduced and corrected via a standard midline celiotomy.

Controversy exists in the literature over the timing of correction of a diaphragmatic hernia. An older study reported a significantly higher mortality rate when surgery was performed within 24 hours or >1 year after trauma [48]. However, a more recent study [49] showed an overall survival rate of 89.7% in dogs and cats with surgical intervention for their diaphragmatic hernia within 24 hours of admission.

Overall, the appropriate timing for surgical intervention in veterinary trauma patients remains unclear and should be based on clinical assessment of each individual case [50].

Prognosis

Studies to date have reported a good outcome in dogs with BTT. In one large retrospective study of 235 dogs

with severe BTT, survival to discharge from hospital was 88%. However, in that study, concurrent head trauma, development of respiratory signs (e.g. ARDS, pneumonia, cough, and the need for mechanical ventilation), hematochezia, lateral recumbency, and development of multiple organ dysfunction syndrome all had a significant negative effect on prognosis. The need for surgery and surgical intervention did not affect survival to discharge [2]. Outcomes in dogs and cats with a flail chest that have been stabilized surgically are similar to those not surgically stabilized [51].

In another prospective study of canine trauma cases, including 173 blunt trauma cases, surgical intervention, an animal trauma triage score less than or equal to 5, modified Glasgow Coma Scale score greater than or equal to 17 and blood lactate concentration less than 4.0 mmol/L at the time of hospital admission were all associated with survival [1]. Additionally, in that study animals that sustained blunt trauma as opposed to other trauma types had a significantly better survival rate of 91% [1].

The outcomes reported in cats sustaining BTT are similar to those for dogs, with approximately 90–97% surviving to discharge [7,8,49]. Although prognosis in cats is good, it may be worse in those with a flail chest, pleural effusion or a diaphragmatic hernia [52].

Unfortunately, there are no veterinary studies addressing long-term survival following BTT but a favorable prognosis is generally assumed if the patient survives to discharge from hospital.

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Look-Alike Causes of Respiratory Distress

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Introduction

Respiratory distress manifested as increased respiratory rate and/or effort is typically caused by disease of the respiratory system. Causes of increased respiratory rate and effort can be divided into eight major categories to aid the clinician in establishing a diagnosis (Box 50.1). “Look-alike” causes are non-respiratory mechanisms of increased respiratory rate and effort.

Regulation of the respiratory system is complex and includes both a voluntary and an autonomic component. The medulla of the brainstem receives and controls afferent signals from peripheral chemoreceptors and mechanoreceptors while the cerebral cortex may consciously affect respiratory rate and pattern [1]. Irritant and stretch receptors in the lungs and diaphragm as well as central and peripheral chemoreceptors, which respond to changes in pH, PaO₂ and PCO₂, are vital in regulating respiration [1]. Increased ventilation occurs with reduced arterial PO₂, an elevated arterial PCO₂, reduced arterial pH, hypoperfusion, and hyperthermia [1].

It is because of the complex regulation of the respiratory system that patients may present with non-respiratory causes of tachypnea or respiratory distress.

Box 50.1 Mechanisms of increased respiratory rate and/or effort.

- Upper airway disease
- Lower airway disease
- Pulmonary parenchymal disease
- Pleural space disease
- Thoracic wall injury
- Abdominal distension
- Pulmonary thromboembolism
- Look-alike causes

Look-alikes are often a diagnosis of exclusion so obtaining a thorough history and performing a physical examination are essential to determine the cause of the patient’s respiratory distress. Since oxygenation and ventilation cannot be completely evaluated with a physical examination, arterial and/or venous blood gas analysis and pulse oximetry (SpO₂) will aid in identifying many of these respiratory disease processes. Thoracic radiographs can be an important diagnostic tool in determining the presence or absence of respiratory disease.

There are many look-alike causes for increased respiratory rate and/or effort. These include decreased oxygen delivery, metabolic causes, central neurological disease, peripheral nervous system diseases, environmental causes, drugs, or behavioral causes. A look-alike cause for respiratory distress is generally considered when the physical examination, evaluation of oxygenation, and thoracic radiographs do not suggest a cause for the increased respiratory rate and/or effort.

Look-Alike Causes of Respiratory Distress

Decreased Oxygen Delivery (DO₂)

Decreased oxygen delivery due to decreased oxygen content or decreased cardiac output may result in tachypnea.

Oxygen delivery is a product of oxygen content and cardiac output:

$$DO_2 = CaO_2 \times CO$$

where CaO₂ is the arterial oxygen content (mL/dL) and CO is cardiac output (L/min).

Arterial oxygen content is calculated with the following formula:

$$CaO_2 = ([Hb] \times SaO_2 \times 1.34) + PaO_2 \times 0.003$$

where:

- [Hb] is the hemoglobin concentration (g/dL)
- SaO_2 is the percent hemoglobin saturation with oxygen (expressed as a decimal)
- 1.34 is the oxygen-carrying capacity of Hb (mL/g); note that this constant varies from 1.34 to 1.38 depending on the reference
- PaO_2 is the partial pressure of oxygen in arterial blood (mmHg)
- 0.003 is the solubility coefficient for oxygen in plasma.

Based on these formulae, it can be appreciated that oxygen delivery may be diminished due to a decreased Hb concentration (anemia), reduced oxygen-binding capacity of Hb (dyshemoglobinemias such as methemoglobinemia or carboxyhemoglobinemia), decreased oxygenation of arterial blood (hypoxemia) or inadequate cardiac output (such as hypovolemia, pericardial tamponade, or myocardial failure).

Hypoxemia is defined as a low PaO_2 and is sensed by peripheral chemoreceptors, primarily in the carotid bodies, which will stimulate an increased respiratory rate and depth in order to deliver more oxygen to the alveoli [2]. Hypoxemia would be a respiratory cause for tachypnea. Other causes of inadequate DO_2 such as anemia or shock can also stimulate the peripheral chemoreceptors and can be a look-alike cause of tachypnea [2,3].

Acid–Base Disorders

Acid–base abnormalities are common in small animals and metabolic acidosis can result in an altered respiratory pattern associated with a compensatory respiratory alkalosis [4,5].

Common causes of severe metabolic acidosis include diabetic ketoacidosis (DKA), uremia, ethylene glycol intoxication, and lactic acidosis. The increased hydrogen ion concentration associated with metabolic acidosis stimulates peripheral and central chemoreceptors and the response is hyperventilation to decrease PaCO_2 . Expected respiratory compensation will result in decrease of PaCO_2 by 0.7 mmHg for each 1 mmol/L decrease in bicarbonate[−] in dogs. This compensatory response may occur less commonly in cats [6,7]. Kussmaul breathing can be seen with severe metabolic acidosis and is defined as an extremely deep, rapid breathing pattern associated with hypocapnia [2].

Brain Disease

Brain disease may result in an abnormal respiratory pattern, hyperventilation or hypoventilation.

Control of ventilation occurs in the medulla and pons, with generation of the respiratory rhythm [8].

Intracranial diseases affecting the brainstem or the cortex, such as infectious, inflammatory or neoplastic diseases, as well as head trauma causing cerebral edema or hemorrhage may cause direct injury to the respiratory center of the brain or lead to increased intracranial pressure, affecting respiratory centers. Irregular breathing patterns such as Cheyne–Stokes, gasping, cluster, and ataxic breathing may indicate brain injury [9].

Behavioral and Thermal Receptor Causes

Pain, stress, anxiety, and excitement can affect the voluntary (cortical) component of the respiratory center, causing tachypnea and panting [10]. Pain will result in sympathetic stimulation and subsequent tachypnea or panting. This may be mistaken for a primary respiratory abnormality.

If tachypnea causes hypocapnia and respiratory alkalosis, cerebral vasoconstriction can occur which may worsen hyperventilation [11]. Hyperventilation cannot be assessed via physical examination findings due to deadspace ventilation associated with panting and requires measurement of PCO_2 .

During hyperthermic conditions, evaporative cooling occurs via the respiratory system. Hyperthermia may result from a combination of environmental heat, increased muscle activity, or increased metabolism with exercise. An increased body temperature activates temperature-sensitive cells in the hypothalamus and subsequently cutaneous heat loss is achieved via increased cutaneous blood flow, reduction of heat by radiation, conduction, and convection. Additionally, the hypothalamus results in increased panting in dogs and heat is lost through evaporation [2,12].

Drugs such as pure mu-agonist opioids may decrease the hypothalamic thermoregulatory setpoint below normal which may result in panting or tachypnea despite a normal body temperature.

Drugs

There are several drugs that have the potential to stimulate tachypnea and can be a look-alike cause of increased respiratory rate and effort. Pure mu-agonist opioids may result in panting or tachypnea secondary to their thermoregulatory effects, as mentioned above [13,14]. Sodium bicarbonate leads to increased carbon dioxide production and may stimulate increased respiratory rate and/or effort in response. Dissociative anesthetics (ketamine, tiletamine-zolazepam), barbiturates (thiopental), and propofol may result in an apneustic breathing pattern (prolonged pauses following inspiration and expiration) [15,16].

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C. Cardiovascular Disease

51

Mechanisms of Heart Failure

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What is Heart Failure?

Heart failure is the inability of the heart to adequately meet the metabolic demands of the peripheral tissues [1]. Congestive heart failure (CHF) describes instances when these demands can only be met by increasing venous filling pressures, which leads to pulmonary or peripheral edema, pleural effusion, or ascites.

The mechanisms responsible for heart failure are numerous and complex, involving interactions between the heart and kidney, activation of neurohormonal systems such as the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), and development of maladaptive compensatory responses, such as cardiac remodeling and hypertrophy (Figure 51.1). Successful treatment of heart failure requires a close understanding of these mechanisms in order to improve cardiac output and alleviate venous congestion.

The clinical signs of heart failure include those relating to decreased cardiac output, such as weakness, exercise intolerance, fainting, hypothermia, and decreased mentation, and signs relating to congestion, such as dyspnea and abdominal distension. Therapy for congestive heart failure (see Chapter 38) typically involves decongestion through diuretics, afterload and preload reduction through arterial and venous vasodilation, and increased cardiac contractility through positive inotropes.

Neuroendocrine Systems in Heart Failure

Activation of neuroendocrine systems, such as the RAAS and SNS, is a critical feature of heart failure (see Figure 51.1). The RAAS is activated secondary to decreased renal blood flow and decreased tubular sodium and chloride concentration as sensed by the macula densa. In response, renin is released from the juxtaglomerular cells and catalyzes the conversion of

angiotensinogen to angiotensin I. Angiotensin I is then rapidly converted to angiotensin II (AngII) by angiotensin-converting enzyme (ACE) within the pulmonary vasculature. AngII is an important mediator of a variety of maladaptive responses, including vasoconstriction, fluid and sodium retention, myocardial and vascular remodeling, cross-activation of SNS, and aldosterone production [2]. Thus, pharmacological suppression of RAAS is a cornerstone of heart failure therapy. ACE inhibitors, such as enalapril or benazepril, and aldosterone antagonists, such as spironolactone, improve survival in dogs with heart failure [3–5]. Other proposed strategies to suppress RAAS include AngII-receptor blockers and direct renin inhibitors. Whether these therapies are useful in veterinary patients requires further study.

The SNS is another neuroendocrine system that is activated in heart failure (see Figure 51.1). Its main effector molecules, epinephrine and norepinephrine, increase heart rate, contractility and cardiac output, and divert blood flow via vasoconstriction to vital organs in response to stress. This classic “fight or flight” mechanism achieves short-term improvements in cardiac function, but is not designed to be chronically activated, as in patients with chronic heart failure. Chronically increased SNS activity is associated with persistent tachycardia, increased myocardial oxygen demand, and myocyte necrosis [2]. In the emergent patient with signs of low cardiac output, temporary augmentation of the SNS can be achieved using sympathomimetics such as dopamine, norepinephrine or dobutamine, but long-term activation of the SNS is not desirable.

The natriuretic peptide system is a neuroendocrine system that, in contrast to the RAAS and SNS, is cardioprotective [6]. B-type and atrial natriuretic peptides are produced by myocardial cells in response to stress and, unlike AngII or norepinephrine, these peptides elicit vasodilation and fluid and sodium excretion. Thus, the natriuretic peptides serve as an endogenous

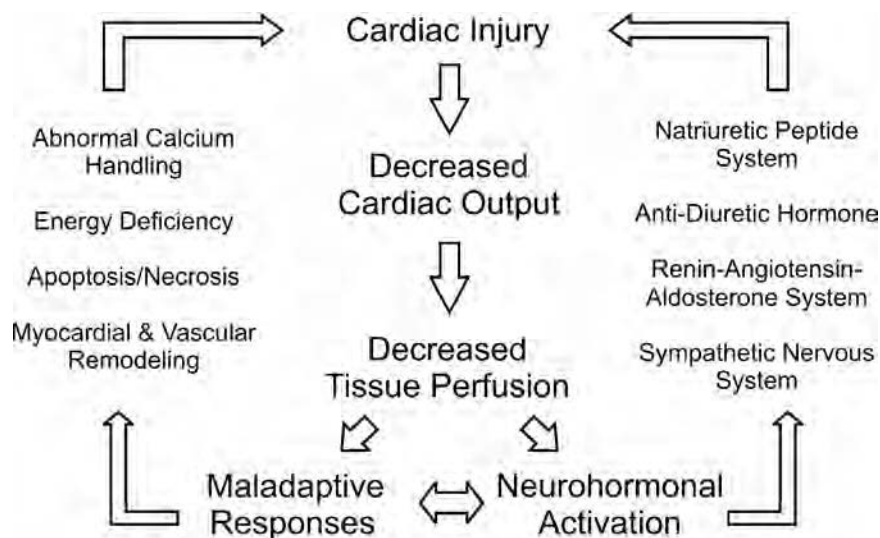


Figure 51.1 Pathophysiology of heart failure. Cardiac injury results in neurohormonal activation and maladaptive responses, such as cardiac remodeling and abnormal calcium handling. These responses further cardiac injury, resulting in a vicious cycle. See text for more details.

counterbalance system to the RAAS and SNS (see Figure 51.1). In chronic heart failure patients, despite increased circulating concentrations of the natriuretic peptides, there is a net retention of fluid and sodium due to natriuretic peptide receptor downregulation, increased peptide clearance or degradation, and abnormal posttranslational modification of the peptides, thus preventing their conversion into an active form.

The endothelin and vasopressin systems are two other important neurohormonal pathways that are activated in heart failure patients. Endothelin-1 is a potent vasoconstrictor that is produced in endothelial cells in response to mechanical disruption, shear stress, AngII, and other circulating cytokines. Circulating endothelin-1 concentrations are increased in dogs and cats with heart disease and, along with AngII, increase cardiac afterload [7,8]. Endothelin-1 might also play a role in pulmonary hypertension, which is an important co-morbidity in patients with chronic left-sided heart failure.

Vasopressin, or antidiuretic hormone, is another neurohormone that is upregulated in patients with heart failure [9]. Vasopressin increases reabsorption of free water within the renal collecting duct and contributes to venous congestion. Excessive free water retention dilutes serum sodium and chloride levels, resulting in so-called dilutional hyponatremia, which is a poor prognostic indicator in dogs with advanced heart disease [10].

Maladaptive Responses in Heart Failure

The morbidity and mortality of heart failure are closely associated with the progressive degree of myocardial hypertrophy that is caused by neurohormonal activation and hemodynamic abnormalities. Eccentric and concentric hypertrophy are caused by volume or pressure

overload, respectively. Eccentric hypertrophy is characterized by dilation of the ventricular chamber and growth of cardiac sarcomeres in series (i.e. end-to-end). Diseases that are commonly associated with eccentric hypertrophy include myxomatous mitral valve disease, dilated cardiomyopathy, and patent ductus arteriosus. Eccentric hypertrophy increases stress on the myocardial walls and myocardial oxygen demand and decreases myocyte contractility.

Concentric hypertrophy is characterized by increased thickness of the ventricular walls and growth of cardiac sarcomeres in parallel (i.e. side-by-side). Diseases that are commonly associated with concentric hypertrophy include hypertrophic cardiomyopathy, systemic or pulmonary hypertension, and subaortic stenosis. Concentric hypertrophy increases myocardial oxygen demand and impairs diastolic relaxation.

Other maladaptive responses in heart failure involve abnormal release and uptake of calcium within cardiomyocytes, resulting in further systolic and diastolic function, respectively (see Figure 51.1).

Global Cardiac Function in Heart Failure

Global function of the heart relates to the ability of the heart to eject an adequate volume of blood at high pressure during systolic contraction and to adequately fill the ventricles with blood at low pressure during diastolic relaxation.

The important relationship between pressure and volume during the cardiac cycle can be graphically represented by the left ventricular pressure–volume loop (Figure 51.2a). The uppermost plateau of the loop occurs during ventricular systole and indicates the volume of blood ejected (i.e. stroke volume) and the pressure developed within the

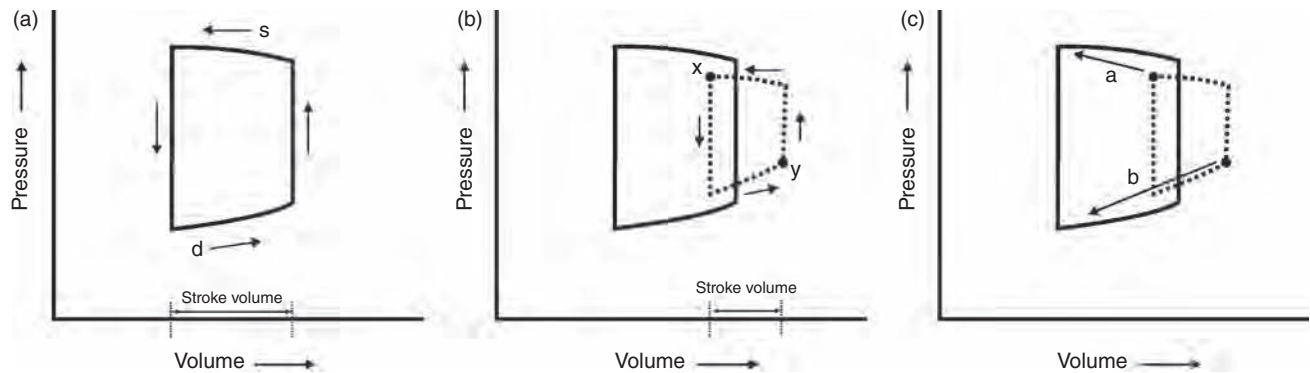


Figure 51.2 (a) Normal left ventricular pressure–volume relationship during systole (s) and diastole (d). The cardiac cycle proceeds around the pressure–volume loop in a counterclockwise fashion (arrows). (b) Left ventricular pressure–volume relationship in heart disease (dotted line). The end-systolic point (x) is shifted downward and rightward, causing lower pressure and reduced stroke volume. The end-diastolic point (y) is shifted upward and rightward, resulting in higher diastolic pressures and congestion. (c) Positive inotropes shift the end-systolic point upward and leftward by improving contractility, thereby increasing stroke volume and arterial pressure (a). Diuretics and venous vasodilators shift the end-diastolic point downward and leftward, thereby improving diastolic filling and reducing pressures (b). In this way, the abnormal cardiac function is restored closer to normal function (solid line).

ventricle and aorta (i.e. systemic arterial blood pressure) as a result of a healthy ventricular contraction. Following systole, the ventricle relaxes and pressure falls, which results in the aortic valve closing and the mitral valve opening. The lower portion of the loop represents ventricular diastolic filling. Importantly, ventricular volume increases with little change in ventricular pressure. This is important since ventricular pressure during diastole is equivalent to venous and capillary pressures, which need to remain low in order to avoid congestion. Finally, following the end of diastole, the ventricle begins its contraction. The mitral valve closes, followed shortly thereafter by aortic valve opening and ejection of blood.

The effect of heart disease on global cardiac function can be easily understood by examination of the pressure–volume loop (Figure 51.2b). Loss of contractility reduces stroke volume and ability to generate normal pressure, resulting in a downward and rightward shift of the end-systolic point of the pressure–volume loop. Clinical signs of impaired systolic dysfunction include systemic hypotension, pallor, muscle weakness, syncope, depressed mentation, hypothermia, tachycardia, and increased blood lactate concentration. Cardiac disease that causes diastolic dysfunction impairs the ability of the ventricle to relax, resulting in an upward and

rightward shift of the end-diastolic pressure–volume relationship. Higher pressures during ventricular filling result in development of venous congestion, leading to pulmonary edema, pleural effusion, or ascites.

Treatment

Treatment of heart failure involves diuretics, positive inotropes, and vasodilators (see Chapter 38), and the effect of each of these drugs on global cardiac function and the pressure–volume relationship is shown in Figure 51.2c. Diuretics and venous vasodilators shift the end-diastolic point downward and leftward by reducing preload or the volume within the heart. Positive inotropes shift the end-systolic point upward and leftward by improving stroke volume and cardiac output and resulting arterial pressures.

Conclusion

In summary, the mechanisms of heart failure are numerous and complex. Clinicians that understand these mechanisms are well positioned to provide rational and effective therapies for their patients.

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52

Congenital Cardiovascular Disease

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Introduction

Congenital heart disease of small animals is a relatively rare presentation to the emergency room, with the vast majority of these defects being identified in asymptomatic patients [1–3]. Although the definition of these conditions dictates their presence from the time of birth, the actual presentation of a patient with congenital heart disease varies in age and signalment [4,5]. While complex congenital defects are frequently identified in newborn babies, these lesions are rarely identified at such a young age in veterinary practice [3,6,7]. Some postulate that this may be secondary to neonatal death and failure to thrive in puppies and kittens with severe congenital heart disease. Diagnosis of congenital heart disease, which is challenging in the unstable patient, relies on identification and therapy of the common disease sequelae [8].

The most common emergency room presentations for small animals with congenital heart disease are left- and right-sided congestive heart failure, cardiovascular collapse/syncope, cyanosis (central and differential), and episodic weakness.

Diagnosis

Congenital heart disease should be considered in any juvenile animals with a moderate-to-loud heart murmur. However, the absence of an obvious heart murmur cannot be used to rule out congenital heart disease. For instance, right-to-left shunting defects are frequently observed without any obvious heart murmur and severe myocardial failure or abnormal pulmonary auscultation can mask potential heart murmurs in severely affected patients. Thoracic radiographs are frequently abnormal in patients with congenital heart disease. They are useful to identify congestive heart failure and establish patterns

of chamber enlargement or vascular abnormalities. Electrocardiography is also recommended in order to identify any significant arrhythmias and provide evidence of chamber enlargement, conduction disturbances or axis deviations, which are commonly encountered in patients with significant structural heart disease. In patients in which right-to-left shunting is suspected or confirmed, a packed cell volume (PCV) is recommended to screen for polycythemia. Focused echocardiography may be sufficient to identify effusions and left atrial enlargement, but is not sufficient in the diagnosis of congenital defects [9].

Congenital heart disease can be divided into two major categories: shunting defects and perivalvular defects. Shunting defects can be left to right, resulting in congestive heart failure and subsequent respiratory distress, or right to left, resulting in hypoxemia and cyanosis. Perivalvular lesions are more frequently associated with congestive heart failure (left- or right-sided), syncope or collapse. Table 52.1 provides differential diagnoses for the various clinical presentations that are encountered with congenital heart disease; the most common lesions are bolded within the table. Each clinical presentation will be briefly reviewed below in the context of congenital heart disease, but additional therapeutic considerations can be found within each respective chapter as noted.

Cyanosis

Congenital heart disease that leads to right-to-left shunts may present for cyanosis. Eisenmenger's physiology is observed when a previously left-to-right shunting lesion reverses in the face of elevated pulmonary pressures. The most commonly identified right-to-left shunting defect in dogs is tetralogy of Fallot (ToF). However, any intracardiac shunt or shunting lesion proximal to the brachycephalic trunk can result in central cyanosis if shunt reversal occurs [4].

Table 52.1 Differential diagnoses for the variable clinical presentations encountered with congenital heart disease. The most common lesions are bolded. The list provides the common presentations and most frequently encountered defects, and as such is not exhaustive.

Clinical presentation	Causative lesions to consider
Central cyanosis	ToF Eisenmenger's physiology (R-L VSD; R-L ASD) Total anomalous pulmonary venous return Transposition of the great vessels
Differential cyanosis	Reverse PDA
Left-sided CHF	PDA , VSD, ASD, AV canal defects, MVD
Right-sided CHF	PS , TVD, DCRV, pulmonary atresia/hypoplasia, ToF
Syncope/collapse	SAS , PS , TVD, ToF, Eisenmenger's physiology (R-L VSD, R-L ASD)
Episodic weakness	Reverse PDA , ToF

ASD, atrial septal defect; AV, atrioventricular; DCRV, double-chambered right ventricle; MVD, mitral valve disease; PDA, patent ductus arteriosus; PS, pulmonary stenosis; SAS, subaortic stenosis; ToF, tetralogy of Fallot; TVD, tricuspid valve dysplasia; VSD, ventricular septal defect.

Tetralogy of Fallot is the constellation of a ventricular septal defect, overriding (dextrapositioned) aorta, pulmonic stenosis (or atresia), and resultant right ventricular hypertrophy. Although this defect is rare in dogs [2,3], the clinical signs may prompt emergency room evaluation. Patients with ToF exhibit Eisenmenger's physiology when their right-sided heart pressures exceed left ventricular pressures and shunt reversal ensues.

Circumstances which increase pulmonary pressures will inherently, often transiently, increase the right-to-left shunt fraction and result in more severe central cyanosis. Excitation, exertion or exercise may worsen the degree of right-to-left shunting in ToF patients precipitously and result in episodic weakness or collapse, sometimes referred to as tet spells in children. Patients with ToF should have a characteristic left basilar systolic ejection murmur secondary to the pulmonic stenosis. Right axis deviation may be observed on electrocardiogram and jugular pulses or abdominal effusion may indicate right-sided pressure elevation or congestion. These patients are frequently cyanotic or cyanotic with exertion and may have varied degrees of polycythemia from prolonged hypoxemia.

Differential cyanosis results from right-to-left shunting defects that occur distal to the brachycephalic trunk. The most commonly observed is reverse patent ductus arteriosus (PDA), which occurs in a small portion of PDA

patients [10]. Reverse PDA is postulated to occur either by retained fetal circulation and persistence of high pulmonary vascular resistance or endothelial response to pulmonary overcirculation and resultant pulmonary hypertension.

Phlebotomy may be necessary for polycythemic patients with congenital heart disease [11]. In a patient with a PCV in excess of 70%, phlebotomy may be a useful means of palliation. Patients with hyperviscosity syndrome secondary to polycythemia may experience weakness, collapse, and seizures [12]. The author's preferred target PCV is 60% and cautions that further reduction below 60% usually results in clinical decompensation. Despite meticulous calculation, it is common for the resultant PCV to be higher than the desired PCV secondary to splenic contraction following phlebotomy. The author prefers to remove the phlebotomy volume in two equal portions, 4–6 hours apart [11]. In patients where the entire volume is removed in one session, a crystalloid fluid bolus of double the phlebotomy volume is administered intravenously. The calculation is pictured in Figure 52.1.

A lateral radiograph (Figure 52.2a) and still echocardiogram image (Figure 52.2b) are presented for a patient with right-to-left shunting PDA. This patient was evaluated for hindlimb weakness and episodic collapse. The PCV measured 72% and the patient responded favorably to sildenafil therapy and phlebotomy.

$$\text{Volume of Blood to Remove (ml)} = \text{Body Weight (kg)} \times \text{Blood Volume (ml/kg)} \times \frac{(\%PCV_{\text{Current}} - \%PCV_{\text{Desired}})}{\%PCV_{\text{Current}}}$$

Feline Blood Volume = 70ml/kg
Canine Blood Volume = 90ml/kg

Figure 52.1 A proposed calculation for palliative phlebotomy in patients with congenital heart disease and polycythemia.

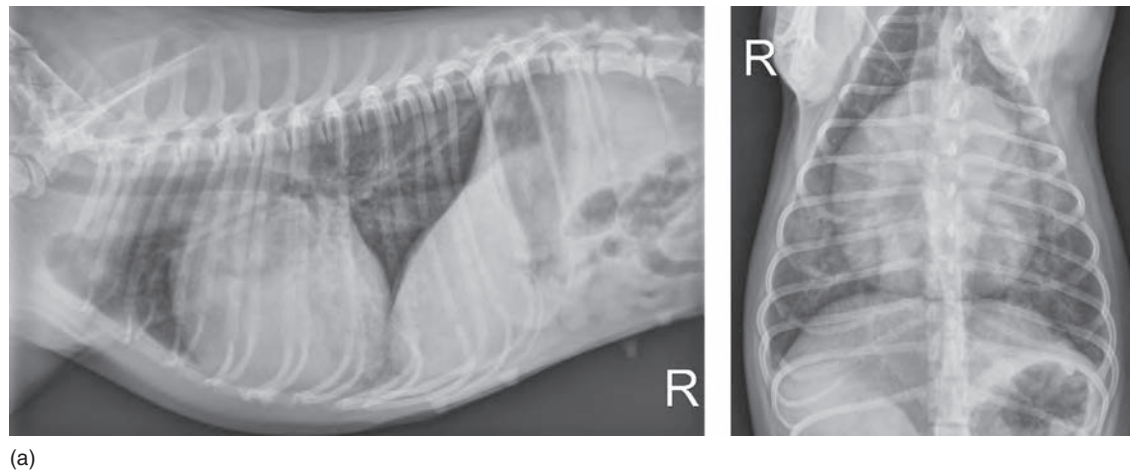
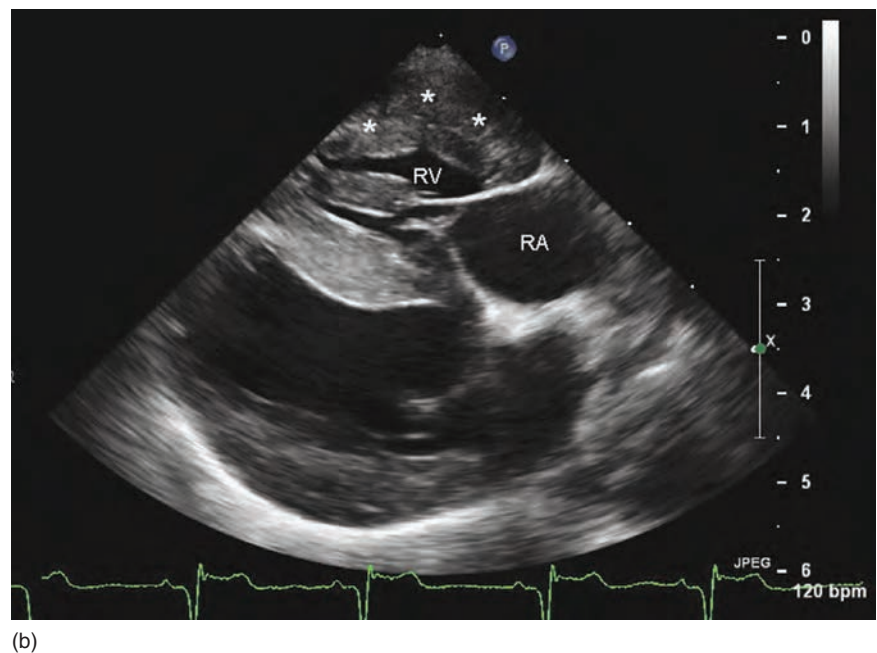


Figure 52.2 (a) Right lateral and dorsoventral thoracic radiographs demonstrate severe right ventricular enlargement with a bulging main pulmonary artery and distended caudal lobar arteries in a patient with reverse PDA. (b) A two-dimensional short axis image demonstrates the massive right ventricular concentric hypertrophy (*asterisks*) secondary to severe pulmonary hypertension in a patient with reverse PDA and polycythemia. Note the negative QRS complexes on the ECG tracing consistent with the patient's right axis deviation.



Congestive Heart Failure

For a thorough review of the pathophysiology and therapeutic considerations in patients with congestive heart failure, please refer to Chapters 38, 51, and 154.

Patients with a left-to-right shunt and left-sided congestive heart failure may benefit from reduced systemic pressure as this has the potential to improve forward blood flow and reduce the shunt fraction. Thus, the use of arterial vasodilators such as sodium nitroprusside, hydralazine or sedative agents that are associated with reduced blood pressure may be beneficial in the acute management of these patients. Similarly, situations that raise blood pressure, including stress or anxiety, may increase the shunt fraction and perpetuate congestion, suggesting the importance of keeping these patients calm via sedative agents as needed.

Syncope/Collapse

Evaluation of cardiac rhythm in patients with congenital heart disease is an important component of patient assessment. Dogs and cats with congenital heart disease may have hemodynamically significant ventricular or supraventricular cardiac arrhythmias [4,13]. Arrhythmias may represent the primary cause for presentation to the emergency room as a cause of syncope/collapse or act as a driving force in congestive heart failure. Additionally, the presence of significant arrhythmias may complicate the treatment of congestive heart failure and management of critical patients. For a thorough review of the mechanisms of cardiac arrhythmias and therapeutic considerations in patients with hemodynamically significant arrhythmias, please refer to Chapters 5 and 53.

Pulmonary hypertension can be a co-morbidity of congenital heart disease. It can be part of the right-to-left shunting physiology or result from severe left-sided heart disease and pulmonary venous origins [14]. Patients with pulmonary hypertension and a right-to-left shunt may benefit from pulmonary vasodilation with drugs such as sildenafil citrate [15]. Pulmonary hypertension in patients with severe left-sided heart disease should be managed cautiously as improving pulmonary blood flow may increase preload and further propagate left-sided congestive heart failure. For additional considerations in pulmonary hypertension, see Chapter 59.

Conclusion

Congenital heart disease is a rare presentation to the emergency room. When encountered, the final diagnosis is reliant upon advanced echocardiographic evaluation that is not feasible in the emergency room [9,16,17]. Management of the patient's clinical signs and stabilization should be the primary goals and typically involve treatment of the most common disease sequelae such as cardiac arrhythmias, congestive heart failure, or polycythemia. Once stable, referral for cardiology evaluation is warranted for definitive diagnosis and in some cases, consideration of interventional therapy.

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Arrhythmias

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Introduction

Cardiac arrhythmias (aka dysrhythmias) are defined as disturbances in the rhythm of the heart [1–4]. Arrhythmias may be normal physiological variants, such as sinus tachycardia due to excitement, clinically insignificant individual variants, such as second-degree AV block type 1 (Wenckebach), markers for underlying structural heart disease, as is often the case with atrial fibrillation, or the primary cause of clinical signs: episodic weakness, syncope, or even sudden death. In the emergency setting, the most important goal is to accurately diagnose the rhythm present, determine which of the above scenarios is most likely, and devise an appropriate treatment plan if indicated. A vagal maneuver is always indicated when a hemodynamically significant tachycardia is present because a positive response is both therapeutic and can be helpful for diagnostic purposes (although ventricular tachycardia is unlikely to respond). Likewise, an atropine response test should be considered for all patients with hemodynamically significant bradycardias, both for diagnostic and therapeutic purposes.

Broadly, arrhythmias can be divided into those disorders where the creation or conduction of impulses is faster than normal, and those where it is slower than normal. Both situations can cause identical clinical manifestations: arrhythmias that involve an excessively high heart rate (tachycardias or tachyarrhythmias) are indistinguishable in their clinical manifestations from those arrhythmias that cause an excessively slow heart rate (bradycardias or bradyarrhythmias). The rapid fluctuations in heart rate brought on by sporadic arrhythmias can alter cardiac output faster than a patient's homeostatic mechanisms can offset the changes. Therefore, forward cardiac failure, manifested classically as syncope, is the chief complaint of cardiac dysrhythmias, in contrast to chronic mechanical pump failure, such as with dilated cardiomyopathy, where backward (congestive)

heart failure occurs as a result of the cardiac pathology exceeding the body's compensatory mechanisms.

The underlying mechanism causing an arrhythmia may be an abnormality of impulse initiation, impulse conduction, or both. Enhanced impulse initiation occurs when a cell or group of cells undergo rapid phase 4 depolarization and can be caused by automaticity (i.e. a subsidiary pacemaker fires at a faster rate than the sinus node and takes over control of the heart rhythm) or triggered (i.e. depolarizing afterpotentials are produced by an initiating beat or trigger). These afterdepolarizations may be early or delayed. Conditions that prolong the action potential will increase the amplitude of early afterdepolarizations and therefore the chance of triggered activity. In contrast, delayed afterdepolarizations occur after full electrical recovery and generally happen when intracellular calcium ion activity is increased. Abnormal impulse conduction can cause bradycardias, when there is blocked conduction, or tachycardias, when re-entrant activation occurs. Re-entry can result in a single or multiple premature depolarizations. When re-entry occurs, the impulse persists to re-excite the chambers of the heart after the refractory period is over, and the activity can occur in the atria or the ventricles.

When bradycardias affect cardiac output, they do so by compromising heart rate (cardiac output [mL/min] = heart rate [beats/min] · stroke volume [mL/beat]) whereas tachycardias limit cardiac output by impacting stroke volume. An ECG diagnosis to identify the arrhythmia is necessary because exactly the same clinical signs can arise from tachycardias and bradycardias. When the ECG has identified an abnormality, defined as a clinically relevant finding not explained by normal physiological changes (i.e. sinus tachycardia caused simply by excitement), then a complete work-up of possible underlying metabolic diseases is appropriate [5]. A complete work-up would include thoracic radiographs, echocardiography, arterial blood pressure, and laboratory tests

such as complete blood count, serum biochemistry, urinalysis, etc. in addition to a thorough history and physical examination. However, often in the emergent situation there is no time to do more than start this process and therapeutic steps must be taken as efficiently as possible.

Tachycardias

When a significant tachycardia is present even intermittently (≥ 240 beats/minute for 60 seconds or more despite a calm environment) and no identifiable systemic illness is present, a pathological tachycardia should be suspected. With such unrelentingly high heart rates, pathological tachycardias including ventricular tachycardia (VT), atrial tachycardia (AT), atrial fibrillation, and macro re-entry need to be ruled out with an ECG. The *morphology or shape of the QRS complex* is an important clue to the site of origin of the rhythm. A QRS complex of different morphology is expected when the complex is ventricular in origin because the pattern of ventricular depolarization spreads in a different orientation if it originates from a focus within the ventricles than if it spreads from the His bundle during a normal sinus beat. The QRS complex of a ventricular complex is always wider than a normal sinus QRS complex because myocyte-to-myocyte electrical transmission is more time-consuming than the normal rapid conduction through the ventricles' His–Purkinje system.

Finally, since the wave of ventricular repolarization follows the same course as the wave of depolarization that preceded it, the T-wave of a ventricular complex is of a different morphology compared to a sinus T-wave.

Several electrocardiographic impostors exist that mimic ventricular ectopic complexes and it is important to keep these in mind when evaluating ECGs. The primary differentials for wide QRS morphology are:

- ventricular ectopic beat
- aberrant conduction due to left or right bundle branch block
- right axis deviation due to right ventricular enlargement or cardiac displacement
- electrolyte abnormalities (i.e. hyperkalemia).

It is important to remember that any of these abnormalities may result in wider than normal QRS morphology on the body surface ECG.

Supraventricular Tachycardia

Supraventricular tachycardia is broadly defined as any tachycardia originating from the SA node, atrial myocardium, AV node/junction, or great vessels connecting to the atria [6]. Specifically included are sinus tachycardia,

sinus node re-entrant tachycardia, automatic atrial tachycardia, intra-atrial re-entrant tachycardia, atrial flutter, atrial fibrillation, AV nodal re-entrant tachycardia, orthodromic atrioventricular reciprocating tachycardia, and automatic junctional tachycardia [7]. Of these, sinus tachycardia is generally a normal physiological response to increased adrenergic activity. The other rhythms may generally be grouped in the broad category of “atrial tachycardia.” This simplification is adequate for practical purposes of dealing with these arrhythmias in the emergency setting because they can be treated similarly. Further work-up to identify the specific rhythm can wait until the patient is stabilized.

An AT is defined as a series of three or more consecutive atrial premature complexes, some or all of which may successfully cross the AV node. Generally, because the depolarizations are entering the ventricles through the AV node, the QRS shape will be narrow (normal in duration). However, if any of the above listed causes of aberrant ventricular depolarization are present (such as bundle branch block), the QRS is wide in spite of originating above the ventricles. When atrial activity is excessively rapid, the filtering function of the normal AV node may limit the number of P'-waves (ectopic atrial depolarizations) admitted into the ventricles, a protective mechanism called physiological AV block. For example, if an ectopic atrial focus fires at a rate of 420 beats/minute and each atrial impulse crosses the AV node normally into the ventricles (“1:1 conduction”), then the ventricular rate would be 420 bpm. Such a rapid heart rate could be expected to cause a substantial decrease in cardiac output due to severely limited diastolic filling time. In some patients with this type of dysrhythmia, physiological 2:1 or 3:1 second-degree AV block may occur, producing heart rates much closer to the normal range: 210 or 140 beats/minute, respectively. This variation in AV nodal conduction explains why some patients may tolerate AT better than others.

Ventricular Tachycardia

There are three electrocardiographic features of ventricular ectopy: premature occurrence; QRS complex of different morphology; and T-wave of different morphology. Premature occurrence refers to a shorter than normal coupling interval: the ventricular premature complex (VPC) occurs earlier than a normal sinus QRS would have occurred. For a VPC to occur, spontaneous firing within the ventricles takes control of ventricular depolarization, meaning the normal depolarization from the SA node courses normally through the atria (and a P-wave is generated) but the impulse does not conduct to the ventricles because they are either still in the midst of the VPC's depolarization or refractory while

repolarizing post-VPC. Thus, P-waves may or may not be visible on the ECG. The QRS morphology is a more important characteristic to identify a complex as ventricular in origin (wide, bizarre morphology or shape) than absence of P-waves. Also, ventricular rhythms are usually regular, a characteristic that can be useful for differentiating VT from AT with aberrant conduction.

The occurrence of four or more VPCs consecutively at a rate of 160 beats/minute in dogs (240 beats/minute in cats) or greater is termed VT. VT may occur for any length of time and at any rate, including rapid VT (>280 beats/minute) wherein diastolic filling of the ventricles is compromised and a reduced, possibly inadequate, cardiac output occurs. A rhythm that consists of four or more VPCs occurring consecutively but where the rate is less than the defined rate for ventricular tachycardia (VT; 160 beats/minute) and faster than a ventricular escape rhythm (30–40 bpm) is called accelerated idioventricular rhythm (AIVR). The major difference is that the slower rate of AIVR provides more time for diastolic ventricular filling, and therefore the rhythm is usually hemodynamically stable and does not require treatment.

Differentiation of the type of tachycardia, as well as a therapeutic benefit if the tachycardia terminates, make a vagal maneuver the first approach in an animal with tachycardia [7]. The purpose of a vagal maneuver is to increase parasympathetic tone to the SA and AV nodes, since they receive a large proportion of the autonomic input to the heart. Slowing of the sinus rate and/or transient physiological AV block are the most common and desired effects. Ventricular rhythms such as VT are less easily influenced by vagal maneuvers, if at all.

Vagal maneuvers can be performed safely and consistently. One form of vagal maneuver, carotid sinus massage, involves the simple application of gentle, sustained digital pressure by the clinician to the external region of the neck overlying one or both of the patient's carotid sinuses, located just caudal to the dorsal aspect of the larynx (a gag reflex may be elicited), for 5–10 seconds, while the ECG tracing is being recorded. Such a maneuver should be tolerated by the patient, and signs of discomfort, resentment, or a marked change in heart rate warrant immediate termination of the maneuver. The other form of vagal maneuver used routinely is ocular pressure. It consists of applying firm but controlled gentle digital pressure to both globes through closed eyelids. Subjectively, the amount of pressure applied should not exceed the digital pressure one would place on a ripe grape without rupturing it. Likewise, this should be acceptable to the patient, and signs that it is not warrant immediate termination. Ocular pressure is contraindicated in patients with ocular problems. The effect of a vagal maneuver should be manifested at some point during the application of pressure (typically within

5–15 seconds of initiation of the maneuver). It must be remembered that vagal maneuvers increase parasympathetic tone but are not a guarantee of parasympathetic override. In an anxious, distraught, or otherwise strongly sympathetically stimulated patient, there may be no response simply because of the sympathetic stimulus, not because the arrhythmia is independent of the SA and AV nodes.

If the vagal maneuver is not effective and if the tachycardia is severe enough to be negatively impacting cardiac output (recumbent patient with weak or absent pulse), intravenous medical management is warranted.

Treating Supraventricular Tachycardias

Intravenous diltiazem hydrochloride or a beta-adrenergic blocker (propranolol or esmolol) are recommended for emergent care (Table 53.1). It is important to remember that beta-adrenergic receptor blockers will negatively affect systolic function. Esmolol is an ultra short-acting beta-adrenergic receptor blocker. For this reason, in a patient at risk of systolic dysfunction (for example, a Doberman pinscher with unknown cardiac status), diltiazem or esmolol should be chosen over propranolol. For the same reason, beta-adrenergic receptor blockers should not be used in animals exhibiting uncontrolled congestive heart failure. For chronic control of AT, digoxin may be effective but one study suggests that for optimal heart rate control, digoxin and diltiazem should be used together [8].

Treating Ventricular Tachycardias

Lidocaine (see Table 53.1) is used as the first-line antiarrhythmic in dogs. Although lidocaine can be used successfully in cats, an alternative to lidocaine for intravenous treatment of VT in cats is a beta-adrenergic receptor blocker (propranolol). The basis is both the narrow safety margin in cats for lidocaine and the observation that beta-receptor stimulation via epinephrine can trigger ventricular arrhythmias even in cats with normal hearts [9], and likely more so in hypertrophied hearts [10]. Both esmolol and propranolol bind beta-1 adrenergic receptors, and therefore their antiarrhythmic effect is not specific to the ventricles but is expected to be relevant when catecholamine stimulation is contributing to VT. Amiodarone (see Table 53.1) is an antiarrhythmic with properties extending into all four Vaughn-Williams classes, but mainly class III. It is one of the most widely used antiarrhythmics in human cardiology, but is less commonly used in veterinary cardiology.

Magnesium deficiency may predispose to cardiac arrhythmias. Magnesium sulfate can be administered at an IV dosage of 30 mg/kg slowly, while monitoring for mental

Table 53.1 Drugs for treating tachycardias (peach-shaded drugs are for supraventricular tachycardias; yellow-shaded drugs are for ventricular tachycardias and blue-shaded drugs can treat either).

Drug	Drug action	Dose	Formulation	Comments
Atenolol	Beta-1 selective adrenergic blocker	D: 0.25–2.0 mg/kg PO q12–24h C: 6.25–12.5 mg PO q12–24h	Tab: 25, 50, 100 mg Oral suspension: 25 mg/mL	Less bronchoconstriction than non-selective beta-blockers; avoid with CHF
Esmolol	Ultra-short-acting beta-1 selective beta-adrenergic blocker	D,C: 25–100 µg/kg IV bolus every 5 min (up to 500 µg/kg max), then 10–200 µg/kg/min CRI	Inj: 10 mg/mL	
Metoprolol	Beta-1 selective beta-blocker	D: 0.25–1.0 mg/kg PO q8h C: Same	Tab: 25, 50, 100 mg Inj: 1 mg/mL	
Procainamide	Class 1 antiarrhythmic agent	D: 10–30 mg/kg IM, PO q6h 2 mg/kg IV over 3–5 min up to total dose of 20 mg/kg 20–50 µg/kg/min CRI C: 2–5 mg/kg PO q6–8h	Cap: 250, 375, 500 mg Tab: 250, 375, 500 mg Tab: CR, SR: 250, 500, 750, 1000 mg Inj: 100, 500 mg/mL Some oral formulations may be unavailable	Beware hypotension with IV administration Effects increased by high potassium and decreased by low potassium Monitor ECG; 25% prolongation of QRS is sign of toxicity May be difficult to obtain Use with caution in cats Reduce dose with severe renal and liver disease
Propranolol	Non-selective beta-blocker	D: 0.2–1.0 mg/kg PO q8h 0.02–0.06 mg/kg IV over 5–10 min C: <4.5 kg: 2.5–5 mg PO q8–12h >4.5 kg: 5 mg PO 8–12h 0.02–0.06 mg/kg IV over 5–10 min	Tab: 10, 20, 40, 60, 80 mg Cap: 60, 80, 120, 160 mg	Beware of possible bronchoconstriction Start with low dose and titrate to effect
Sotalol	Antiarrhythmic agent with class II (beta-blocking) and class III effects	D: 1–2 mg/kg PO q12h (medium-size dogs: start with 40 mg per dog, then increase to 80 mg, if needed) C: 2 mg/kg PO q12h	Tab: 80, 120, 160 mg	Monitor closely with CHF due to negative inotropic properties
Digoxin	Cardiac glycoside	D: 0.003–0.005 mg/kg PO q12h C: 0.01 mg/kg PO q48h (use pill as elixir is distasteful to cats)	Tab: 0.0625, 0.125, 0.1875, 0.25, 0.5 mg Elixir: 0.05 mg/mL	Toxicity potentiated by hypokalemia, hyponatremia, hypercalcemia, hypothyroidism; dose on lean body weight; therapeutic range 1–2 ng/mL 8h after dose

Drug	Drug action	Dose	Formulation	Comments
Diltiazem	Calcium channel blocker	D: 0.5–5 mg/kg PO q8h; 0.1–0.2 mg/kg IV bolus, then 2–6 µg/kg/min IV CRI Dilacor XR: 3–4 mg/kg PO q24h C: 1–2.5 mg/kg PO q8h 0.1–0.2 mg/kg IV bolus, then 2–6 µg/kg/min IV CRI	Tabs: 30, 60, 90, 120 mg Inj: 5, 10, 50, 125 mg/mL Dilacor XR: 120, 180, 240 mg Cardizem CD: 120, 180, 300 mg	Extended-release formulations have unpredictable bioavailability
Amiodarone	Class III antiarrhythmic with some class I, II, and IV effects	D: Loading dose of 10 mg/kg PO q12h for 1 week, thereafter 5 mg/kg PO q12–24h C: None	Tablets: 200 mg Inj: 50 mg/mL	Use as last resort for recurrent unstable ventricular tachycardia; takes weeks to achieve therapeutic levels. Side-effects include anorexia, liver, thyroid, and pulmonary dysfunction
Lidocaine	Class I antiarrhythmic	D: 2 mg/kg slowly IV or IO (double the dose IT) in 2 mg/kg boluses followed by IV drip at 30–80 (occasionally up to 100) µg/kg/min CRI C: 0.25–0.75 mg/kg IV over 5 min	Inj: 5, 10, 15, 20 mg/mL (without epinephrine)	Use with caution in cats as may cause seizures. Drug of choice for initial control of ventricular tachycardia. Effects increased by high potassium and decreased by low potassium
Magnesium sulfate	Electrolyte	D: 0.75–1 mEq/kg/24 h IV infusion (50% of total dose can be given in 2–4 h if necessary) For ventricular fibrillation: 0.15–0.30 mEq/kg IV over 5–10 min C: 30 mg/kg slow IV	20% MgCl ₂ solution for injection (contains 1.97 mEq of Mg++ per mL)	
Mexiletine	Class I antiarrhythmic	D: 5–8 mg/kg PO q8–12h C: None	Cap: 150, 200, 250 mg	Reduce dose with liver disease Take with food to reduce GI side-effects

C, cat; CHF, congestive heart failure; CR, controlled release; CRI, continuous-rate infusion; D, dog; ECG, electrocardiogram; GI, gastrointestinal; IM, intramuscular; IO, intraosseous; IT, intrathecal; IV, intravenous; PO, by mouth (*per os*); SR, sustained release; XR, extended release.

depression or dullness, weakness, bradycardia, hypotension, or hypocalcemia as signs that warrant termination of administration. Magnesium sulfate is a logical choice in a patient with VT requiring antiarrhythmic treatment when hypomagnesemia has been documented or is suspected, such as when electrolyte-wasting drugs (e.g. furosemide) have been used. Similarly, hypokalemia may increase the likelihood of ventricular ectopy and should be kept in mind as a possible contributing factor, particularly since it is treatable with potassium supplementation.

For chronic therapy, mexiletine and/or sotalol are most commonly used for control of VT (and amiodarone can be used for chronic therapy as well).

The therapeutic goal is to reduce or eliminate extremes of tachycardia that would reduce cardiac output, that is, to provide medication at a level that prevents a persistent

HR > 160 and stops tachycardia-associated syncope or other arrhythmia-associated clinical signs. Follow-up is warranted after 7–14 days of antiarrhythmic therapy, or sooner if clinical signs worsen or new clinical signs appear.

Bradycardias

Bradycardias may be physiological (due to high vagal tone) or pathological and arise from faulty intracardiac conduction (atrioventricular block), electrolyte abnormalities such as hyperkalemia (atrial standstill), sinus node dysfunction (sick sinus syndrome), etc.

Assessment of the physiological (generally harmless) versus pathological (may cause clinical signs such

Table 53.2 Drugs for treating bradycardias.

Drug	Drug action	Dose	Formulation	Comments
Atropine	Anticholinergic	D, C: 0.01–0.04 mg/kg IV, IM, IO 0.02–0.04 mg/kg SC q6–8h (IT: double dose)	Inj: 0.05, 0.1, 0.3, 0.4, 0.5, 0.8, 1.0 mg/mL	May transiently worsen bradyarrhythmia after intravenous administration
Dobutamine	Beta-adrenergic agonist	D: 2.5–20 µg/kg/min (titrate up to effect). C: 2–10 µg/kg/min (titrate up to effect)	Inj: 12.5 mg/mL	Inotropic effect is dose dependent Less arrhythmogenic than most other catecholamines Use with caution in cats; may cause seizures
Glycopyrrolate	Anticholinergic	D,C: 0.005–0.01 mg/kg IV, IM, 0.01–0.02 mg/kg SC	Inj: 0.2 mg/mL	Longer duration of action
Hyoscyamine	Anticholinergic	D: 0.003–0.006 mg/kg PO q8h	Tab: 0.125 mg	
Isoproterenol	Sympathomimetic agent	D,C: 0.04–0.09 µg/kg/min IV (titrate up to effect) 10 µg/kg/min IM, SC q6h	Inj: 1:5000 (0.2 mg/mL)	Used as an emergency treatment until artificial pacing can be accomplished
Propantheline bromide	Anticholinergic	D,C: 0.25–0.5 mg/kg PO q8–12h	Tab: 7.5, 15 mg	
Terbutaline	Beta-2 agonist bronchodilator	D: 1.25–5 mg/dog PO q8–12h C: 0.1 mg/kg PO q8h or 0.625–1.25 mg/cat q12h; 0.01 mg/kg SC, IM, IV	Tablet: 2.5, 5 mg Inj: 1 mg/mL	Reduce dose by 50% first 4 days to prevent restless behavior. Decrease dose with renal disease
Theophylline	Methylxanthine bronchodilator	D: 9 mg/kg PO q8–12h Extended release: 10 mg/kg PO q12h C: 4 mg/kg PO q12h Extended release: 19 mg/kg PO q24h at night	Tab: 100, 200, 300, 450 mg Cap: 50, 75, 125, 200 mg (availability of extended-release formulations may be variable)	Dose on lean body weight

C, cat; D, dog; IM, intramuscular; IO, intraosseous; IT, intrathecal; IV, intravenous; SC, subcutaneous.

as syncope) nature of bradycardias can be ascertained with an atropine response test: an ECG strip is recorded, and 0.04 mg/kg atropine is immediately administered IV or IM. One or both follow-up ECGs recorded 15 and 30 minutes later should demonstrate sinus tachycardia if the bradycardia is vagally mediated. Respiratory, central nervous system, gastrointestinal, and ocular diseases can increase vagal tone and result in secondary bradycardia. If the patient is asymptomatic for the bradycardia, addressing the underlying disease may be all that is necessary. However, if the heart rate increases with atropine administration, and the patient displays symptoms consistent with poor arterial perfusion, such as syncope, treatment with terbutaline or theophylline (Table 53.2)

may be useful to reduce vagal influence. Propantheline bromide (see Table 53.2) is an oral vagolytic drug and a good choice if there is a positive atropine response.

An atropine response test is indicated in all patients with bradycardia for diagnostic and possible therapeutic effects. However, it is unlikely to be effective in patients with third-degree AV (complete heart block) or high-grade second-degree AV block. These patients and those that do not respond adequately to atropine administration (i.e. patients with sick sinus syndrome) usually require a pacemaker. Until a permanent pacemaker can be implanted, dobutamine or isoproterenol (see Table 53.2) may be effective in increasing the heart rate and stabilizing the patient.

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Pericardial Effusion

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Etiology

Abnormal accumulation of pericardial effusion (PE) is the most common type of pericardial disorder seen in small animal emergency practice as a clinically relevant finding in dogs. One urban hospital determined that PE accounted for 7% of all dogs presenting with cardiac disease [1]. Most dogs with PE are older, large-breed dogs, most commonly represented by golden retrievers [2–8]. German shepherd dogs, Labrador retrievers, and St Bernards are also commonly affected [4,5]. In cats, the incidence of PE appears to be much lower than in dogs, accounting for only 1–2% of all cats admitted to referral hospitals [9,10]. PE in the cat is often an incidental finding discovered during diagnostic work-up of other diseases, frequently secondary to congestive heart failure (CHF) [9–11].

In dogs, the majority of PE cases result in hemorrhagic effusions due to neoplasia or idiopathic pericarditis [12]. Cardiac hemangiosarcoma (HSA) is by far the most common cause of PE in dogs, accounting for 61% of all canine PE cases [2]. It is also the most common neoplastic cause of canine PE, resulting in approximately two-thirds of all cardiac tumors in the dog [13]. Cardiac HSA typically grows from the wall of the right atrium or right auricle and is highly malignant. At the time of diagnosis, HSA has usually metastasized to other organs, most commonly the lungs, liver, or spleen [5]. Micrometastatic disease may predominate when cardiac HSA is initially diagnosed, as concurrent splenic, pulmonary or hepatic tumors may be identified in only about 25% of all cases [2]. Cardiac HSA is rarely seen in the cat, although it has been documented in a case report [14].

Heart base tumors (HBT), including chemodectomas (aortic body tumors) and ectopic thyroid tumors, occur with some regularity but are still relatively uncommon, with an incidence that is 10-fold lower than cardiac HSA [2,13]. Boxers, English bulldogs and Boston terriers are

predisposed to HBTs, but other breeds commonly diagnosed with PE are affected too [2,15]. Other neoplasms that cause PE include mesotheliomas, lymphosarcoma, rhabdomyosarcomas, fibrosarcomas, thymomas, and adenocarcinomas. Mesotheliomas are often difficult to diagnose without histopathology because they may not form discrete masses and cytological analysis of effusions often fails to differentiate neoplastic cells from reactive mesothelial cells [16,17]. There is some evidence that golden retrievers with idiopathic pericarditis may develop mesotheliomas over time due to chronic inflammation [16]. PE caused by cardiac tumors in cats is uncommon but lymphosarcoma, adenocarcinoma, and mesothelioma have all been reported [2,9–11,18].

Idiopathic pericarditis is the second most common cause of PE in dogs and may account for nearly 23% of all cases [2,19]. Idiopathic pericarditis is a diagnosis of exclusion; all other differentials are ruled out through diagnostic testing (radiography, echocardiography, pericardial fluid cytology and/or culture, and histopathology) [7]. Idiopathic pericarditis is usually seen in middle-aged to older medium and large-breed dogs, and effusion is hemorrhagic in nature [12]. In cats, idiopathic causes of pericardial effusion are infrequently reported and are not a principal cause of clinical disease [11].

Septic pericarditis is uncommonly reported in dogs and rarely seen in cats. Causes of septic pericarditis reported in the dog include foreign body migration [20], penetrating trauma [21,22], and various bacterial, fungal, and protozoal infections [20,22–31]. Immunosuppressive drugs were implicated in the development of septic pericarditis in one dog [32]. In the cat, documented causes of septic pericarditis include dental infection [33], pyometra [34], feline infectious peritonitis [2,10,12], or other systemic infections [10].

Other reasons for hemorrhagic PE in dogs and cats include coagulopathy, trauma, and left atrial rupture in small-breed dogs with severe endocardiosis. CHF,

hypoalbuminemia, uremia, and congenital malformations such as pericardial cysts or peritoneopericardial diaphragmatic hernias, will cause a transudative PE [2,12]. Hypothyroidism may be associated with a cholesterol-based effusion [2,35]. CHF is a common cause of PE in cats, but is rarely voluminous enough to cause clinical disease [2,10,11]. Hypertrophic cardiomyopathy is the most common cause of PE secondary to CHF in cats [10,11].

Pathophysiology

Cardiac tamponade (CT) occurs when accumulation of fluid within the pericardial space causes intrapericardial pressure to rise and exceed normal cardiac diastolic pressures. Compression collapses the compliant right atrium during diastole, followed by the right ventricle and, in severe cases, the left ventricle. Ventricular filling during diastole becomes impaired, resulting in decreased stroke volume, cardiac output, and increased systemic venous congestion. Because the pericardium is relatively non-compliant, a sudden, acute increase in PE can result in severe CT, even with small volumes of effusion. With chronic accumulation of PE, neurohormonal activation of the renin-angiotensin-aldosterone system increases fluid retention and offsets the rise in intrapericardial pressure by increasing preload. The pericardial space will also gradually stretch and expand. Both factors allow for large volumes of PE to develop before the onset of CT [2,12,36].

Pulsus paradoxus is a typical finding with CT. Normally, decreased intrathoracic pressure during inspiration enhances right atrial and ventricular filling and pulmonary blood flow by its effect on these more compliant vessels and chambers. Blood pools in the pulmonary circulation, decreasing left ventricular preload and stroke volume, resulting in a slightly decreased arterial pressure during inspiration. This effect becomes exaggerated during CT, resulting in pulsus paradoxus. The respiratory variation in arterial pressure during pulsus paradoxus can exceed 10 mmHg [2,12,36].

Clinical Presentation

Clinical signs associated with PE are largely due to the effects of CT. Common reasons for dogs with PE to present to the emergency service include dyspnea, lethargy, inappetence, exercise intolerance, weakness or collapse, and abdominal distension. Some dogs will also exhibit vomiting, diarrhea, polydipsia, or cough. Common physical exam findings include muffled heart sounds, lethargy, weak pulses, tachypnea or dyspnea, ascites, and

tachycardia. Other exam findings may include arrhythmias, jugular venous distension, pale or congested mucous membranes, cachexia, hepatomegaly, muffled lung sounds, and pulsus paradoxus [2,4,5,12]. Right-sided congestive heart failure is common, but severe cases of CT may present in biventricular heart failure or cardiac arrest.

Even though CT is rarely seen in cats, they may experience it and present with any of the aforementioned clinical signs.

Diagnostic Testing

Clinical presentation should trigger the clinician to rule out PE, especially in breeds predisposed to cardiac tumors and idiopathic pericarditis. Echocardiography is the gold standard for diagnosing PE, but thoracic radiography, electrocardiography, and analysis of pericardial fluid can all aid in diagnosis. More recently, computed tomography and magnetic resonance imaging have been used to identify cardiac tumors in dogs, but neither modality has proved more effective than echocardiography [12,37,38].

The classic appearance of pericardial effusion on thoracic radiographs is an enlarged, globoid cardiac silhouette seen in both lateral and ventrodorsal views. In one study, 87% of all PE cases demonstrated this finding [5]. Absence of this finding could be due to pleural effusion obstructing the views, while acute development of PE may simply not enlarge the cardiac silhouette. Marked cardiac enlargement from other cardiac diseases, such as dilated cardiomyopathy, may mimic globoid cardiac enlargement and should be ruled out [2,12]. Vertebral heart scores are only moderately accurate at differentiating PE from other cardiac diseases [39], and no radiographic finding is useful for predicting the presence of CT [40]. Other radiographic findings seen with PE include tracheal elevation, pleural effusion, distention of the caudal vena cava, hepatomegaly, and ascites [2,12].

Echocardiography is highly sensitive and specific for detection of PE, even in small volumes. PE appears as an echolucent zone surrounding the heart between the bright parietal pericardium and the epicardium. Identification of the brighter parietal pericardium helps differentiate PE from pleural effusion, if present. The heart may swing abnormally in PE, and cardiac chambers may appear small or pseudohypertrophied from increased compression [2]. Diastolic collapse of the right atrial free wall provides evidence of CT; severe cases may also demonstrate collapse of the right ventricle [2,12]. Echocardiography is also highly sensitive and specific for the detection of right atrial masses and HBTs [3].

Electrocardiography may support a diagnosis of PE but is an insensitive test. Large volumes of PE allow the heart greater mobility to swing back and forth during contractions and may result in electrical alternans, a beat-to-beat variation in the size or shape of the QRS complex and potentially the ST segment and T-wave [2,12]. Many different arrhythmias are possible with PE or CT, including sinus tachycardia, ventricular arrhythmias, and supraventricular arrhythmias [2,12].

The diagnostic utility of pericardial fluid cytology is variable, depending on the cause. Pericardial fluid cytology is effective at diagnosing lymphoma or infectious agents, but is ineffective at discriminating neoplastic from benign hemorrhagic PE [41]. HSA and chemodectomas rarely exfoliate into PE, and reactive mesothelial cells may resemble neoplastic cells [12]. Pericardial fluid pH, lactate, glucose, hematocrit, urea nitrogen, and electrolytes have been compared between neoplastic and benign PE samples, and although some differences were demonstrated, overlap between the groups rendered these biomarkers ineffective as discriminators [42,43].

Pericardiocentesis

Pericardiocentesis is recommended through the right thorax with the patient in left lateral or sternal recumbency because this provides access to the right cardiac notch and avoids the left paraconal coronary artery [44]. If the patient is stable and not in CT, pericardiocentesis may be delayed until after echocardiography because the presence of PE may improve visualization of cardiac masses [2,12]. Prior to starting, the patient should be connected to a continuous ECG and an intravenous catheter is placed for sedation and, if warranted, antiarrhythmic therapy. A dose of 2% lidocaine (2 mg/kg for dogs, 0.5–1.0 mg/kg for cats) should be prepared for administration in case ventricular arrhythmias are induced if the catheter contacts the epicardium. Intravenous sedation is helpful in dogs and usually necessary in cats. Safe and effective protocols used by the author include 0.1–0.3 mg/kg butorphanol with 0.1–0.3 mg/kg midazolam for dogs, and 0.2 mg/kg butorphanol with 2–4 mg/kg ketamine to provide additional restraint for cats [12,44].

The hemithorax is clipped from the third to the seventh intercostal space between the sternum to midthorax and aseptically prepared. Ultrasound is recommended to locate the site for optimal catheter placement. If ultrasound is unavailable, pericardiocentesis should be performed where the strongest cardiac impulse is palpated, frequently between the third and fourth intercostal spaces. A small volume of lidocaine should be infused at the puncture site into the muscular and subcutaneous

layers as the needle is withdrawn. In dogs, a 14 G or 16 G, 1.5–2 inch long (up to 5 inch for larger breeds) over-the-needle catheter works well, but in cats or small-breed dogs, 20–22 G over-the-needle catheters or 21 G butterfly catheters can be used. A stab incision is made in the skin, and the catheter is inserted perpendicular to the thorax and just cranial to the rib to avoid the neurovascular bundles located caudal to each rib. Resistance is felt at the skin and upon entering the pleural space. In most dogs, a flash of blood occurs in the hub of the stylet after piercing the pericardial sac; cats may more frequently exude a transudate or modified transudate. If no fluid appears in the stylet, ultrasound may be used to confirm positioning of the catheter before the catheter is advanced off the needle. A scratching sensation may occur if the needle or catheter is advanced too far and contacts the heart [12,44].

Once the catheter is carefully advanced into position within the pericardial space, it should be attached to a 30–60 mL syringe by way of extension tubing and a three-way stopcock for fluid evacuation. PE is collected for cytological analysis and, in the presence of exudate, submitted for culture. Hemorrhagic fluid should be placed in a clotting tube and examined for clot formation. Typically, hemorrhagic PE should be almost completely defibrinated and fail to clot. Presence of a clot should alert the clinician that the catheter may have inadvertently entered one of the cardiac chambers and should be repositioned. Fluid is withdrawn until negative pressure is attained. Ultrasound should be used to evaluate the pericardial space before withdrawal of the catheter [12,44].

The frequency of adverse events due to pericardiocentesis is low, with an incidence of 10.7% within 1 hour and 15.2% within 48 hours of pericardiocentesis. Most adverse events consist of ventricular premature complexes caused by the catheter contacting the heart, but coronary artery laceration and pneumothorax are also possible [12]. Post pericardiocentesis, ventricular tachycardia is the most common adverse event, but supraventricular arrhythmias, cardiac arrest, and continuous bleeding into the pericardial space also occur [45].

Management and Prognosis

Cardiac HSA carries the worst prognosis amongst all causes of PE in dogs. Although pericardiocentesis may provide substantial relief, the recurrence rate of PE and CT is high. Many dogs die or are euthanized within a few days of diagnosis, reflected in one reported median survival time of 11 days (range 0–208 days) [2]. Resection of HSA is challenging and may be impossible because of location and extent of infiltration. If performed, HSA

resection may only improve median survival time to 42 days, and resection with chemotherapy increases survival to about 6 months [46]. HBTs are also difficult to surgically remove because of their extensive local infiltration. For HBTs, however, pericardectomy can provide both relief and long survival times of nearly 2 years, compared to approximately 1–4 months with medical management alone [15,47].

Idiopathic pericarditis has a relatively good prognosis compared to HSA. It is initially managed by pericardiocentesis but recurrent cases warrant pericardectomy, especially considering that PE often recurs within a few months and is usually accompanied by CT [2]. In one

study of 25 dogs surgically treated for idiopathic pericarditis, 72% survived at least 18 months after pericardectomy, while 44% were still alive after 5 years [7].

Other less common causes of PE have variable long-term prognoses. Mesotheliomas are difficult to treat, but long-term survival in one dog after pericardectomy, intrathoracic cisplatin, and intravenous doxorubicin has been reported [48]. Cardiac lymphoma is classified as stage Vb and has a poor prognosis for remission and survival [2]. Septic pericarditis, however, has a good prognosis if the underlying infection is identified and eliminated through medical management and pericardectomy [24,34].

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Dilated Cardiomyopathy

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Introduction

Dilated cardiomyopathy (DCM) is a progressive myocardial disease characterized by primary systolic dysfunction or “pump” failure of the left ventricle, thinning of the left ventricular walls, and cardiac chamber dilation. DCM is the most common cardiomyopathy seen in dogs and is an important cause of morbidity and mortality in affected breeds. Common sequelae of DCM include congestive heart failure (CHF), arrhythmias, and sudden death.

Etiology

Most cases of DCM are considered idiopathic and likely have a genetic component. In boxer dogs, the DCM phenotype has been associated with the same genetic mutation in the striatin gene that is associated with arrhythmogenic right ventricular cardiomyopathy.

Possible infectious causes of DCM in dogs include myocarditis, parvovirus in puppies that are infected at 2–4 weeks old, and Chagas’ disease in endemic areas such as Texas or Mexico. Dilated cardiomyopathy may develop secondary to treatment with anthracycline chemotherapeutic agents such as doxorubicin (Adriamycin) which are commonly used in lymphoma protocols.

Nutritional etiologies include taurine deficiency; this is uncommon in dogs but can be seen in cocker spaniels, juvenile Portuguese water dogs (PWD), and occasionally in Newfoundlands fed a lamb and rice diet or in dogs fed an unbalanced vegan diet. Taurine deficiency is the best described cause of DCM in cats, but many cases of apparent DCM may represent the end-stages of hypertrophic cardiomyopathy in affected cats.

Tachycardia-induced cardiomyopathy (TICM) can occur secondary to persistent tachyarrhythmias (e.g. Supraventricular tachycardia) which can induce myocardial failure and ventricular dilation. This can be

reversible with adequate heart rate control or restoration of sinus rhythm.

Signalment, Prevalence, and Incidence

Predisposed breeds include large or giant-breed dogs such as Doberman pinschers, Irish wolfhounds, Great Danes, Newfoundlands, Scottish deerhounds, German shepherds, St Bernards, airedales, and boxers. Cocker spaniels and juvenile PWD may also develop DCM secondary to taurine deficiency. DCM is usually diagnosed in dogs between the ages of 4 to 9 years, with an increase in incidence with advancing age, except for the juvenile form recognized in PWD, which usually develops in the first 6 months of life.

The lifetime incidence of DCM in Dobermans has been reported to be 45–62% in the US and Canada, and 58.2% in Europe. The incidence of DCM is 24.2% in Irish wolfhounds, and 17.6% in Newfoundlands.

Stages

Dilated cardiomyopathy has been described in three different stages in Dobermans.

- Stage I: asymptomatic dogs with no detectable morphological or electrical abnormalities; currently no test to detect dogs within this stage.
- Stage II: occult stage; asymptomatic with development of electrical or structural abnormalities. This is the early, preclinical stage that may be characterized by only ventricular premature complexes (VPCs), only echocardiographic changes, or both with the absence of clinical signs. NT-proBNP testing may also assist in the detection of dogs with structural changes.
- Stage III: overt stage; symptomatic dogs with clinical signs of heart failure, syncope, or sudden death.

Diagnosis

The diagnosis of DCM is typically made on the basis of clinical presentation, physical examination, and echocardiographic findings. Ancillary diagnostic tests include electrocardiography (ECG), Holter monitoring, thoracic radiographs, NT-proBNP levels, genetic testing, and whole-blood and plasma taurine levels.

Presentation, Clinical Signs, and Physical Examination Findings

Initial clinical signs such as exercise intolerance or fatigue may be subtle and go unnoticed. DCM is most commonly diagnosed when clinical signs of CHF develop, including tachypnea and dyspnea or cough in the presence of left-sided CHF or jugular venous distension and ascites in the presence of right-sided CHF. Some animals may present with biventricular heart failure. Other clinical signs may include syncope, exercise intolerance or sudden death secondary to tachyarrhythmias.

On physical examination, a soft low-grade holosystolic left apical murmur secondary to mitral regurgitation may be heard. Even in the presence of significant mitral regurgitation, the intensity of the murmur is typically reduced due to systolic dysfunction and/or the presence of pleural effusion. Other common auscultatory findings may include S3 gallop or arrhythmia. Additional physical examination findings observed secondary to CHF include dyspnea, tachypnea, increased bronchovesicular sounds, crackles, and jugular venous or abdominal distension. Femoral pulses may be of poor or weak quality and pulse deficits may occur if arrhythmias are present.

Diagnostic Tests

Clinical tests useful for diagnosing DCM on an emergency basis include ECG and/or telemetry, thoracic radiographs, and thoracic ultrasonographic evaluation.

Electrocardiographic Findings

Electrocardiogram or telemetry may reveal sinus tachycardia or arrhythmias such as atrial fibrillation or atrial or ventricular premature contractions. Atrial fibrillation is characterized as a rapid, irregularly irregular rhythm with the absence of P-waves; an undulating baseline with fibrillation waves may be seen, but this is not a consistent finding (Figure 55.1). Therapy for this arrhythmia is aimed at slowing the ventricular response rate by delaying conduction through the atrioventricular node versus conversion to normal sinus rhythm (see treatment section). In a retrospective 10-year evaluation of 39 Irish wolfhounds, 46% had atrial fibrillation at time of their first examination and all 39 dogs developed atrial fibrillation by the time they presented in CHF with overt DCM [1]. As atrial fibrillation can be present in dogs with occult disease, a finding of atrial fibrillation should always prompt further diagnostic investigation.

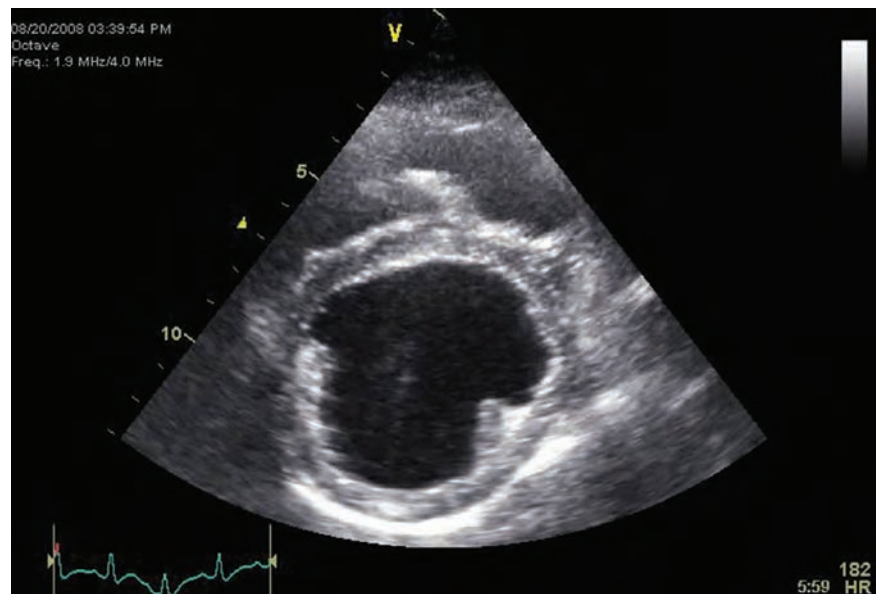
Ventricular arrhythmias are also commonly identified in patients with DCM. Ventricular arrhythmias can include single isolated VPCs, couplets, with or without R-on-T morphology, or ventricular tachycardia (see Chapter 53). Ventricular ectopic beats occur early and appear as wide and bizarre complexes in comparison to a sinus beat. Ventricular ectopy can be of left or right ventricular origin, or may be multifocal. Ventricular arrhythmias can lead to sudden death and treatment should be instituted based on the frequency and severity of arrhythmia (see treatment section).

Ventricular arrhythmias often precede the onset of overt DCM in Dobermans. More than 300 There are new guidelines published in 2017 VPCs in a 24h period or between 50- 300 VPCs on 2 subsequent recordings within a year based on recently updated guidelines[2], or any couplets or runs of ventricular tachycardia, are considered to be diagnostic for the early phase of DCM in Dobermans. A cut-off of at least one VPC on evaluation of a 5-minute ECG was found to have a sensitivity of 64.2% and specificity 96.7% for the diagnosis of DCM [3] so any number of VPCs in a predisposed breed should prompt further investigation.

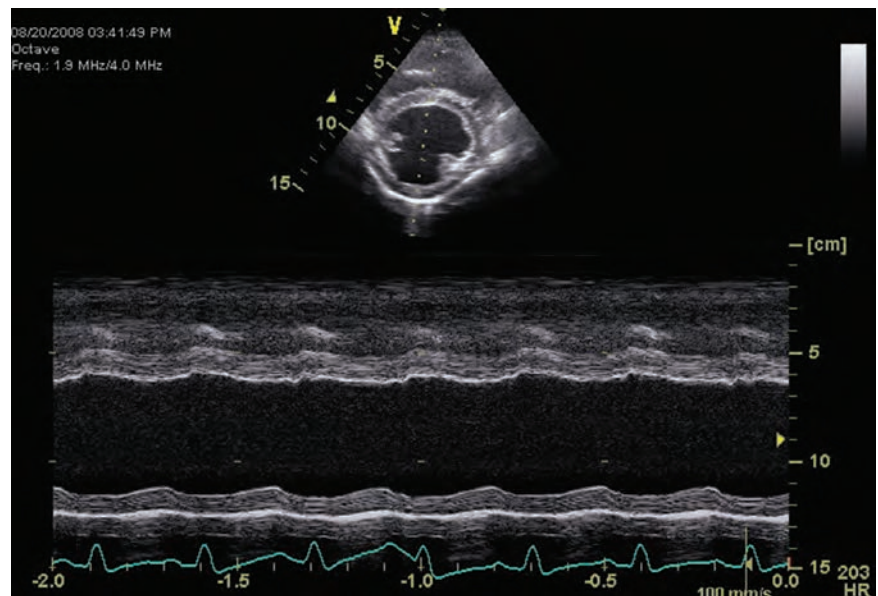


Figure 55.1 ECG showing atrial fibrillation in a dog with dilated cardiomyopathy. Note the rapid, irregularly irregular rhythm and lack of P-waves. 25 mm/sec; 1 cm = 1 mV.

Figure 55.2 Two-dimensional (a) and M-mode (b) right parasternal short axis echocardiographic images of the left ventricle of a dog with dilated cardiomyopathy. The left ventricular cavity is dilated in both diastole and systole and the fractional shortening is markedly reduced.



(a)



(b)

Focused Ultrasound Findings

A thoracic ultrasonographic examination can be performed in the ER to evaluate for a dilated hypocontractile left ventricle (see Chapter 182) (Figure 55.2a). The left ventricular walls may appear thin. The left atrium may be dilated as well as the right heart.

Thoracic Radiographic Findings

Radiographic findings may include generalized cardiomegaly with a globoid-shaped cardiac silhouette. If there is active congestive heart failure then the pulmonary vasculature,

especially the lobar veins, may be dilated with the presence of an interstitial to alveolar pattern in the perihilar or caudal lung fields. Pleural effusion may also be present.

After stabilization, an echocardiogram should be performed. A 24h ambulatory ECG Holter monitor and NT-proBNP level can provide additional supporting evidence.

Echocardiographic Findings

Findings typical of DCM include ventricular dilation with reduced left ventricular wall thickness, reduced systolic function, reduced aortic root motion, increased sphericity ($SI < 1.65$), and large (> 6.5 mm)

E-point-to-septal separation (EPSS) (Figure 55.2b; see Video Clip 55.1). Dilation of the left atrium and right heart chambers is also frequently observed. Left ventricular systolic dysfunction can be identified via reductions in fractional shortening ($<20\text{--}25\%$), calculated ejection fraction ($<40\%$), or calculated end-systolic (ESVI $> 55\text{ ml/m}^2$) and end-diastolic left ventricular (EDVI $> 95\text{ ml/m}^2$) volumes with Simpson's Method of Discs (SMOD) normalized to body surface area. In a 2010 study, SMOD measurements were found to be superior to M-mode in detection of early changes in Dobermans with occult DCM [4]. Sensitivity of M-mode cut-off values in this study of left ventricular internal dimension LVIDd $>49\text{ mm}$ and LVIDs $>40\text{ mm}$ were 71.6% and 60.5%, respectively. However, when the cut-off values were decreased to $>47\text{ mm}$ and $>38\text{ mm}$, the sensitivity and specificity increased to 84.6% and 82.7%, respectively. Recently published updated guidelines for diagnosis of occult DCM in Dobermans by Wess *et al.* use cut off values of LVIDd (male any weight) $>48\text{ mm}$, LVIDd (female any weight) $>46\text{ mm}$, or LVIDs (male and female any weight) $>36\text{ mm}$.

Doppler echocardiography may show mitral and tricuspid regurgitation, and spectral Doppler evidence of elevated LV filling pressures, and systolic and diastolic dysfunction. Though echocardiography is the screening tool of choice for DCM, it can be difficult to distinguish between early DCM and systolic function at the lower end of normal variation, and a normal echocardiogram does not rule out future development of DCM in predisposed breeds [5].

NT-proBNP Testing

NT-proBNP concentrations may be elevated with DCM and this is a relatively inexpensive screening test with a turnaround time of about 1–2 days. This is a useful adjunct to echocardiogram and Holter monitoring. Elevated NT-proBNP concentration is a sensitive indication of echocardiographic changes of DCM and increased levels should warrant further evaluation with an echocardiogram. An NT-proBNP $>735\text{ pmol/L}$ is associated with an increased risk of occult DCM in Dobermans. In a study with 348 Dobermans, a cut-off of $>400\text{ pmol/L}$ for NT-proBNP to detect all stages of DCM had a sensitivity of 81.1% and specificity of 75.0% and a sensitivity of 90% and specificity of 75% to detect changes on echocardiogram [5]. In other studies, a cut-off of $>457\text{ pmol/L}$ has been used for diagnosis of occult DCM; cut-off values for Dobermans with occult DCM are lower than other breeds.

Other Ancillary Tests

Genetic testing can be performed to evaluate for PDK4 (pyruvate dehydrogenase kinase 4, mitochondrial

protein) gene in Dobermans and the striatin gene mutation in boxers. However, at present this may be more helpful in decision making about breeding and the clinical utility is uncertain.

In breeds that are predisposed to taurine-deficiency DCM such as cocker spaniels or dogs fed a vegetarian/vegan or lamb and rice diet, it may be worthwhile to submit whole-blood and plasma taurine levels.

Treatment

Therapeutic interventions may be variable based on the stage of DCM, presence of clinical signs associated with CHF, and severity of arrhythmias. (Tables 55.1 and 55.2). Specific therapeutic interventions for preclinical DCM that have been studied in veterinary medicine include pimobendan and ACE inhibitors.

Treatment of Dobermans in the occult phase of DCM with pimobendan may result in improved outcomes. Pimobendan is an inodilator, with potent positive inotropic and vasodilatory effects. The combined effect of preload and afterload reduction, in addition to the positive inotropic support, may help to reduce cardiac size and filling pressures in animals with preclinical DCM, which may in turn be beneficial in prolonging this subclinical, occult stage. In the PROTECT study, a randomized, blinded, placebo-controlled, multicenter study with 76 Dobermans, administration of pimobendan to Dobermans with preclinical DCM was shown to prolong the time to onset of clinical signs and extend survival [6]. The median time to primary endpoint of CHF or sudden death in the pimobendan group was 718 days (range 441–1152 days) versus the placebo group with 441 days (range 151–641 days). The overall median survival time was greater in the pimobendan group with 623 days (range 491–1531 days) versus the placebo group with 466 days (range 236–710 days).

Angiotensin converting enzyme inhibitors have been shown to be beneficial for people with left ventricular systolic dysfunction when initiated during the occult phase. Similar results were observed in a retrospective study of Dobermans receiving benazepril ($n = 57$) versus no ACE inhibitor ($n = 24$); median time to onset of overt DCM was significantly longer for the benazepril group (425 days, range 264–628 days) than the group that did not receive an ACE inhibitor (339 days, range 181–547 days). The dogs receiving benazepril had a 43% decrease in the likelihood of developing overt DCM in this retrospective study. To the authors' knowledge, there are currently no prospective studies looking at the combination of pimobendan and an ACE inhibitor in delaying the onset of subclinical DCM.

The addition of low-dose beta-blockers for the treatment of DCM in humans has demonstrated a reduction

Table 55.1 Treatments for dilated cardiomyopathy (DCM) in dogs.

Treatment	Dose
Asymptomatic subclinical DCM	
ACE inhibitor	Enalapril 0.5 mg/kg PO q12–24h Benazepril 0.25–0.5 mg/kg PO q24h Lisinopril 0.5 mg/kg PO q12–24h
Inodilator	Pimobendan 0.25 mg/kg PO q12h
Beta-blocker*	Carvedilol 0.2–0.4 mg/kg, increase incrementally by 50–100% every 1–2 weeks until reaching target dose of 0.8–1 mg/kg PO q12h* Metoprolol 0.4–1 mg/kg PO q12h*
Congestive heart failure	
Diuretics	Furosemide 2–4 mg/kg IV, SC, IM, PO q8–12h Torsemide 0.2–0.3 mg/kg PO q12–24h Spironolactone 1–2 mg/kg PO q12–24h Hydrochlorothiazide 1–4 mg/kg PO q12–24h Spironolactone/hydrochlorothiazide (Aldactazide) 0.5–1 mg/kg PO q12–24h
Inodilator	Pimobendan 0.25 mg/kg PO q8–12h
ACE inhibitor	Enalapril 0.5 mg/kg PO q12h Benazepril 0.25–5 mg/kg PO q24h Lisinopril 0.5 mg/kg PO q12–24h
Antiarrhythmics	
Atrial fibrillation	
Digitalis glycoside	Digoxin 0.0025–0.005 mg/kg PO q12–24h
Calcium channel blocker (class IV)*	Diltiazem short-acting 0.5–1.5 mg/kg PO q8h* Diltiazem ER (Dilacor) 1–3 mg/kg PO q12h*
Potassium channel blocker (class III)	Amiodarone 8–10 mg/kg PO q12h (loading) for 1 week, then decrease to 5–10 mg/kg PO q24h
Ventricular ectopy	
Sodium channel blockers (class Ib)	Lidocaine 2 mg/kg IV bolus over 1–2 min, repeated PRN q5–10 min up to 6 mg/kg for ventricular tachycardia Lidocaine CRI 25–100 µg/kg/min Mexiletine 5–8 mg/kg PO q8h
(class Ia)	Procainamide 2–4 mg/kg IV over 2–4 min (up to 20 mg/kg) up to 20 mg/kg Procainamide CRI 20–50 µg/kg/min
Beta-blockers (class II)*	Carvedilol 0.2–0.4 mg/kg, increase incrementally by 50–100% every 1–2 weeks until reaching target dose of 0.8–1 mg/kg PO q12h* Metoprolol 0.4–1 mg/kg PO q12h*
Potassium channel blockers (class III)	Sotalol 1–3 mg/kg PO q12h* Amiodarone 8–10 mg/kg PO q12h (loading) for 1 week, then decrease to 5–10 mg/kg PO q24h
Dietary supplements	
Amino acid	Taurine 20–50 mg/kg PO q8–12h
Nutrient	L-carnitine 50–100 mg/kg PO q8h

*Use with caution or lower doses with CHF.

ACE, angiotensin converting enzyme; CHF, congestive heart failure; CRI, continuous-rate infusion; ER, extended release; IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); PRN, as required (*pro re nata*); SC, subcutaneous.

Table 55.2 Treatments for dilated cardiomyopathy in cats.

Treatment	Dose
Congestive heart failure	
Diuretics	Furosemide 1–2 mg/kg IV, SC, IM q8–12 h
	Furosemide 6.25 mg PO q12–24h
	Torsemide 0.2–0.3 mg/kg PO q12–24h
	Spirinolactone 1–2 mg/kg PO q12–24h
	Hydrochlorothiazide 1–2 mg/kg PO q12–24h
	Spirinolactone/hydrochlorothiazide (Aldactazide) 0.5–1 mg/kg PO q12–24h
Inodilator	Pimobendan 1.25 mg PO q12h per cat
	0.25 mg/kg PO q12h
Digitalis glycoside	Digoxin ¼ of a 0.125 mg tablet PO EOD (<3 kg)
	¼ of a tablet q24h (3–6 kg)
	¼ tablet q12–24 h (>6 kg)
ACE inhibitor	Enalapril 1.25–2.5 mg PO q24h per cat
	0.25–0.5 mg/kg PO q24h
	Benazepril 0.25–5 mg/kg PO q24h
	Lisinopril 0.25–0.5 mg/kg PO q24h
Antithrombotics	Clopidogrel 18.75 mg PO q24h; 9.375 mg PO q24h (<3 kg)
	Aspirin 5 mg PO q2–3d or 81 mg PO q3d per cat
	Dalteparin (Fragmin) 150 IU/kg SC q8–12h
	Enoxaparin (Lovenox) 1 mg/kg SC q12h
	Rivaroxaban (Xarelto) 2.5 mg PO q24h
Antiarrhythmics	
Ventricular ectopy	
Sodium channel blockers (class Ib)	Lidocaine 0.5 mg/kg IV slowly, repeat at 0.15–0.25 mg/kg in 5–20 min
	Lidocaine CRI 10–25 µg/kg/min
	Use cautiously in cats due to CNS effects
Beta-blockers (class II)*	Carvedilol 0.2–0.4 mg/kg, increase incrementally by 50–100% every 1–2 weeks until reaching target dose of 0.8–1 mg/kg PO q12h*
	Atenolol 6.25 mg PO q12h per cat*
Potassium channel blockers (class III)	Sotalol 1–3 mg/kg PO q12h*
Dietary supplements	
Amino acid	Taurine 250–500 mg PO q12h per cat
Nutrient	L-carnitine 250 mg PO q24h per cat

*Use with caution or lower doses with CHF.

**Note that this is not recommended/sufficient for thromboprophylaxis in cats.

ACE, angiotensin converting enzyme; CNS, central nervous system; CRI, constant-rate infusion; EOD, every other day; IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

in both mortality and morbidity. Beta-blockers can be considered for dogs with occult DCM but should not be started in patients with active congestive heart failure due to the negative inotropic and chronotropic effects. Carvedilol may be an optimal beta-blocker in this scenario due to its balanced effects on both alpha- and

beta-receptors. Starting a beta-blocker in a patient with DCM should be undertaken cautiously, with gradual increases in dosing after a 2-week period if well tolerated. The authors start carvedilol at a 0.2–0.4 mg/kg dose PO BID and increase the dose every 2 weeks to reach a maximal dose of 0.8–1 mg/kg dose twice daily. Monitor heart

rate, blood pressure, and clinical signs while increasing the dose.

If the patient with DCM is in active heart failure then standard triple therapy includes pimobendan, an ACE inhibitor (enalapril, benazepril, lisinopril, etc.), and furosemide. Additional diuretics such as spironolactone or torsemide may be added in dogs with refractory CHF.

If atrial fibrillation with a rapid ventricular response rate is identified on ECG or telemetry, therapy can be initiated with diltiazem, digoxin, or amiodarone. The combination of oral digoxin and diltiazem has been shown to be more effective in lowering heart rate than either of these drugs alone. Intravenous administration of diltiazem can lead to significant hypotension and cardiovascular collapse and it is best to avoid this formulation and stick with oral dosing whenever possible. If concurrent ventricular arrhythmia is present then oral amiodarone can be considered, as it may aid both in ventricular rate control of atrial fibrillation and treatment of ventricular ectopy. Some IV formulations of amiodarone can be associated with anaphylaxis and should be reserved for cases of refractory ventricular tachycardia. The oral formulation appears to be well tolerated. However, liver enzyme values $\pm$ thyroid hormone levels should be obtained prior to starting oral amiodarone as side-effects can include a reversible hepatotoxicity and thyroid dysfunction. Liver enzyme values and an amiodarone level are typically checked 3–4 weeks after starting amiodarone. If digoxin is started, monitor for signs of toxicity such as vomiting, diarrhea, and inappetence. Digoxin has a narrow therapeutic index and a 4–8h post-pill digoxin level should be obtained 7–10 days after starting this medication, with a target serum level in the lower therapeutic range.

Frequent or complex ventricular ectopy such as multifocal VPCs, couplets with R-on-T morphol-

ogy, or ventricular tachycardia warrants treatment with ventricular antiarrhythmic therapy (see Chapter 53). Antiarrhythmics for ventricular ectopy include intravenous lidocaine (bolus or continuous-rate infusion (CRI)), procainamide (bolus or CRI), amiodarone (IV bolus, CRI, or oral), sotalol, mexiletine, flecainide, and beta-blockers. Oral beta-blockers or sotalol should be used cautiously with significant systolic dysfunction or in the presence of active CHF as they may not be tolerated.

If DCM is suspected to be secondary to taurine or L-carnitine deficiency then those patients should be supplemented.

Prognosis

The prognosis associated with DCM can be variable based on disease stage, severity, breed, etiology, and concurrent diseases, as well as owner dedication and finances. There can be a prolonged asymptomatic phase with occult DCM up to 2–4 years before the development of clinical signs. Sudden death secondary to ventricular tachycardia-fibrillation may be the first clinical sign of disease in greater than 25–30% of affected dogs. The prognosis associated with overt DCM is guarded to poor with reported median survival times of 2–6 months. Some dogs may do well for a more protracted period of time but the case fatality rate after 1 year is $>90\%$ in some studies.

Negative prognostic indicators include a young age at onset of clinical signs (<5 years), presence of pleural effusion, pulmonary edema, ascites, atrial fibrillation, increased end-systolic volume index, restrictive trans-mitral inflow pattern, short E-wave deceleration time (<80 msec), higher plasma creatinine, and greater than 50–100 VPCs in 24 hours.

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Feline Hypertrophic Cardiomyopathy

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Introduction and Definitions

Feline hypertrophic cardiomyopathy (HCM) is a myocardial disease defined by idiopathic left ventricular hypertrophy and is the most commonly diagnosed cardiac disease in cats. A diagnosis of primary HCM assumes secondary causes of ventricular wall thickening are absent, including systemic hypertension, hyperthyroidism, and dehydration (“pseudo-hypertrophy”). Research in cats and humans with HCM has revealed that primary HCM can be the result of genetic mutations of sarcomeric proteins [1–3]. Familial HCM has been recognized in Maine coon and ragdoll cats and is due to a mutation of myosin binding protein C [2,3]. The etiology of primary HCM in other cats remains unknown but is assumed to be due to unrecognized genetic mutations of sarcomeric proteins. HCM can exhibit tremendous phenotypic diversity and phenotype may change over time. Cats with long-standing HCM can develop systolic dysfunction and ventricular wall thinning (termed “end-stage HCM”). Many cats with HCM exhibit dynamic left ventricular outflow tract (LVOT) obstruction and mitral regurgitation secondary to systolic anterior motion (SAM) of the mitral valve whereby the anterior leaflet of the mitral valve is malpositioned and progressively obstructs the LVOT (termed “hypertrophic obstructive cardiomyopathy”).

Pathology and Pathophysiology

Diastolic Dysfunction and Congestive Heart Failure

The net pathophysiological consequence of HCM is diastolic dysfunction leading to increased left ventricular (LV) filling pressure. Initially, a genetic mutation leads to cardiomyocyte stress that triggers hypertrophy, excessive collagen production, and myofiber disarray. These changes contribute to diastolic dysfunction caused by

increased myocardial stiffness and delayed relaxation. The net effect is increased LV filling pressure, which is transmitted to the left atrium (LA) and pulmonary veins, causing dilation of these structures. Left-sided congestive heart failure (CHF) develops once LV diastolic pressure exceeds approximately 25 mmHg and is manifested by any combination of pulmonary edema, pleural effusion, or pericardial effusion in cats. Severe diastolic dysfunction compromises cardiac output and renal blood flow, a potent stimulator of sodium and water retention via the renin-angiotensin-aldosterone system (RAAS) (see Chapter 51). On a tissue level, the RAAS promotes adverse cardiac remodeling, which exacerbates CHF.

Arterial Thromboembolism

Cats with HCM that have moderate-to-severe LA enlargement or spontaneous echogenic contrast are at risk for developing an intracardiac thrombus. Thrombi usually form within the LA/left auricle and may embolize to the systemic arterial circulation, notably the aortic trifurcation (“saddle thrombus”). The profound collateral vasoconstriction secondary to release of vasoconstrictive molecules (e.g. thromboxane and serotonin) [4,5] and, later, build-up of toxic intracellular substances in the blood that may lead to acidosis, hyperkalemia, renal dysfunction, and arrhythmias (i.e. reperfusion injury), are the major causes of morbidity and mortality.

Presentation and Clinical Signs

The vast majority of cats with HCM present with clinical signs secondary to CHF, which is most commonly manifest as respiratory difficulty. Cats may present at any age but median age of onset is 6–7 years [6–8]. In cats with HCM, there appears to be a slight male predilection, and despite pure-bred predilections (e.g. Persian, Himalayan,

Maine coon, ragdoll, birman), the domestic short-hair is the most common breed diagnosed with HCM [6–8]. Early signs of CHF secondary to feline HCM are often non-specific, including inappetence, vomiting, weight loss, hiding or less owner interaction. Cough and syncope are rarely associated with cardiac disease in cats [8].

Antecedent events are commonly reported in cats with HCM presenting for CHF [8]. Events may include recent boarding, hospitalization, parenteral fluid administration, general anesthesia, or receiving corticosteroids. The mechanism of corticosteroid administration contributing to CHF in cats with HCM is unresolved [9]. It is important to question owners about potential antecedent events as this may improve the prognosis by future avoidance of these events. Other co-morbidities such as brady- or tachyarrhythmias, anemia, hyperthyroidism, diabetes mellitus, or systemic hypertension may precipitate CHF in cats with HCM. These diseases in and of themselves are unlikely to cause cardiac disease significant enough to lead to CHF but they can worsen preclinical HCM, thus precipitating CHF.

In addition to breathing difficulty, abnormal physical examination findings of cats with CHF may include decreased heart and lung sounds secondary to pleural +/- pericardial effusion, increased and/or adventitial lung sounds (e.g. inspiratory crackles), prolonged capillary refill time, cyanotic or pale mucous membranes, or distended jugular veins. Cardiac auscultation may reveal an arrhythmia, gallop sound or murmur. In contrast to a systolic murmur, gallop sounds are a more specific indicator of cardiac disease. Cats presenting in CHF may also have a slow, normal or fast heart rate and one may encounter hyper-, normo- or hypothermia. Also, cats in CHF may not have any abnormality on cardiac auscultation. Cats rarely develop ascites as a manifestation of biventricular CHF secondary to HCM.

Lastly, cats with HCM may first present with clinical signs secondary to an arterial thromboembolism (ATE) +/- CHF. The hindlimbs and tail are most commonly affected but smaller thromboemboli may affect a single fore- or hindlimb, GI tract, kidney, or brain. In the case of an ATE at the level of the aortic trifurcation, clinicians may recognize the following characteristic findings: palor and later purple (cyanotic) coloration of nail beds or footpads; loss of pulses; pain/vocalization; paresis/paralysis; firm/contracted gastrocnemius muscle(s); and hypothermia.

Initial Stabilization

Congestive Heart Failure

Initial management of cats with respiratory difficulty can be challenging, particularly if they cannot tolerate

thoracic radiographs or ultrasonic documentation of atrial enlargement cannot be performed. A cautious and step-wise approach is advised. If cardiac disease is suspected due to acute onset of presenting signs, signalment, or murmur/gallop sound, administration of empirical furosemide 1–2 mg/kg prior to confirmatory diagnostics is reasonable. A sedative and supplemental oxygen is strongly advised in cats with respiratory difficulty and should help facilitate the physical examination and diagnostics. Butorphanol 0.2–0.3 mg/kg IM/IV is commonly utilized. If feasible and as early as possible, a brief thoracic ultrasound is performed to determine if pleural effusion and/or atrial enlargement are present (see Chapter 182).

Mild pericardial effusion may be encountered. CHF is the most common cause of pericardial effusion in cats [10] and cats in CHF should not require pericardiocentesis. The pericardial effusion should resolve with medical management of CHF. If moderate-to-severe pleural effusion is visualized, thoracocentesis is advised as soon as possible. This procedure is often life saving. Some clinicians may utilize transdermal nitroglycerin ointment (¼ inch applied to the inside of the ear pinna) as a venodilator to help alleviate congestion. Initial stabilization of cats without pleural effusion ideally following radiographic confirmation of pulmonary edema will involve further administration of furosemide (1 mg/kg IV) after 30–60 min of rest in an oxygen-enriched environment if respiratory rate and effort do not improve. The amount and frequency of furosemide administered will vary from cat to cat and will be dictated by clinical response.

Arterial Thromboembolism

Initial management of cats with ATE should first include analgesia. Pure mu-agonist opioids (e.g. fentanyl, methadone, oxymorphone) administered intravenously are strongly advised, as this condition is extremely painful in the acute stage. Next, determining CHF status is recommended and, if present, this should be stabilized as suggested above. Initiating antithrombotic therapy is also advised in the acute stage of an ATE (48–72 h). Options include unfractionated heparin (100–200 U/kg IV followed by 200 U/kg SC q8h). Alternatively, a low molecular weight heparin such as enoxaparin (0.75 mg/kg q6h) can be utilized. Although there are advantages and disadvantages of both forms of heparin, there is currently no evidence to support the use of one over the other. Some clinicians, including the author, prefer to start clopidogrel (19 mg/cat PO q24h) +/- aspirin (20 mg/cat q48–72h) at this time [11]. Be aware that it may take 2–3 days before maximal antiplatelet effect of clopidogrel is reached in cats [12] whereas aspirin's antiplatelet effects should be more rapid. The goal of antithrombotic therapy is to help prevent thrombus formation.

In contrast, the use of thrombolytic therapies, such as human recombinant tissue plasminogen activator (TPA), is considered controversial. This approach has the potential to enhance reperfusion injury by accelerating the release of toxic metabolites such as potassium, organic acids, and oxygen free radicals into the systemic circulation. Conversely, some argue that if the ATE event was witnessed to occur within a short time period (e.g. <3–4h), TPA might be beneficial, as has been demonstrated in humans with acute thromboembolic complications. However, current evidence has failed to demonstrate an advantage of thrombolytic therapy, and therefore TPA is not routinely recommended in cats with ATE [11,13]. Further study of thrombolytic therapy, and in particular case selection, is warranted.

Diagnostic Tests

Without prior knowledge of HCM, a diagnosis of CHF may not be straightforward. A brief “triage” echocardiogram can be helpful during initial work-up (see Chapter 182). Left atrial enlargement (a LA:Ao > 1.5 in short axis or > 1.6 cm diameter in long axis) sometimes with right atrial enlargement should increase the suspicion of CHF (Figure 56.1). However, in the majority of cats, thoracic radiography coupled with the history and physical examination may be all that is necessary to diagnose CHF. If a

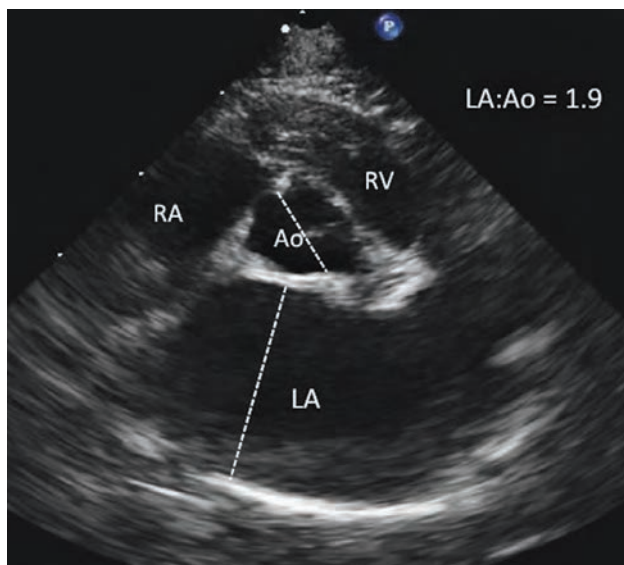


Figure 56.1 A right parasternal short-axis two-dimensional echocardiographic image obtained from a cat with hypertrophic cardiomyopathy and congestive heart failure. Left atrial size is commonly assessed by indexing its maximum dimension to that of the aorta (just after aortic valve closure) as shown. LA:Ao greater than 1.5 indicates enlargement. Ao, aorta; LA, left atrium; RA, right atrium; RV, right ventricle.

cat exhibits respiratory difficulty in the absence of pleural effusion on thoracic ultrasound or if thoracic ultrasound is unavailable, attempting a single dorsoventral radiograph while the cat is supplemented with flow-by oxygen is advised. The remainder of the radiographic study can be completed later once the cat has stabilized.

Thoracic Radiography

Thoracic radiography is an essential diagnostic tool for confirmation of CHF and to exclude other causes of respiratory difficulty. The radiographic appearance of cardiogenic pulmonary edema can be highly variable but usually consists of patchy interstitial and/or alveolar infiltrates without a typical distribution location within the pulmonary parenchyma (Figure 56.2). Cardiogenic pulmonary edema rarely consists solely of a bronchial pattern (but may have a peribronchial component) and should not be confined to one lung lobe. Cats with CHF should also demonstrate cardiomegaly usually manifest by dorsal deviation of the trachea on the lateral projection and a “base-wide” appearance (“valentine shape”) on the ventrodorsal/dorsoventral projection (see Figure 56.2). Specific cardiac chamber enlargement is difficult to diagnose in cats and therefore documenting generalized cardiomegaly is sufficient. Dilation of the pulmonary vasculature may also be apparent but its absence should not exclude a diagnosis of CHF.

Echocardiography

Early on, a brief “triage” echocardiogram is often helpful to assist in the diagnosis of CHF (see Chapter 182). The goal of this brief echocardiogram should be to determine if there is significant enough cardiac disease to cause clinical signs. Later and once stabilized, a comprehensive echocardiogram should be performed in all cats with CHF. The gold standard antemortem diagnosis of HCM requires echocardiography. It involves documenting idiopathic LV hypertrophy, which is generally accepted to be represented by an end-diastolic LV wall thickness (interventricular septum and/or freewall) greater than 6 mm [14]. It is important to note that volume-depleted cats that do not have cardiac disease may exhibit increased LV wall thickness status, mimicking HCM [15]. Atrial size is typically decreased in these cats. Conversely, volume-overloaded cats without cardiac disease can exhibit LA enlargement [15]. Therefore, hydration status should be considered at the time of echocardiographic examination.

Biomarkers

Until recently, cage-side tests capable of measuring cardiac biomarkers such as cardiac troponin I, a marker of

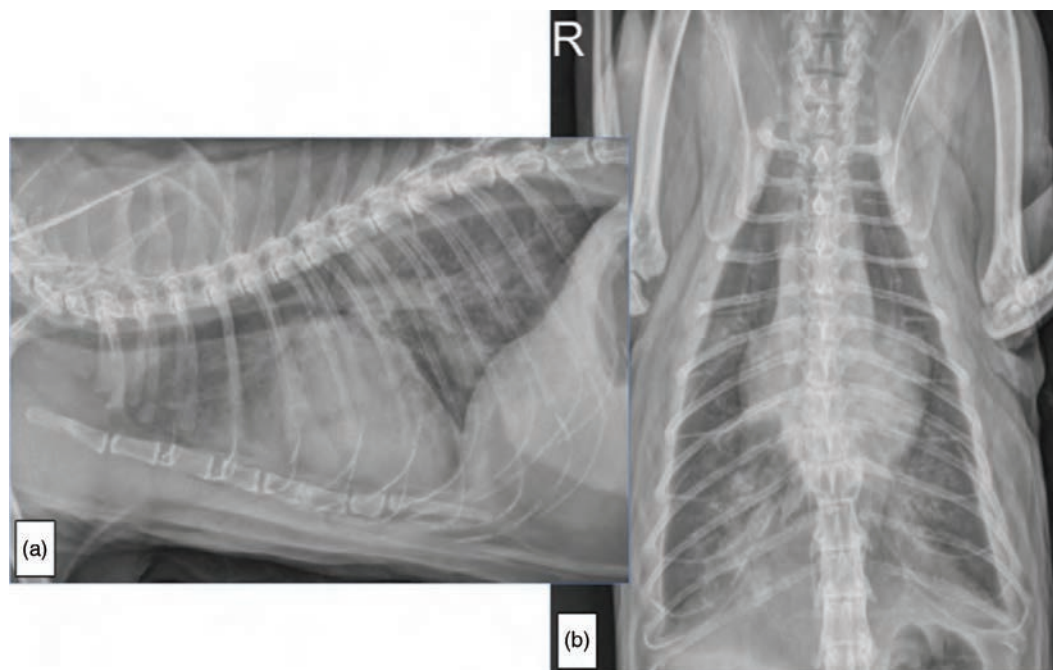


Figure 56.2 Right lateral (a) and ventrodorsal (b) radiographic projections of the thorax of a cat with congestive heart failure caused by hypertrophic cardiomyopathy. Note the enlargement of the cardiac silhouette as determined by dorsal deviation of the trachea on the lateral projection and the base-wide appearance or “valentine shape” on the ventrodorsal projection. Patchy interstitial densities are distributed throughout the lungs. Mild pleural effusion is also evident.

cardiomyocyte damage, and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), a marker of cardiomyocyte stretch, have been unavailable. Both biomarkers have shown promise in identifying, monitoring, and prognosticating cats with CHF and assisting with the diagnosis of preclinical cardiac disease [16,17]. A categorical (normal versus abnormal) NT-proBNP cage-side test has recently become available but there are currently no data published on its accuracy and reliability for the diagnosis of CHF. The cage-side assay has only been analyzed in the setting of preclinical feline heart disease [18]. Conversely, data on a quantitative cage-side cardiac troponin I assay in differentiating cats with cardiac and non-cardiac causes of dyspnea have recently been published [19]. Although these should be considered preliminary data, the cage-side cardiac troponin I assay appeared to help differentiate cardiac from non-cardiac causes of dyspnea in studied cats.

Biomarker tests to help identify CHF in cats appear promising. However, until further evidence becomes available the role of these tests should be one that complements but does not replace the cornerstones of CHF diagnosis in cats: history, physical exam, thoracic radiographs, and echocardiography.

Other Diagnostics

Blood sample collection for, at minimum, baseline renal function and electrolyte status is advised soon after presentation for CHF or ATE. If an ATE is suspected, skeletal muscle biomarkers, particularly creatine kinase (CK) and aspartate aminotransferase (AST), are helpful and usually markedly elevated. Systolic blood pressure is ideally performed in cats with HCM and CHF to rule out systemic hyper- or hypotension. In cats over 6 years of age that are affected with HCM, a serum thyroid hormone (T4) concentration should be measured. Low sensitivity prohibits the routine assessment of an ECG in cats suspected to have heart disease unless an arrhythmia is ausculted. Continuous ECG monitoring is strongly advised for cats with an ATE due to the adverse effects of reperfusion injury (e.g. hyperkalemia) on the cardiac conduction system.

Other diagnostics such as cytological analysis of pleural effusion (cases where a diagnosis of cardiogenic pleural effusion is unclear) and a fundic examination (cases where systolic BP > 160 mmHg) may be performed on a case-by-case basis.

Chronic Therapy

The mainstays of chronic management of CHF in cats with HCM include the diuretic furosemide (starting doses are usually 1–2 mg/kg PO q8–12 h), an angiotensin converting enzyme (ACE) inhibitor (enalapril or benazepril 0.25–0.5 mg/kg PO q12 h), and anticoagulant therapy. The use of an ACE inhibitor is encouraged once cats are stabilized (at home) and is unnecessary for acute management of CHF. Therapies aimed to enhance diastolic function or to reduce dynamic LVOT obstruction (atenolol) in cats with HCM are not typically utilized once CHF is present due to their potent negative inotropic effects.

Although it is debatable when to initiate them, anticoagulant(s) are recommended for cats with moderate or severe atrial dilation, which nearly always include cats in CHF. Options for chronic anticoagulant therapy include clopidogrel, aspirin, low molecular weight heparin, and warfarin. Clopidogrel (+/– aspirin) is a popular choice due to tolerability, cost-effectiveness, and oral dosing, and in a recent clinical trial clopidogrel decreased the likelihood of recurrent feline ATE when compared to aspirin [20].

Additional drugs such as the “inodilator” pimobendan (1.25 mg/cat PO q12 h) and the aldosterone antagonist spironolactone (1–2 mg/kg PO q12–24 h) may also be utilized in some cats with CHF. Despite a potential benefit to a subset of cats with non-obstructive HCM and CHF [21], pimobendan is not routinely recommended due to its potential to worsen LVOT obstruction. Spironolactone is not routinely recommended because it may cause

an ulcerative facial dermatitis in cats [22]. However, both medications may be utilized on a case-by-case basis, for example in refractory CHF or systolic dysfunction (pimobendan).

Prognosis

Adverse outcomes for cats with HCM include ATE, CHF, and sudden cardiac death. Some cats with HCM, particularly those with mild non-progressive hypertrophy and normal LA size, may live a normal lifespan. Thus, the prognosis for cats with HCM is variable. Reported median survival times of cats with CHF and HCM range from 92 to 563 days, and negative prognostic factors include tachycardia at presentation (heart rate > 200 bpm), increased age, and increased LA size [6,8]. Conversely, cats with HCM and CHF with a correctable precipitating event have a much more favorable prognosis.

Cats with ATE generally have a poor long-term prognosis. However, some cats with ATE are able to maintain a good quality of life for extended periods of time. Cats that experience an ATE affecting a single limb, and cats that maintain motor function carry a more favorable prognosis. Concurrent CHF in cats with an ATE may adversely affect long-term prognosis but does not appear to affect survival to discharge [23]. Decreased heart rate and rectal temperature have been shown to adversely affect survival, and a rectal temperature of < 98.9 °F has been shown to predict a < 50% survival probability [23].

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Valvular Heart Disease

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Introduction

Valvular heart disease (VHD) is one of the most common canine heart conditions encountered in the ER setting. VHD is the most common acquired heart disease in dogs. It is generally a result of myxomatous degeneration of the cardiac valves and the mitral and tricuspid valves are the most commonly affected. Other causes of VHD include congenital causes and bacterial endocarditis. Since the manifestations of VHD are similar regardless of cause and endocarditis is dealt with elsewhere in this text, the focus of this chapter will be on myxomatous valvular disease and the common endpoints of valvular heart disease regardless of cause. Additionally, while valvular heart disease does occur in feline patients, it is quite rare and thus will not be considered as a primary topic.

Emergency manifestations of VHD generally fall into four categories: left-sided congestive heart failure (LCHF), left-sided heart disease leading to pulmonary hypertension (PHT), right-sided congestive heart failure (RCHF), and pericardial effusion (PE) due to left atrial tears. Other potential considerations about VHD, such as its impact on treatment of co-morbid conditions or anesthesia, while important, will not be addressed here.

Myxomatous Valvular Degeneration

Valvular heart disease is the most common form of canine heart disease in North America, accounting for approximately 75% of cases [1–4]. It most commonly affects the mitral valve but 30% of cases involve the tricuspid valve as well. It may affect up to 90% of small-breed dogs over 8 years of age and the likelihood of any dog having developed VHD over the age of 12 is close to 100% for most breeds [1,2]. The most commonly affected dogs are older, smaller breed, male dogs but any dog can

be affected. In smaller dogs, the disease is thought to progress more slowly than in larger dogs [5–8].

The cause of VHD is not yet completely characterized but it has an inherited component in some, if not all, affected dogs. Some dog breeds, including Cavalier King Charles spaniels, bull terriers, and Norfolk terriers, have earlier onset of VHD than other breeds [1,9]. High amounts of biomechanical loading can induce changes in mesenchymal cells similar to those seen in VHD [10–12], and serotonin, TGF-beta-1, and metalloproteinases are increased in VHD although their role has not been completely elucidated [13–18].

Valvular heart disease is pathologically characterized by changes in the amount and type of collagen in the affected valves and chordae tendoneae. The valve leaflets have increased deposition of glycosaminoglycan and changes in the extracellular matrix, including disorganization of collagen and elastin. The spongiosa layer of the valve becomes thicker and the fibrosa layer becomes disrupted as a result. Valvular interstitial cells are increased in number [19] and injury occurs to the endothelial cells lining the valves, including loss of these cells in severe VHD [2,19]. The valve leaflet becomes progressively thicker overall and is characterized by thickened, curled edges and nodule formation. Affected chordae tendoneae can become thickened, stretched, and less elastic [2]. The changes in the valve make it less competent and valvular insufficiency results. This in turn leads to progressive left atrial and left ventricular enlargement [20].

Diagnosis (Table 57.1)

Signalment and Historical Findings

Although the typical patient with clinically significant VHD is an older, smaller dog, VHD can occur in any size dog, including breeds that generally are more

Table 57.1 Utility of tests for determining whether clinical signs are due to valvular heart disease.

Testing modality	Finding	Utility
History and physical examination	Cough	Less reliable
	Breathing rate	Most reliable
	Crackles	Less reliable
FAST	Lung rockets	Reliable for LCHF if echo positive
	Pericardial effusion	Diagnostic for LAT if LAE and clot present
	Abdominal effusion	Reliable for RCHF if echo positive
Radiographs	Pulmonary edema	Reliable for LCHF if echo positive
	Heart enlargement	Permissive for LCHF, RCHF
Echocardiography	LAE, LVE and MR	Permissive for LCHF
	RAE, RVE and TR	Permissive for RCHF
	Septal flattening*, increased TR velocity*, increased PI velocity	Diagnostic for PHT
	Pericardial effusion with clots and signs of VHD	Diagnostic for LA tear
Biomarkers	Increased levels of ANP, BNP, cTnI, NT-proANP, NT-proBNP	Reliable for LCHF (per test guidelines)

* In the absence of pulmonic stenosis.

ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; cTnI, cardiac troponin I; LAE, left atrial enlargement; LAT, left atrial tear; LCHF, left-sided congestive heart failure; LVE, left ventricular enlargement; MR, mitral regurgitation; NT-proANP, N-terminal end resulting from cleaving of prohormone proANP; NT-proBNP, N-terminal end resulting from cleaving of prohormone proBNP; PI, pulmonic insufficiency; RAE, right atrial enlargement; RCHF, right-sided congestive heart failure; RVE, right ventricular enlargement; TR, tricuspid regurgitation.

predisposed to other acquired forms of cardiac disease [7,8]. Younger dogs with signs typical of VHD may have mitral or tricuspid valve dysplasia (TVD) or mitral stenosis, although these are very rare. TVD is most commonly seen in Labrador retrievers. While any dog can develop VHD from bacterial endocarditis, the most common presentation is a large-breed male dog [21].

Dogs with left-sided VHD severe enough to produce congestive heart failure, pulmonary hypertension or a left atrial tear generally have had a murmur for a significant period of time. In contrast, dogs with right-sided VHD may not have had a murmur appreciated as the murmurs are often lower intensity due to the lower systolic pressures generated by the right ventricle, unless pulmonary hypertension is present. Collapse due to VHD may be caused by pericardial effusion resulting from left atrial tears, syncope associated with coughing or pulmonary hypertension caused by left-sided VHD.

Physical Examination

Physical examination plays an important part in diagnosing VHD. Patients with clinically relevant VHD almost always have an audible murmur and the intensity of the murmur generally correlates with the severity of the disease [22]. The murmur for left-sided VHD is systolic and

has a point of maximum intensity (PMI) on the lower left side of the patient's thorax (fifth intercostal space, ICS). Patients with right-sided VHD have a systolic murmur with a PMI on the right lower thorax (third–fifth ICS). Dogs with pulmonary hypertension from left-sided disease often have a stronger right than left apical murmur and if there is ascites or syncope, pulmonary hypertension is often present [23].

Recently, a clinical severity score for left-sided VHD was developed. Cough, syncope, exercise intolerance, dyspnea, and decreased appetite in conjunction with a murmur grade of III–VI and loss of sinus arrhythmia were correlated with worsening disease and outcome [24].

Echocardiography

Echocardiography is the only way to diagnose VHD definitively. VHD has typical echocardiographic findings, including thickening of the valve leaflets and chordae tendoneae and progressive enlargement of the affected atria and ventricles [25]. Color flow Doppler is essential for the diagnosis of valvular insufficiencies and spectral Doppler is needed for the accurate diagnosis of PHT. This is accomplished by measuring the velocity of either tricuspid or pulmonic insufficiency or by examining the ratio

of the acceleration time:ejection time of flow through the pulmonary artery [26]. Echocardiography can also help to diagnose congestive heart failure by utilization of diastolic indices, including the ratio of early ventricular filling (E) to isovolumic relaxation time (IVRT) [27].

Focused Assessment by Sonographic Technique

Focused assessment by sonographic technique (FAST) can be used to assess patients for findings compatible with pulmonary edema due to LCHF, abdominal effusion from RCHF and PE from left atrial tears (see Chapter 182). It cannot, however, distinguish between disease caused by VHD and other causes of similar ultrasonographic findings [28,29].

Radiography

Thoracic radiographs are useful in determining whether or not there is sufficient heart enlargement to be compatible with any of the conditions that can result from VHD. Additionally, they can be used to determine whether pulmonary edema and pulmonary overcirculation are present. Abdominal radiographs can confirm the presence of abdominal fluid.

Biomarkers

The levels of various circulating substances provide information about the likelihood that VHD is present and about the severity of the disease. Additionally, the levels of the substances can, in some cases, have strong correlation with whether or not a patient is in congestive heart failure.

Chief among these substances is brain natriuretic peptide (BNP). BNP secretion is stimulated by stretching of the ventricles. It is secreted as a prohormone that includes the active BNP molecule and the inactive amino terminus end (NT-proBNP). The prohormone is cleaved when the ventricle is stretched and so both BNP and NT-proBNP have utility in detecting heart enlargement caused by VHD. The NT-proBNP has a longer half-life in circulation and therefore is easier to measure. BNP and NT-proBNP levels are quite elevated in patients with VHD and there is good correlation between significant elevations and clinical signs that are due to VHD [30]. Other biomarkers include atrial natriuretic peptide (ANP), NT-proANP and high-sensitivity cardiac troponin I (cTnI). NT-proBNP has been more extensively tested in canine and feline patients, but ANP has been shown to correlate with severity of cardiac disease [31], NT-proANP has been shown to predict CHF [32], and serial cTnI has been shown to correlate with clinical cardiac findings [33].

Pathophysiology of Congestive Heart Failure (see Chapter 51)

Congestive heart failure is defined as the state that occurs when the heart is not able to maintain function at a level that can support the organism's needs at normal filling pressures. Congestive heart failure occurs when elevated diastolic filling pressure leads to increased venous hydrostatic pressure that exceeds the net pressure holding fluid within these vessels. Subsequent to this, edema or effusion results from the net flow of fluid out of the vessels. VHD causes increased left or right atrial filling pressure due to valvular insufficiency. When there is decreased cardiac output, changes occur in neuroendocrine function, resulting in the activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system which are short-term compensatory mechanisms that place additional stress on the heart long term and are part of the pathogenesis of congestive heart failure as well [34].

Left-Sided Congestive Heart Failure

Historical Findings

The historical information that is most consistent with LCHF caused by VHD is tachypnea and/or dyspnea. There is a strong correlation with resting breathing rate and LCHF [26,35–37]. Additionally, although cough has been generally regarded as a sign of congestive heart failure in dogs, this correlation is not as strong. Cough in canine cardiac patients may be due to non-cardiac causes or to an enlarged heart pushing on the trachea rather than congestive heart failure [38]. Coughing in cats is rarely associated with cardiac disease and is much more commonly due to feline airway disease.

Physical Examination

In dogs suspected of having LCHF due to VHD, an audible murmur should be present. If it is not, searching for another cause for dyspnea should be prioritized. Additionally, while pulmonary crackles are often auscultated in dogs with LCHF, other causes of crackles such as pulmonary fibrosis and lower airway disease can occur and crackles are *not* pathognomonic for pulmonary edema. The temperature of the patient is also a finding that can help determine whether LCHF is present. Patients with LCHF often have a subnormal temperature and almost never have a supranormal temperature unless bacterial endocarditis is the cause.

Radiography

Radiographs of dogs with LCHF due to VHD disease generally have many things in common. The overall heart size is enlarged and the left atrium and left atrial

appendage are significantly enlarged. In dogs, pulmonary edema is present in the perihilar region first but can be present elsewhere. This region is best viewed in a DV radiograph. The perihilar region is difficult to interpret in lateral radiographs and a DV highlights the region better than a VD. In cats, pulmonary edema can be present anywhere in the thorax. Pleural effusion may be present as well in cats (see Chapter 56).

FAST

Thoracic FAST (tFAST) of dogs with LCHF typically will show “lung rockets” (see Chapter 182) if pulmonary edema is present. Pulmonary edema or pleural effusion could be present in feline patients.

Blood Tests

Typically, dogs with LCHF due to VHD show very elevated BNP, NT-proBNP, cTnI, ANP and NT-proANP levels.

Echocardiography

Echocardiograms of patients with LCHF generally show severely enlarged left atria and ventricles or significantly ruptured chordae tendoneae or both. Valve leaflets are generally very thickened. Color flow Doppler shows significant mitral regurgitation. It is difficult for echocardiography to determine whether LCHF is present in a typical study (not including diastolic indices) but it can eliminate VHD (and LCHF) as differential diagnoses.

Right-Sided Congestive Heart Failure

Historical Findings

Right-sided CHF due to VHD primarily occurs in young dogs with congenital heart disease such as tricuspid valve dysplasia or in older dogs with myxomatous disease. It frequently occurs subsequent to significant left-sided heart disease that has led to increased pulmonary vascular resistance.

Physical Examination

Dogs with RCHF have abdominal effusion manifested by a distended abdomen, often with a palpable fluid wave. RCHF is often accompanied by a serious loss of muscle and body condition called cardiac cachexia. A right-sided heart murmur may predominate. Rarely heart sounds may be muffled if pericardial effusion results from RCHF.

Radiography

Abdominal radiographs show abdominal effusion and thoracic radiographs show an enlarged heart. Right-sided cardiomegaly is present but this is a commonly overdiagnosed condition and should be verified with other imaging modalities.

FAST

Thoracic FAST may show slight pericardial effusion in dogs. Abdominal FAST (aFAST) shows abdominal effusion (see Chapter 182).

Echocardiography

Right-sided CHF is accompanied by large right atria and large right ventricles. Color flow Doppler shows significant tricuspid regurgitation.

Pulmonary Hypertension Due to Left-Sided Heart Disease

Historical Findings

Pulmonary hypertension due to VHD occurs most commonly in dogs with long-standing, severe left-sided heart disease. Dogs with PHT from VHD most often present for collapse or ascites but can also experience significant shortness of breath although this is less common than dogs with PHT from pulmonary disease.

Physical Examination

Dogs with PHT from VHD sometimes have abdominal effusion and a distended abdomen with a palpable fluid wave. They generally have weak pulses and frequently have a loud right apical murmur [23].

Radiography

Radiographs can show right-sided cardiomegaly.

FAST

Abdominal FAST could show abdominal effusion (see Chapter 182).

Echocardiography

Echocardiograms for patients with PHT from VHD show typical structural signs of pulmonary hypertension – an enlarged right ventricle with thickened walls and papillary muscles. There is some degree of septal flattening – the septum does not curve into the right ventricle in the short axis view but less than is noted with other causes of PHT. There may also be some degree of diminution of the left ventricle and left atrium although they are generally still enlarged. Tricuspid regurgitation pressure gradient obtained by spectral Doppler is elevated but usually not above 70–80 mmHg, unlike the higher pressure gradients seen in pulmonary hypertension not due to VHD. Pulmonic insufficiency pressure gradients can also be elevated in the 8–20 mmHg range. Marked to severe mitral regurgitation is also present in cases of PHT due to VHD.

Despite these typical findings, echocardiography cannot strictly determine the contribution of VHD to PHT to the exclusion of other causes of PHT and sometimes

assessing response to therapy is the only way to determine this.

Left Atrial Tears

Left atrial tears (LAT) can produce pericardial effusion in dogs with significant mitral valve disease. They typically happen because of a high-pressure “jet” type mitral regurgitation that focally injures an already thin left atrial wall. If the left atrial wall tears, the pericardial space becomes filled with blood from the left atrium.

Historical Findings

Dogs with left atrial tears usually have a long-standing history of mitral valve disease and become acutely weak or lethargic. On rare occasions, they will experience collapse.

Physical Examination

Patients are generally weak and have poor pulse quality, with pulsus paradoxus present in many cases. Heart sounds can be muffled and murmur intensity is often diminished from previous reports.

Radiography

Left-sided cardiomegaly and left atrial enlargement are present, often with a slightly rounded cardiac silhouette. There is often no pleural or abdominal effusion as the condition's acute nature precludes development of fluid in these spaces.

FAST

On tFAST, pericardial effusion is present (see Chapters 54 and 182).

Echocardiography

Marked to severe left atrial and left ventricular enlargement are present. No heart base, right atrial or other masses that could account for pericardial effusion are present. The pericardial effusion is often more sonographically dense in appearance than typically seen. Often, a clot can be seen in the pericardial space. Marked to severe mitral regurgitation is present and oriented towards the free wall of the left atrium [39].

Treatment (Table 57.2)

Treatment for all the above in an acute setting is very similar. Furosemide (2 mg/kg) intermittent IV boluses with frequent assessment of clinical response or furosemide CRI (0.5–0.1 mg/kg/h) are recommended. However, in cases of left atrial tears, since the clinical signs can be due

Table 57.2 Emergency therapy for conditions associated with VHD.

Medication	Dosage
Furosemide	Repeated bolus of 1–2 mg/kg IV PRN or IV CRI 0.5–1 mg/kg/h
Enalapril*	0.5 mg/kg PO q12(dog)–24 (cat)h
Pimobendan	0.25–0.3 mg/kg PO q12h
Spironolactone*	0.25–2.0 mg/kg PO q12–24h (dogs only)
Oxygen supplementation	PRN via nasal cannula or temperature-controlled oxygen cage
Nitroglycerin*	2% ointment ½ inch per 10 kg q8h
Nitroprusside (for refractive cases)	Starting at 0.5–1 µg/kg/min titrated up until 5–10% drop in systemic blood pressure observed but systemic blood pressure not to drop below 85 mmHg (dogs only)
Sedation for anxiety associated with dyspnea	Butorphanol 0.2–0.25 mg/kg
Mechanical ventilation for cases where acute change in regurgitation suspected	

* Not consensus recommendations but recommended by some authors in ACVIM consensus statement regarding treatment of congestive heart failure in VHD.

Source: Adapted from the ACVIM Consensus Statement Guidelines for Diagnosis and Treatment of Canine Chronic Valvular Heart Disease [41].

to pericardial effusion, furosemide should be given more conservatively (1–2 mg/kg q8–12h). Pimobendan (0.2–0.3 mg/kg q12h) should also be started [40,41]. Patients should be started on enalapril (0.5 mg/kg q12–24h) and spironolactone (0.5–1.0 mg/kg q24h) as well, except in cats (see Chapter 56) [41]. There is disagreement about when to start enalapril and spironolactone, with some clinicians opting to start them immediately and others electing to wait 5–7 days before starting them [41]. For dogs with RCHF due to VHD, abdominocentesis should be performed if the patient is judged to be having respiratory difficulty due to abdominal distension. Pericardiocentesis should *not* be performed in cases of LAT unless the pericardial effusion is judged to be causing significant hemodynamic compromise and lowering of left atrial pressure can be attempted by treating as if the patient were in congestive heart failure.

Prognosis

Valvular heart disease generally has a slow progression and unless the emergent conditions listed above are

present, most patients have an extended survival. The conditions above generally have an average survival of approximately 1 year.

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58

Heartworm Disease

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Introduction

Dirofilaria immitis, the canine heartworm, is a common cause of morbidity and mortality in dogs around the world. Although canids (domestic and wild) serve as definitive hosts, other species such as the domestic cat and ferret are susceptible to infection with *D. immitis* and any of these species may present acutely or peracutely for complications associated with heartworm infection. This chapter will focus on the clinical manifestations of heartworm infection (HWI) in the canine and feline patient.

There are important pathophysiological differences between dogs and cats. The most important emergent manifestations of heartworm disease in the dog include respiratory distress (resulting from pneumonitis and/or pulmonary thromboembolism), right-sided congestive heart failure (due to pulmonary hypertension), and caval syndrome. Cats may present with asthma-like signs due to heartworm-associated respiratory disease (HARD), anaphylaxis-like reaction (due to worm death), and rarely right-sided congestive heart failure and caval syndrome.

Pathophysiology

The lifecycle of *D. immitis* is complex and is covered more completely elsewhere [1–4]. After transmission of infective L3 from the mosquito vector, the larvae undergo two molts to the immature adults, which penetrate the venous system. Heartworms are thus carried to the pulmonary vasculature, with some arriving as early as 2.5 months after infection and most arriving by 6 months. In the dog, heartworms reach sexual maturity approximately 6 months after infection and circulating microfilaria are usually present 6–9 months post infection. The susceptibility of dogs to experimental HWI is

nearly 100% whereas cats appear to be less suitable hosts, with infection rates of 60–73% [5–7].

Feline HWI differs from canine HWI in several important ways. Most cats “clear” the majority of immature adults prior to their maturation. This results in either abortion of an adult infection or a decrease in the number of heartworms that reach maturity, explaining the relatively low worm burdens in naturally infected cats. These worms are also smaller and shorter lived. Due to the low number of adult heartworms (hence, unisexual infection) and immune-mediated clearance, most cats have few or no circulating Mf and only transient microfilaremia. Some cats with mature HWI “self clear” infections [3,8–11]. Overall, these phenomena are likely related to the cat’s innate resistance to *D. immitis*, which is due in part to a strong immune response [8,12]. This does not, however, mitigate the potential severity of HWI in cats and even a small number of heartworms can be life-threatening. Aberrant migration of worms to ectopic sites has been described in dogs and cats, but may be more common in cats [6].

Generally, the severity of HWI and the likelihood for clinical complications (heartworm disease, HWD) increase with the duration of infection and relative worm burden. Mature *D. immitis* are usually found on the distal pulmonary arteries, with the right caudal lobar artery accumulating the most worms [13]. The presence of these worms leads to physical obstruction, intimal proliferation, activation and attraction of leukocytes and platelets, and endothelial dysfunction within the pulmonary arteries. With chronicity, villous myointimal proliferation and fibrosis develop [14,15]. Furthermore, embolization of worm fragments tends to cause thrombosis. Pulmonary hypertension results from obliterative endarteritis in small, peripheral pulmonary arteries and hypoxia due to ventilation:perfusion mismatching and pulmonary arterial vasoconstriction [2]. With chronicity, pulmonary hypertension (causing right ventricular

pressure overload) can lead to right-sided heart disease (cor pulmonale) and, relatively uncommonly, congestive heart failure (RCHF), which is characterized by an elevation in systemic venous pressures and cavitory effusions (usually ascites in the dog). Spontaneous or postadulthood worm death can produce or worsen pulmonary hypertension and signs of RCHF, due to exacerbation of vascular damage, enhancement of coagulation, and obstruction. Severe, acute pulmonary thromboembolism (PTE), usually associated with worm death (after adulticide or spontaneously), can precipitate forward heart failure (hypotension, cardiogenic shock).

Caval syndrome is a relatively uncommon but serious manifestation of HWD. Large worm burdens and an increase in pulmonary artery pressures (PAP) (often acute) lead to passive, retrograde worm migration to the right heart and cavae. This leads to tricuspid regurgitation, obstruction of right ventricular inflow (and stroke volume), hemolysis of red blood cells, increases in systemic venous pressures, diminished hepatorenal perfusion, and possibly disseminated intravascular coagulation (DIC).

In cats, respiratory signs result from the inflammatory reaction to either the arrival and death of juvenile heartworms in the pulmonary vasculature (3–4 months post infection), or the presence and/or death of the adult heartworm. *D. immitis* evokes pulmonary arteritis with increased thickness of the tunica media and intima and thromboses contribute to luminal obstruction. Airway pathology includes fibrin deposition in the bronchi and bronchioles and hyperplasia of the bronchiole glands. Infiltration of macrophages and eosinophils into the pulmonary parenchyma contributes to an interstitial pneumonia [16]. Antigens released from the dying worm(s) are capable of evoking systemic anaphylaxis and a shock-like reaction [17]. Even the death of one heartworm can precipitate a respiratory crisis and/or sudden death.

This sudden death syndrome in cats with HWI can occur in those either with or without prior symptoms [11,18]. Most cats clear the immature juvenile HWI as worms arrive in the pulmonary vasculature, thereby aborting the adult infection. The sequel to this exposure, immature worm death, and the resultant inflammatory response produces asthma-like clinical signs, a syndrome that has been dubbed heartworm-associated respiratory disease or HARD [2]. The long-term effect of this “infection” is not well understood, but the severe inflammatory response in vessels, bronchioles, and pulmonary parenchyma likely produces sequelae in some cats.

As with most filarial parasites, *D. immitis* harbors the gram-negative bacterium *Wolbachia*. This symbiotic organism is required for normal development, reproduction, and survival of all stages (including Mf) of *D. immitis* [19]. Fortunately, *Wolbachia* are susceptible to

doxycycline and this antibiotic reduces *Wolbachia* numbers in all heartworm life-stages. *Wolbachia* not only helps the parasite thrive and reproduce, it also contributes to the pathological response to *D. immitis*, as the release of this endosymbiont during both worm death and Mf release incite an inflammatory response [20].

Clinical Presentation and Physical Examination

Many dogs with HWI do not have clinical signs for months or even years, with the severity of signs varying depending on relative worm burden, the individual's reactivity, and exercise level [2]. Some dogs with HWI will present with a cough as the only clinical sign of HWI. When infection is severe or prolonged, more significant pulmonary and cardiac pathology can lead to HWD. Dogs with more advanced HWI (i.e. HWD) may present with clinical signs related to pneumonitis, pulmonary thromboembolism, pulmonary hypertension, and/or elevated systemic venous pressures and RCHF. Clinical signs may include exercise intolerance, cough, hemoptysis, dyspnea, collapse, and abdominal distension (ascites). Rarely, dogs can expectorate adult heartworms, likely due to pulmonary artery rupture and extravasation [21]. Aberrant migration to body cavities, systemic arteries, eyes, or the central nervous system may be clinically silent or result in clinical signs relating to the site of migration [2,22]. Pneumothorax arising from HWI is rare, but has been described in two cats [23]. Clinical signs associated with caval obstruction (caval syndrome) include weakness, depression, collapse, pigmenturia, and dyspnea.

The clinical signs in cats are variable and likely dependent upon the magnitude of the pulmonary vascular and parenchymal inflammatory response. One study estimated that approximately 25% of cats with natural HWI remain asymptomatic [18]. Clinical signs of HWI in the cat range from mild respiratory signs to respiratory failure and even sudden death. Acute or peracute presentations usually occur due to dead worm embolization, an anaphylaxis-like reaction, or migration of worms to the central nervous system. Signs may include salivation, tachycardia, shock, dyspnea, cough, hemoptysis, vomiting and diarrhea, syncope, dementia, ataxia, circling, head tilt, blindness, seizures, and death.

Auscultation findings in animals with HWD include increased lung sounds, adventitious lung sounds such as crackles, splitting of the second heart sound (due to the development of pulmonary hypertension and delayed pulmonary valve closure), murmurs (usually right-sided systolic murmur due to tricuspid valve insufficiency), and arrhythmia. Arrhythmias may occur with severe infections and warrant further evaluation via

electrocardiography. With RCHF, findings usually suggest elevated systemic venous pressures (jugular distension) and resultant cavitory effusions (usually ascites, but may include pleural effusion, pericardial effusion, or subcutaneous edema). Caval syndrome, in addition to signs of RCHF, causes “forward failure” (prolonged capillary refill time, poor pulse quality, cardiogenic shock) and intravascular hemolysis (pallor, pigmenturia).

Diagnosis (Table 58.1)

Serology

Highly sensitive antigen tests provide rapid “cage-side” confirmation of HWI. Dogs that have been treated

with macrocyclic lactone preventives are often amicrofilaremic (occult), however, and this should not be the sole test to confirm HWI. Cats, with their lower worm burden, are often antigen negative and usually amicrofilaremic. The antibody test is a useful screening tool in cats with respiratory disease, and a positive test confirms exposure with maturation to at least the L4 stage (some experts define this as “infection” even if aborted at this premature adult stage). Respiratory signs may be due to HARD or mature HWI. A negative antibody test makes HARD and HWI less likely, but the antigen test, while specific, is relatively insensitive in cats. Therefore, cats with mature HWI are typically antibody positive and often antigen negative, while cats with “immature HWD” (HARD) are antibody positive and antigen negative.

Table 58.1 Manifestations of heartworm infection (HWI) (heartworm disease, HWD) are listed. The species affected, physical examination findings, diagnostic test recommended, and treatment strategies are outlined.

Manifestation of HWD	Species affected (uncommon to rare)	Physical examination findings (less common)	Diagnostic tests	Treatment strategies
Eosinophilic pneumonitis	Dog, cat	Cough, wheeze, dyspnea, lassitude, (hemoptysis)	HW Ag test, thoracic radiographs, ± tracheobronchial wash	Oxygen, rest, corticosteroid
HARD	Cat	Cough, wheeze, dyspnea, lassitude	HW Ag (neg) and Ab (pos) test, thoracic radiographs, ± echocardiogram (neg)	Oxygen, corticosteroid, bronchodilator
PTE	Dog (cat)	Cough, wheeze, dyspnea, lassitude, collapse, hemoptysis, CHF, death	HW Ag test (& Ab for cat), thoracic radiographs, D-dimers, ± CT angiogram	Oxygen, rest, corticosteroids, antithrombotic, ± thrombolytic, ± sildenafil, ± pimobendan
RCHF	Dog (cat)	Ascites, (pleural effusion), lassitude, weight loss, collapse, death	HW Ag (& Ab for cat), echocardiogram, tFAST/aFAST, thoracic radiographs, minimum database	Oxygen, rest, paracentesis, furosemide, ACEI, pimobendan, sildenafil, antiplatelet drug, ± HW removal, if necessary
Caval syndrome	Dog (cat)	Collapse, cardiovascular shock, pallor, weak pulses, pigmenturia, (ascites)	Echocardiogram/tFAST, minimum database, coagulation profile	HW removal, fluids, ± vasopressors, ± blood products; later – melarsomine
Sudden death	Cat (dog)	Premonitory signs, if observed, include cough or vomiting (cat); end stage-CHF or arrhythmia (dog)	Postmortem	CPR, if possible
Pulmonary eosinophilic granuloma	Dog, cat	Dyspnea, cough, weight loss, lassitude	Thoracic radiographs, CBC, fine needle aspiration, ± biopsy, ± tracheobronchial wash	Corticosteroid, immunosuppressive therapy, surgery
Aberrant migration	Cat, dog	Location dependent: seizures, vision impairment, inter-digital abscesses, or incidental finding	Imaging (depends on location), surgical exploration	Symptomatic treatment, HW removal, if possible

Ab, antibody; ACEI, angiotensin converting enzyme inhibitor; aFAST, abdominal focused assessment with sonography for trauma; Ag, antigen; CHF, congestive heart failure; CPR, cardiopulmonary resuscitation; HARD, heartworm-associated respiratory disease; HW, heartworm; Neg, negative; Pos, positive; PTE, pulmonary thromboembolism; tFAST, thoracic focused assessment with sonography for trauma.

Radiography

Radiographic signs of heartworm disease include right ventricular hypertrophy, dilation of the main pulmonary artery, dilation (and sometimes truncation and tortuosity)

of the branch pulmonary arteries, pulmonary parenchymal infiltrates (often interstitial and alveolar), and hepatomegaly and ascites. The immune-mediated destruction of Mf within the pulmonary microcirculation can result in eosinophilic pneumonitis (Figure 58.1). Findings

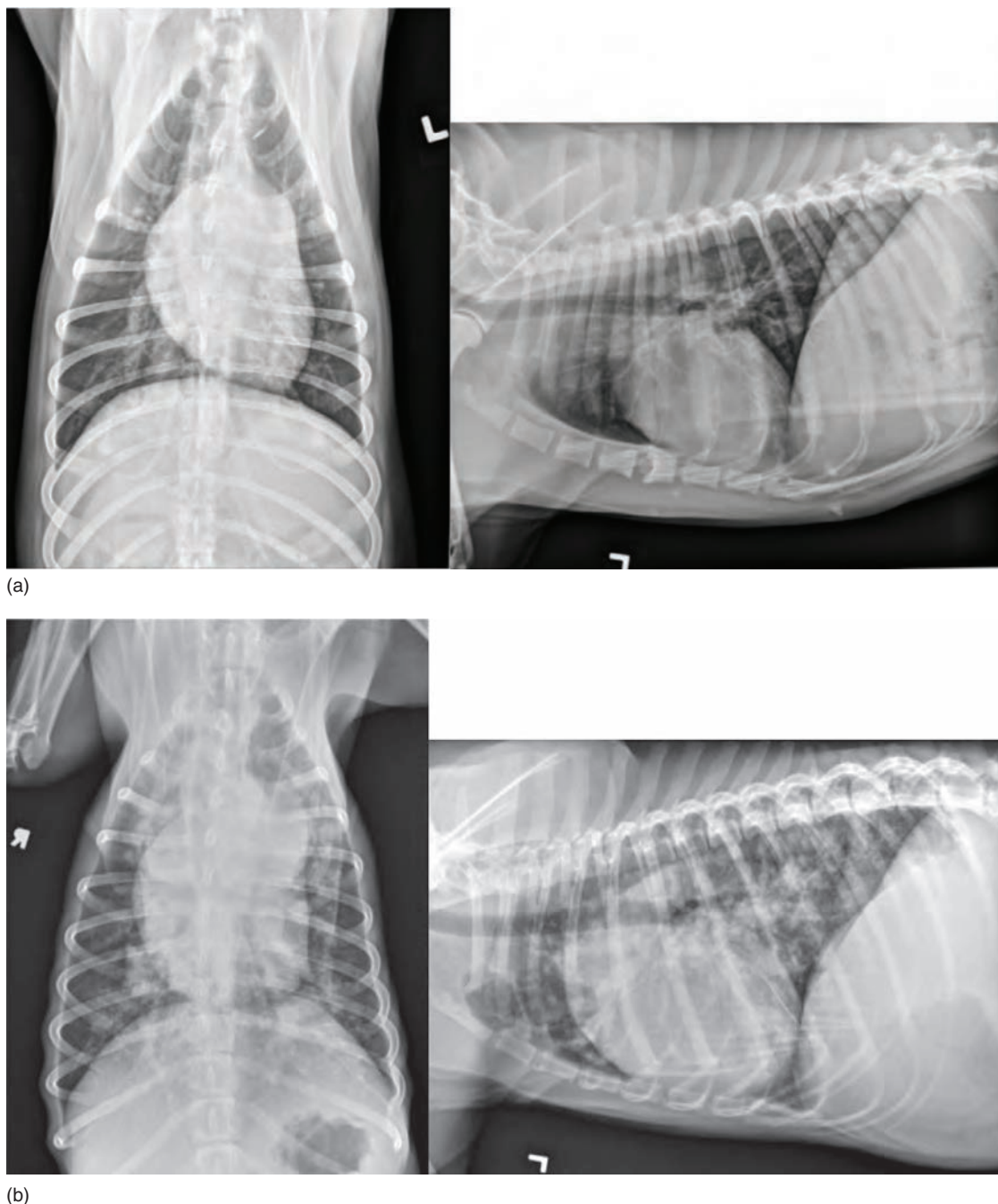


Figure 58.1 (a) Left lateral and ventrodorsal thoracic radiographs from a 2-year-old female dog with HWI. She was presented for cough. There is mild-moderate right heart enlargement, as well as main pulmonary artery and right caudal lobar artery enlargement. There is also a diffuse interstitial infiltrate. (b) left lateral and dorsoventral thoracic radiographs from a 2-year-old male Labrador retriever with HWD, that was presented for cough, tachypnea, and severe exercise intolerance. There is right heart and main pulmonary artery enlargement and peripheral pulmonary arteries are enlarged and tortuous. There is a diffuse, mixed bronchial and nodular-interstitial pattern. The loss of abdominal serosal detail is due to ascites. This dog demonstrates the combined HWD sequelae of right heart failure, active pulmonary disease, pulmonary hypertension, and (likely) chronic and acute pulmonary arterial embolism.

supportive of PTE include interstitial-coalescing-to-alveolar infiltrates, especially in caudal lung lobes or evidence of consolidation. Rarely, this granulomatous inflammation can lead to eosinophilic granulomatosis, which is characterized by granuloma formation and bronchial lymphadenopathy [24].

Radiographic findings in cats include central and peripheral pulmonary artery enlargement, pulmonary parenchymal changes (from mild interstitial or bronchial infiltrates to severe infiltration and lung lobe consolidation), and pleural effusion when RCHF is present [25]. As previously noted, pneumothorax, though rare, has been described in cats with HWI. A ratio of the left caudal lobar pulmonary artery (measured at the ninth intercostal space) to the ninth rib greater than 1.6 supports a diagnosis of HWI, yet is only present in approximately half of HWI cats [26].

Echocardiography

Echocardiography is not a sensitive screening test for HWI in the dog. However, it does allow for investigation of cardiac murmurs that may be related to HWI. Possible scenarios include tricuspid valve incompetency due to disruption by heartworms and pulmonary hypertension, with resultant tricuspid insufficiency. Also, when tricuspid valve regurgitation is present, pulmonary artery pressures can be estimated. With heavy infestations, worms may be visualized in the main pulmonary artery and its branches and/or the right heart (Figure 58.2). In the cat, echocardiography is more sensitive for detecting worms, which may be visualized in

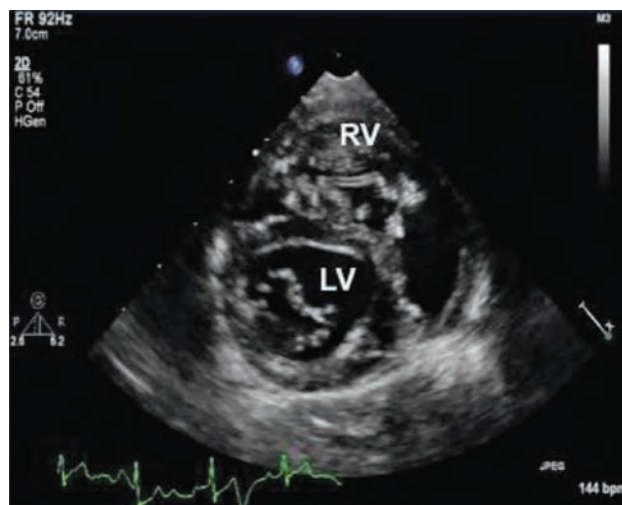
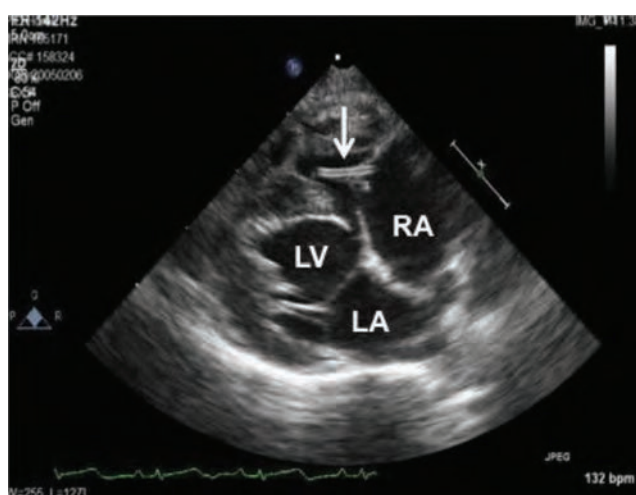
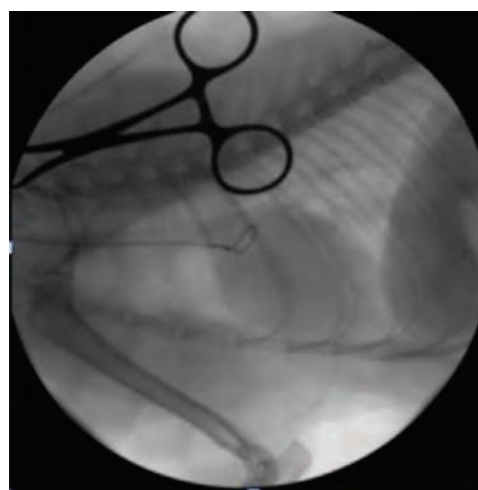


Figure 58.2 Right parasternal short axis echocardiographic view (at the level of the mitral valve) from a 3-year-old female dachshund. A mass of heartworms is seen within the dilated right ventricle. Heartworms appear as echogenic parallel lines.

the pulmonary artery and its branches, right heart, or vena cavae (Figure 58.3a) [27]. The finding of heartworms in the right atrium and cavae, in conjunction with evidence of elevated systemic venous pressures, and intravascular hemolysis confirms the diagnosis of caval syndrome. As previously noted, acute, severe PTE may lead to abrupt changes in right ventricular afterload, resulting in right ventricular dilation and dysfunction, paradoxical septal motion, and leftward shifting of the interventricular septum.



(a)



(b)

Figure 58.3 (a) Right parasternal axis echocardiographic view from a 6-year-old female domestic short-hair cat presented for cough and syncope. There is a heartworm (arrow) traversing the tricuspid valve. There is right atrial dilation. (b) Fluoroscopic image from the same cat shown in (a). A Nitinol Gooseneck® snare is open within the right atrium. A single worm was retrieved.

Clinical Pathology

Relatively common findings include eosinophilia and basophilia. Additional findings include neutrophilia, anemia (usually mild, unless caval syndrome present), thrombocytopenia (most common 1–2 weeks after adulticide therapy) and hyperglobulinemia [15,28]. Hemoglobinuria in a dog with HWD is supportive of caval syndrome. Renal lesions and proteinuria have been documented in both dogs and cats with HWI/D and are likely due to antigen-antibody deposition in the glomerulus [29–31]. Hypoalbuminemia can develop if glomerular disease is severe and contributes to the formation of cavitory effusions and peripheral edema in dogs with RCHF. Additionally, renal and hepatic dysfunction may be evidenced on bloodwork and occur secondary to systemic venous congestion and decreased perfusion of these organs.

Findings of hypoxemia, hypocapnia, increased alveolar to arterial oxygen tension gradient on arterial blood gas analysis, and significant elevation in D-dimers (>1000 ng/mL) add support for the diagnosis of PTE [32,33]. Fluid analysis of cavitory effusions (usually ascites) is most often a modified transudate.

Finally, cytology from tracheobronchial washings may be suggestive of parasitic infection (with eosinophils as the predominant cell type), but is not specific for infection with *D. immitis*.

Treatment of Specific Syndromes

Eosinophilic Pneumonitis

Radiographic findings consistent with HWI/D, including an interstitial infiltrate in dogs with HWD that present with cough, dyspnea, and/or exercise intolerance, is supportive of eosinophilic pneumonitis. Inflammatory infiltrates in perivascular tissues can cause perivascular edema, but this is not a cardiogenic edema and furosemide is not indicated. Instead, corticosteroids should be given (dexamethasone at 0.2 mg/kg IV) in addition to oxygen and rest. Ideally, tracheobronchial washing for cytology and culture is performed in cases where examination and clinicopathological findings are equivocal. Eosinophilic pneumonitis, however, is generally steroid responsive and prednisolone/prednisone is started at 1 mg/kg PO q24h for 3–5 days and tapered as clinical conditions allow [28,34,35].

Heartworm Disease in Cats and Heartworm-Associated Respiratory Disease

For embolic or anaphylactic emergencies, oxygen, corticosteroids (dexamethasone 0.5 mg IV or IM per cat),

and bronchodilators (aminophylline 6.6 mg/kg q12h IV or IM, terbutaline 0.01 mg/kg IV, IM, or SC, or theophylline, sustained-release formulation, 15–25 mg/kg q24–48h PO) may be administered. Cats with cough and/or tachypnea suspected to be related to HARD should receive a monthly heartworm preventive and short-term corticosteroid therapy (prednisolone 1–2 mg/kg q12–48h PO) to manage respiratory signs. If signs recur, alternate-day steroid therapy (at the lowest dosage that controls signs) may, by necessity, be continued indefinitely. Inhaled corticosteroids may also be useful.

Pulmonary Thromboembolism

Dogs with PTE due to HWD may present after adulticide therapy, often 1–3 weeks afterwards, as worms die and disintegrate [36]. Prevention of PTE by strictly curtailing exercise for a month or more post adulticide is **very** important. D-dimers, when used to monitor dogs before, during, and after adulticide therapy, are variably elevated, appear to correlate to worm burden, and, on average, are highest 2 weeks after adulticide administration [37]. Spontaneous worm death can also precipitate PTE.

Therapy for PTE usually consists of supportive care and individually tailored acute and chronic pharmacotherapy. Strict cage confinement, oxygen administration via oxygen cage or nasal insufflation (50–100 mL/kg/min), and prednisone/prednisolone (1 mg/kg/day) have been advocated for severely affected dogs [28,38]. There is no consensus regarding the use of antithrombotics and their use remains controversial. Heparin (75 IU/kg subcutaneously three times a day until platelet count has normalized (5–7 days)) and aspirin (ideal dosage unknown; 5–7 mg/kg/day) have been suggested [28,39,40]. The use of pulmonary vasodilator therapy (sildenafil) and inotropes (pimobendan) is speculative at this time (see next section).

Right-Sided Congestive Heart Failure

Cavitory effusions should be mechanically removed via paracentesis. Furosemide (typically between 2 and 6 mg/kg/day) is then used as part of the “at home therapy” to prevent recurrence of these effusions. If fluid accumulation is refractory despite this, additional diuretics are added (spironolactone 2 mg/kg PO q24h and/or hydrochlorothiazide 1–2 mg/kg PO q24–48h). Torsemide, a more potent and longer acting loop diuretic, can be used to replace furosemide at 10% of its current dosage in the case of refractory RCHF [41,42]. Though not specifically studied in this setting, ACE inhibitors (e.g. enalapril, benazepril, lisinopril, ramipril) are likely indicated, as

they counteract angiotensin II and aldosterone secretion, blunting sodium and water retention and possibly decreasing cardiovascular remodeling. The combination of the “inodilator” pimobendan (0.25 mg/kg PO q12h) and pulmonary artery vasodilator sildenafil (starting at 1.0 mg/kg PO q8h) is used with the theoretical benefits of reduced right ventricular afterload in concert with increased inotropy, therefore, improving pulmonary venous return and cardiac output. Antiplatelet drugs (aspirin, clopidogrel) may reduce platelet-induced vasoconstriction. Finally, strict exercise restriction should be imposed.

Caval Syndrome

Caval syndrome results in part from right atrioventricular valvular insufficiency and obstruction to right ventricular inflow, both via mechanical obstruction, superimposed on PHT. Worm extraction (usually via jugular venotomy) is required for palliation. A minimum database (CBC, biochemistry, and urinalysis) and coagulation profile should be performed to understand the extent of organ system involvement. Stabilization may include fluid resuscitation, vasopressors, and blood products to normalize coagulopathy. Removal of the heartworms, however, is a crucial part of stabilization and should not be delayed.

The patient is usually placed under general anesthesia, though sedation and local anesthetic blocking of the venotomy site may be enough in the severely compromised patient. The patient is placed in left lateral recumbency and the right jugular vein is surgically prepared and draped. The right jugular vein is exposed and a 2–3 mm venotomy is created. Silk suture, tied in open loops proximal and distal to the venotomy site, help with manipulation of the vessel and provide hemostasis. If available, fluoroscopy is used to direct the retrieval equipment within the right heart. Retrieval instruments include Ishihara forceps (no longer available), the Nitinol goose-neck snare kit (Amplatz Gooseneck® Snare Kit, eV3 Endovascular Inc., Plymouth, MN 55441, USA), endovascular snare (EN Snare®, Merit Medical Systems Inc., South Jordan, UT 84095, USA), endoscopic retrieval basket, and long alligator forceps. The retrieval device can be directly introduced into the venotomy site, but great care must be taken when handling the jugular vein to prevent trauma and hemorrhage. Alternatively, a vascular sheath can be introduced, and the retrieval device introduced through the sheath [43]. Worms are pulled into the sheath then the retrieval device is removed simultaneously with the sheath with each pass. When using the retrieval equipment to grasp or ensnare, excessive force (pulling the snare or basket too hard into its catheter or tension on grasping forceps) should be avoided, as this

can result in worm laceration and release of antigen and subsequent anaphylaxis. Once there are several negative passes or transthoracic or transesophageal echocardiography confirm successful reduction of worms, the venotomy is ligated or repaired, and the skin incision is closed in routine fashion. Medical stabilization is then continued post procedure.

In dogs, planning for adulticide therapy (three-dose “split” protocol) is started once the HWD is stabilized. A recent retrospective described one institution’s experience with caval syndrome in the dog [44]. Fifty percent of dogs were not treated and were euthanized (or discharged with the intent for euthanasia) and 50% underwent worm retrieval. In one dog, the HW migrated back to the distal pulmonary artery and retrieval was not performed. In the remaining dogs, 70% survived to discharge and 30% died intraoperatively or perioperatively. For those that survived, 71% were alive at 18 months post procedure and 50% were alive at 24 months post procedure.

Similar HW extraction techniques have been described in cats (Figure 58.3b) [45,46]. Care must be taken, however, not to tear the worm(s), as this can lead to severe anaphylaxis-like reaction and even death [46]. Unfortunately, there is insufficient experience with melarsomine adulticide therapy in cats and it is not currently recommended [2,3,47].

Complications After Microfilaricidal or Adulticidal Therapy

It is currently recommended to initiate macrocyclic lactone (ML) preventives at the time of HWI diagnosis. There is risk for hypersensitivity reactions after ML therapy in dogs with Mf, particularly milbemycin (at preventive dosage) and ivermectin (at the microfilaricidal dosage of 50 µg/kg). Dogs may present within hours with depression, shock, hypothermia, salivation, and vomiting [28,48]. Treatment should include diphenhydramine (2 mg/kg IM), dexamethasone (0.2 mg/kg IV), and fluid therapy. This can also be used as a pretreatment to reduce the chances of an adverse reaction in dogs.

In many if not most cases of canine HWI, melarsomine is a safe and effective HW adulticide, when used as directed by the manufacturer. Mild-to-moderate injection site reactions (pain/swelling at site) occur in approximately one-third of dogs treated with melarsomine intramuscularly. If a patient is not receiving corticosteroids, non-steroidal anti-inflammatory drugs, given for several days, will often prevent or palliate this discomfort. Acute side-effects after IM injection may include pain, coughing/gagging, and hypersalivation [49]. Therapy for these acute effects is symptomatic

and, if an anaphylaxis-like reaction is suspected, should include diphenhydramine (2 mg/kg IM), dexamethasone (0.2 mg/kg IV), and supportive care.

Side effects to worm death occurring, on average, within 5–10 (3–21) days of the melarsomine injection include lethargy, depression, gastrointestinal signs (inappetence, vomiting, diarrhea), and cough. The exact mechanism(s) for gastrointestinal signs associated with HWI and adulticide therapy are not known and this is usually treated supportively. Rare side-effects, associated with melarsomine treatment, include sterile or septic abscesses at the injection site. In some cases, firm nodules can persist indefinitely [49]. Dogs with more severe HWI are more likely to have complications associated with adulticidal therapy [50]. Finally, hematological abnormalities (anemia, leukocytosis) and disseminated intravascular coagulation have been rarely reported [49].

The exact incidence of neurological complications after melarsomine injection is not known, but is likely rare. These complications, when mild, include unilateral hindlimb lameness or gait abnormalities and when more severe, include proprioceptive deficits and paresis, which

can be bilateral in severe cases [49,51]. The onset of neurological complications can occur acutely or weeks to months after melarsomine therapy.

Mechanisms for neurologic side-effects after IM melarsomine injection include migration of compound via fascial planes and ascending inflammation along nerve roots (potentially leading to compressive myelopathy), vasospasm or vasculitis of spinal vascular branches and ischemia of spinal cord segments and injection through the dura and into the spinal cord [51,52]. In rare cases, sterile abscesses can contribute to compressive myelopathy, which may require surgical decompression [51,53]. Other mechanisms of neurological complications with HWI include thromboembolic events and aberrant heartworm migration.

The treatment of these neurological complications involves supportive care and management of paraparesis or paraplegia [51]. The use of corticosteroids remains controversial [51]. Though case reports are sparse, it appears that neurological deficits often resolve (though sometimes incompletely) and only rarely lead to death [51].

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59

Pulmonary Hypertension

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Defining Pulmonary Hypertension

The normal pulmonary circulatory system consists of a low-pressure, low-resistance, high-capacitance vascular bed [1]. In human medicine, normal mean pulmonary artery pressure (mPAP) ranges from 10.7 to 20.6 mmHg [2]. Pulmonary hypertension (PH) is defined as an increase in the pulmonary vascular blood pressure, with a mPAP exceeding 25 mmHg [3,4]. Pulmonary hypertension is further categorized based on pulmonary artery pressures (PAP) as mild (<50 mmHg), moderate (51–75 mmHg), or severe (>75 mmHg) [5].

Pulmonary Hypertension at the Cellular Level

Pulmonary hypertension occurs when there is an imbalance between the factors that control pulmonary arterial vasodilation and vasoconstriction, platelet activity, and smooth muscle cell proliferation [6]. Decreases in factors associated with vasodilation, and increases in substances associated with vasoconstriction, platelet activity, and vascular remodeling are well established in human PH [6–9].

Vasodilators

Nitric oxide (NO) is produced from L-arginine and oxygen by the enzyme nitric oxide synthase (NOS). Nitric oxide travels to smooth muscle, where it stimulates the enzyme guanylate cyclase (GC) to convert guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). cGMP inhibits calcium release and ultimately leads to pulmonary vasodilation; cGMP is inactivated by phosphodiesterases. Nitric oxide also inhibits platelet activation and smooth muscle cell hypertrophy [7]. Prostaglandin I₂ (prostacyclin or PGI₂) is an eicosanoid produced by vascular endothelial cells via the

enzyme prostacyclin synthase. PGI₂ stimulates adenylate cyclase (AC) and enhances the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). cAMP decreases intracellular calcium stores, leading to pulmonary vasodilation. PGI₂ also inhibits platelet aggregation [8].

Vasoconstrictors

Alveolar hypoxia is associated with pulmonary vasoconstriction. This response targets perfusion to better ventilated lung regions, improving ventilation:perfusion matching. While acutely beneficial, in chronic alveolar hypoxia persistent pulmonary vasoconstriction can result in PH. Alveolar hypoxia also induces vascular remodeling via stimulation of growth factors such as platelet-derived growth factor and vascular endothelial growth factor [8].

Endothelin-1 is a peptide made by the vascular endothelium. Binding of endothelin-1 to the endothelin-1 A receptor (ETA) causes vasoconstriction, stimulates growth factors, and promotes vascular remodeling [8,9]. Thromboxane is synthesized and stored by platelets, and is associated with vasoconstriction and platelet activation [10]. Serotonin is produced in the gastrointestinal tract by tryptophan. Once in circulation, serotonin is taken up by platelets, and is later released in response to vascular endothelial damage, resulting in local vasoconstriction. Serotonin also acts as a growth factor and causes vascular remodeling [8].

Classification of Pulmonary Hypertension

Pulmonary hypertension is a complex syndrome, and in veterinary medicine is most often a secondary condition rather than a primary disorder [6]. Pathology of the pulmonary vasculature, lungs, or left side of the heart may result in elevations in mPAP and lead to clinical signs of PH.

The classification of pulmonary hypertension in veterinary patients has been adopted from the human Evian classification scheme; the original human classification of PH was established in 1998, and has been revised in recent years as knowledge of PH has increased [11,12]. The Evian scheme defines five classes according to underlying causes and pathological findings: class 1 pulmonary arterial hypertension (PAH), class 2 PH due to left-sided heart disease, class 3 PH due to pulmonary disease, class 4 PH due to thromboembolic disease, and class 5 PH due to unclear or multifactorial mechanisms [12].

Common Veterinary Causes of Pulmonary Hypertension

Pulmonary arterial hypertension is characterized by changes in the small pulmonary arteries, mostly consisting of proliferative, fibrotic, and inflammatory changes in the artery walls [13]. While idiopathic and hereditary PH are common causes of class 1 disease in human medicine, these have not been investigated in veterinary medicine. Several medications have also been associated with class 1 PH in human patients, including serotonin reuptake inhibitors, phenylpropanolamine, tyrosine kinase inhibitors, chemotherapeutic agents, and interferons [12]. These medications are not documented causes of PH in veterinary medicine, but to date have not been investigated.

One of the most common causes of class 1 PH in veterinary medicine is heartworm disease (see Chapter 58). In heartworm disease (*Dirofilaria immitis*), local damage to the pulmonary arteries results in inflammation and remodeling [14]. Another common cause of class 1 PH in veterinary medicine is congenital shunts (patent ductus arteriosus, atrial septal defects, and ventricular septal defects) (see Chapter 52). Congenital shunts allow blood to travel from the left side of the heart to the right side, and lead to increased pulmonary blood flow and alterations in the vascular walls such as hypertrophy and fibrosis [15]. Congenital shunts are likely the most common cause of PH in cats.

One of the most severe consequences of congenital shunts is the development of Eisenmenger's syndrome (see Chapter 52). In this syndrome, a large or chronic left-to-right shunt allows significant blood flow to the right side of the heart, leading to severe pulmonary vascular changes. These changes promote increased right-sided cardiac pressures, and eventually the right-sided cardiac pressures exceed left-sided pressures; due to the pressure differences, shunt reversal occurs, and blood flows through the shunt from the right side of the heart to the left. As a result of right-to-left shunting through the defect, deoxygenated blood enters the systemic circulation and leads to cyanosis and polycythemia [15].

Chronic degenerative mitral valve disease (CVD) is the most prevalent acquired cardiac disease in dogs.

Given the high prevalence of CVD in canine patients, it is not surprising that most dogs with PH are class 2. Chronic mitral valve regurgitation leads to elevated left atrial volume and elevated left atrial pressure, resulting in increased pulmonary venous pressure and pulmonary hypertension [6]. While many patients with mild-to-moderate PH are asymptomatic, those with increasing mPAP often develop symptoms of PH prior to or at the onset of congestive heart failure (CHF). While less commonly diagnosed, dilated cardiomyopathy and hypertrophic cardiomyopathy may also lead to PH.

Previous studies have indicated that class 3 PH is also relatively common in canine patients [16,17]. Common pulmonary conditions associated with PH include tracheal collapse, chronic bronchitis, and interstitial fibrosis. Although less commonly documented, infectious pneumonia and pulmonary neoplasia are also potential causes of PH.

Common causes of thromboembolic disease (see Chapter 62) in veterinary patients include heartworm disease, immune-mediated hemolytic anemia, protein nephropathy and enteropathy, Cushing's disease, neoplasia, and sepsis [18]. In class 4 PH, vascular obstruction results in increased pulmonary pressures.

Class 5 PH is largely unrecognized in veterinary medicine. In human medicine, patients with complicated or multiform health conditions such as chronic hemolytic anemia, myeloproliferative disorders, and obstructive tumors or granulomatous disease may develop PH [12]. While these conditions exist in veterinary medicine, no clinical association between them and PH has been made.

Cor Pulmonale

Definition and Description

Cor pulmonale is a common consequence of PH. In cor pulmonale, diseases of the pulmonary arteries, lungs, and upper airway disease cause PH and ultimately lead to right ventricular enlargement or hypertrophy. Right-sided cardiac changes may be associated with asymptomatic right ventricular dysfunction or right-sided CHF [19].

Clinical Presentation

Patient Signalment and History

As PH is often due to CVD, most patients are middle-aged to older small-breed dogs. Other breeds prone to upper airway disease (Yorkshire terriers with collapsing trachea) or lower airway disease (West Highland white terriers with pulmonary fibrosis) may be overrepresented [20]. Those dogs with a history of travel

to areas with high incidence of heartworm may also be overrepresented. While cats can develop PH, no specific breeds have been identified.

Recognizing Pulmonary Hypertension

Dogs and cats with PH may present with various clinical signs, ranging from complaints of coughing or exercise intolerance to respiratory distress (dyspnea, tachypnea, or cyanosis), abdominal distension, or syncope. Initial cardiovascular physical exam often reveals distended jugular veins, increased jugular distension during inspiration (Kussmaul's sign), a right apical heart murmur consistent with tricuspid regurgitation, or a split S2 sound indicating delayed pulmonic valve closure. Other common physical exam findings can include left-sided heart murmurs, pulmonary crackles, pulmonary wheezes, and abdominal distension due to hepatomegaly or abdominal effusion.

Patient History

Given that PH is most often a secondary disorder in veterinary patients, obtaining accurate and detailed patient histories is essential to diagnosis.

- Determine if the patient has a long-term history of a heart murmur or prediagnosed heart disease.
- Find out if the patient has a history of upper or lower airway disease.
- Review recent systemic illnesses and previous health problems.
- Obtain a list of current medications.

Diagnosis

Emergent Diagnostics

Pulmonary hypertension can be challenging to diagnose and, given the long list of potential underlying causes and non-specific symptoms, is often confused with other conditions. One of the goals of emergency diagnostics is to determine if the patient has PH, and if possible to discover the etiology. The importance of this is paramount, as the symptoms of PH can remain unresolved if the underlying cause cannot be identified and treated.

Initial assessment to rule out other causes of respiratory symptoms, weakness, or syncope should be completed. Electrolytes, blood glucose, and packed cell volume should be evaluated. An electrocardiogram and blood pressure reading should be performed in order to confirm sinus rhythm and normotension. Sonography for trauma (FAST) of the thorax (tFAST) and abdomen (aFAST) can be employed to evaluate the patient

for effusions (see Chapter 182); if effusions are present, centeses should be completed for gross and microscopic evaluation. The experienced emergency clinician should also use ultrasound to assess the right side of the heart for common subjective evidence of PH, including right atrial and ventricular dilation, interventricular septal flattening, and pulmonary artery dilation.

Thoracic radiographs are non-specific for PH, but often demonstrate right ventricular hypertrophy, main pulmonary artery dilation, and left and right pulmonary artery branch dilation. In cases of cor pulmonale and right-sided heart failure, effusions may also be noted on radiographs (Figure 59.1). Abnormal pulmonary patterns are common in PH patients. Pulmonary undercirculation may be noted in class 1 PH patients with Eisenmenger's syndrome. Class 2 patients often have concurrent CHF and interstitial pulmonary patterns, while class 3 patients with lung disease may have bronchointerstitial or alveolar pulmonary patterns. Class 4 patients may have evidence of thromboembolic disease, although this is challenging to identify on radiographs. Regardless of the underlying cause of PH, many patients have transient alveolar infiltrates that make differentiating between etiologies quite difficult [21].

Completing the Diagnostic Plan

When possible, a complete blood count, chemistry profile, heartworm test, urinalysis, and urine protein:creatinine should be performed to help identify possible causes of PH. Additional labwork, such as endocrine testing or thromboelastography, may be warranted in some patients. Biomarkers, such as ANP and NT-proBNP, may become valuable in the future, but the current long turn-around times prohibit effective use of these diagnostics when evaluating PH patients in the emergency setting.

While right heart catheterization and direct measurement of pulmonary pressures are considered the gold standard for diagnosis of PH in humans, they are rarely performed in veterinary management of PH due to financial constraints and patient instability. Echocardiography is considered the diagnostic modality of choice, as both subjective observations and objective measurements help identify PH.

Most patients with clinical symptoms of PH, regardless of the underlying cause, have moderate-to-severe right-sided cardiac changes: right atrial enlargement, right ventricular dilation and/or hypertrophy, septal flattening, and pulmonary artery dilation. Based on the specific class of PH, additional echocardiographic findings are likely.

Patients with class I PH due to heartworm disease may have heartworm organisms present in the right heart or pulmonary artery (see Chapter 58). Those with

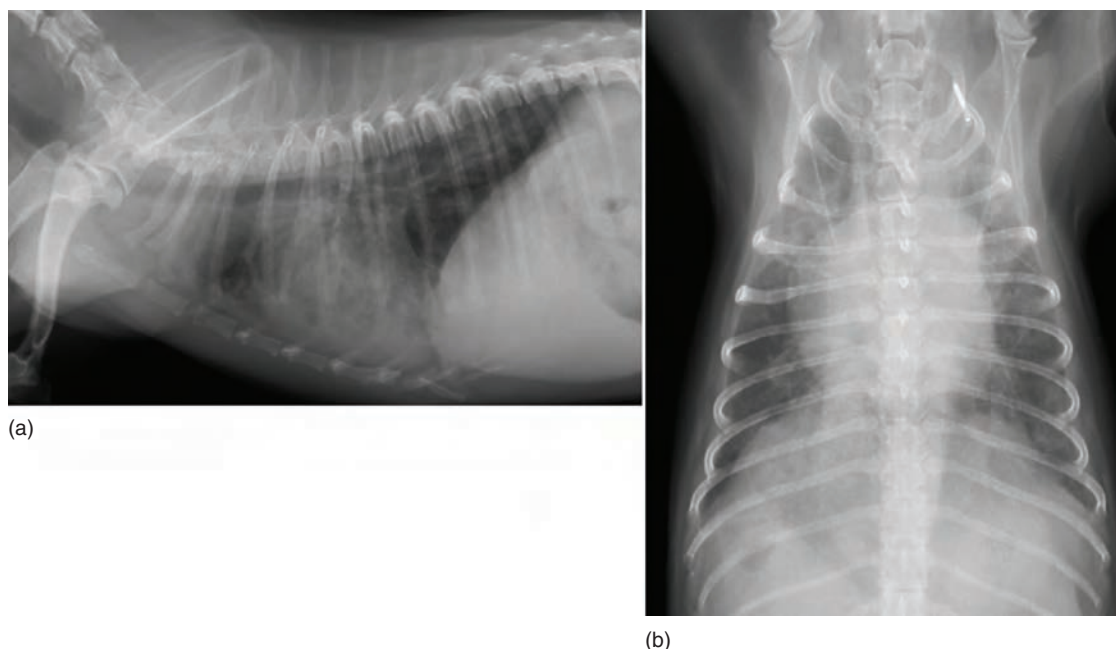


Figure 59.1 Thoracic radiographs obtained from a dog with chronic pulmonary interstitial disease and class 3 PH. (a) Right lateral thoracic radiograph and (b) ventrodorsal radiograph. The patient has a patchy bronchointerstitial pulmonary pattern consistent with lower airway disease. There is right ventricular hypertrophy and main pulmonary artery dilation. Hepatomegaly and mild pulmonary effusion are present, consistent with cor pulmonale and subsequent hepatic congestion and right-sided congestive heart failure.

class I PH due to congenital shunts have shunting lesions noted on 2D echo and Doppler studies. In cases with Eisenmenger's syndrome, a bubble study is often needed to document blood flow from the right side of the heart to the left. In patients with class 2 PH due to left-sided heart disease, evidence of valvular lesions, left atrial enlargement, or left ventricular dilation or hypertrophy is noted in addition to right-sided cardiac enlargement (Figure 59.2a–c). Those with class 3 PH have normal left-sided cardiac structures with evidence of severe right-sided cardiac changes (Figure 59.3a–c). In class 4 PH, although rare, it is possible to identify thromboemboli in distal pulmonary arteries.

Specific echocardiographic diagnosis of PH requires estimation of the PAP. This is accomplished indirectly by measuring the pressure difference between the right atrium and right ventricle, as right ventricular pressure is assumed to be the same as pulmonary artery pressure in the absence of pulmonary stenosis. Tricuspid regurgitation (TR) velocity is measured in right parasternal short axis basilar views and left parasternal apical views. Using the modified Bernoulli equation (pressure gradient (mmHG) = maximum TR velocity (m/s)² × 4), the TR velocity is converted to pressure and is considered an adequate indirect measurement of PAP (Figures 59.2d and 59.3d) [5]. If PH is suspected but can-

not be confirmed, more advanced echocardiographic techniques can be employed in the absence of TR. These are most accurately performed by a specialist in the non-emergent setting, and include evaluation of the pulmonary artery profile, measurement of pulmonary artery acceleration time and ejection time, tricuspid annular plane systolic excursion (TAPSE), and assessment of right ventricular myocardial function via the TEI Index and tissue Doppler imaging [22,23]. Doppler echocardiography, while essential to PH diagnosis in veterinary patients, does have pitfalls if not performed or interpreted correctly.

Treatment

Therapy in the Acute Setting

Oxygen therapy is required to stabilize the patient and relieve symptoms of hypoxia; fractional inspired oxygen (FiO₂) of 40–60% delivered via nasal cannulation or oxygen cage often helps relieve symptoms of PH (see Chapter 181). In the most severe cases, mechanical ventilation may be needed.

Targeted therapeutic plans aimed at treating the cause of PH should be utilized when possible.

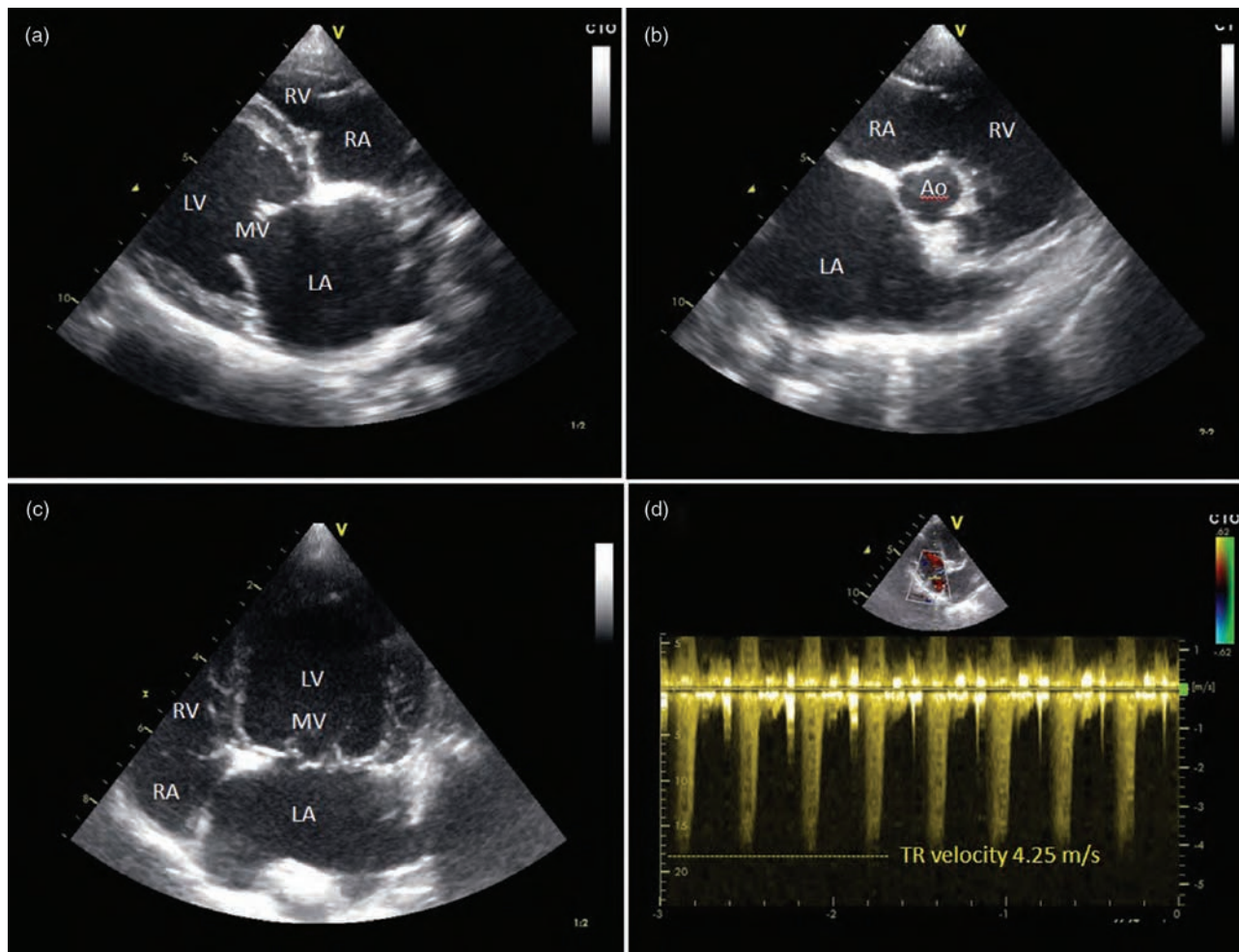


Figure 59.2 The echocardiographic images were obtained from a dog with severe chronic degenerative valvular disease and class 2 pulmonary hypertension. Note that the left atrium and ventricle are severely dilated consistent with left-sided cardiac disease. (a) Right parasternal long axis view demonstrating dilated LA, LV, and thickened MV. (b) Right parasternal short axis basilar view confirming severe LA dilation in relation to the Ao. (c) Left parasternal long axis view depicting dilated LA and LV and thickened MV with prolapse. (d) Left parasternal long axis view demonstrating Doppler interrogation of TR. The TR velocity is elevated at 4.25 m/sec; using the modified Bernoulli equation, the estimated pulmonary artery pressure is 72.5 mmHg, indicating moderate pulmonary hypertension. Ao, aorta; LA, left atrium; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; RA, right atrium; RV, right ventricle; TR, tricuspid regurgitation.

Class 1

- Patients with heartworm disease may benefit from anti-inflammatory doses of corticosteroids and bronchodilators (see Chapter 58).
- Clinical symptoms associated with congenital shunts, especially in the presence of Eisenenger's syndrome and secondary polycythemia, can be relieved by phlebotomy (see Chapter 52).

Class 2

- Patients with CVD and severe left atrial enlargement causing class 2 PH may benefit from pimobendan therapy (0.2–0.3 mg/kg PO BID). In general, patients

with left-sided heart disease and concurrent CHF and PH should be treated with appropriate diuretic therapy and angiotensin converting enzyme inhibitors (see Chapter 57).

Class 3

- Various interstitial lung diseases require specific therapies, such as antibiotics in cases of infectious pneumonia, and inhaled or oral corticosteroids and bronchodilators in inflammatory airway disease.
- Upper airway obstruction due to collapsing trachea may require sedation, cough suppressants, and in some cases antibiotics to treat secondary tracheitis or

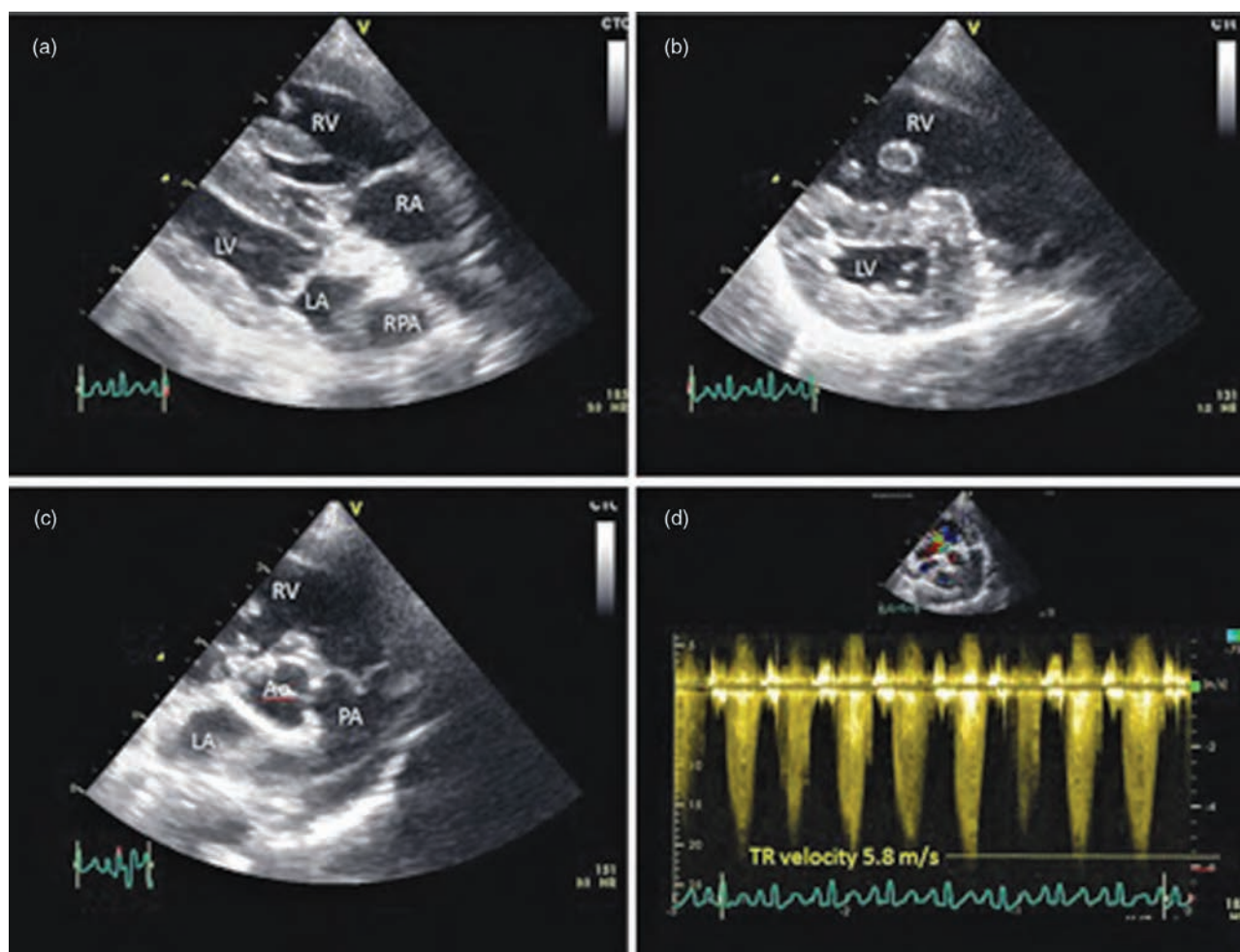


Figure 59.3 The echocardiographic images were obtained from a dog with severe chronic pulmonary interstitial disease and class 3 pulmonary hypertension. Note that the left atrium and ventricle appear normal, with no evidence of left-sided cardiac disease. (a) Right parasternal long axis view demonstrating dilated RA, RV, and RPA. (b) Right parasternal short axis apical view demonstrated RV dilation and septal flattening due to high right-sided pressures. (c) Right parasternal short axis basilar view depicting PA dilation. (d) Right parasternal short axis basilar view demonstrating Doppler interrogation of TR. The TR velocity is elevated at 5.8 m/sec; using the modified Bernoulli equation, the estimated pulmonary artery pressure is 134.5 mmHg, indicating severe pulmonary hypertension. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; TR, tricuspid regurgitation.

corticosteroids to treat associated tracheal inflammation (see Chapter 31).

Class 4

- Antiplatelet therapy (aspirin 0.5 mg/kg PO SID or clopidogrel 2 mg/kg PO SID) should be instituted in cases of PH due to thromboembolic disease (see Chapter 42). Anticoagulant therapy (rivaroxaban 2 mg/kg PO BID) could also be considered. Other therapies, such as fibrinolytics, have not been studied in veterinary PH. Specific therapies addressing the cause of the thromboembolic should be instituted.

If clinical evidence of PH persists despite treatment of the underlying condition, or if an underlying cause of PH cannot be found, other therapies aimed specifically at reducing PAP may be necessary. Phosphodiesterase 5 (PDE-5) is highly concentrated in pulmonary vessels, and leads to the breakdown of cGMP. Inhibition of PDE-5 results in higher concentrations of cGMP, decreased calcium release, and therefore improved vasodilation. Sildenafil is the most common PDE-5 inhibitor used in veterinary medicine, with a recommend dose of 0.5–2 mg/kg PO BID–TID. Studies suggest that onset of action is relatively quick, and that dogs treated with sildenafil demonstrate

decreased PAP, increased exercise capacity, and improved quality of life [24,25].

While antiplatelet therapy has been well researched in human PH, there is very little information available regarding its use in veterinary PH. In patients in which class 4 PH is confirmed or highly suspected, medications such as aspirin or clopidogrel can be used. The anticoagulant rivaroxaban is an alternative therapy, and can be used alone or in combination with clopidogrel. Given that PH is associated with cellular changes that promote platelet-induced vascular changes, such as serotonin-associated vascular remodeling, there is some rationale for use of platelet inhibitors in other classes of PH (see Chapter 71) [26].

Long-Term Therapy Options

Patients with severe PH typically require combination therapy for long-term success. Examples of this include patients with class 2 PH associated with CVD and CHF treated with sildenafil, furosemide, pimobendan, and angiotensin converting enzyme inhibitors. Class 3 patients with chronic bronchitis may require sildenafil along with bronchodilators and corticosteroid therapy (see Chapter 33). While combination therapies often result in resolution of clinical symptoms and an improved prognosis, some patients remain refractory to therapy and continue to suffer the symptoms of PH. In these cases, alternative therapies may be considered.

Recent studies evaluating use of the long-acting PDE-5 inhibitor tadalafil show promise, but its use is

not well studied in veterinary medicine and a dosing regimen has not been established [27]. The pharmacokinetics of bosentan, an oral endothelin-1 receptor, have been studied in cats and this may be a promising PH therapy in the future [28]. Other therapies, such as the subcutaneous or inhaled prostacyclin analogs treprostinil and iloprost, are currently cost-prohibitive and poorly studied in clinical veterinary medicine, but in time may become more available. Interestingly, low-dose therapy with imatinib may inhibit growth factor-induced vascular remodeling and lead to improved PAP and clinical symptoms [29]. While imatinib therapy is unlikely to benefit patients in the emergent setting, long-term therapy may improve quality of life.

Follow-Up and Prognosis

After initial stabilization, PH patients should establish care as indicated with a cardiologist or internal medicine specialist for long term management. Recheck exams often include echocardiograms to assess PAP, thoracic radiographs to evaluate for effusions and pulmonary infiltrates, and labwork as needed to monitor the patient's underlying illness and response to medical therapy.

The prognosis for veterinary patients with PH varies, and largely depends on the management of the underlying cause. That said, patients who respond well to initial therapy may survive anywhere from 3 months to 2 years with excellent quality of life [16].

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60

Bradyarrhythmias and Pacemakers

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Introduction and Definitions

Bradyarrhythmias can be defined as cardiac rhythm abnormalities that result in heart rates that are lower than normal for the given clinical context. Generally, hospitalized dogs with rates persistently less than 60 bpm and hospitalized cats with rates less than 140 bpm can be considered abnormal, particularly if the rate does not increase with stimulation or activity. Following the diagnosis of a bradyarrhythmia, it is important to determine if the cause is physiological, iatrogenic, or pathological, as this will help guide diagnostic and therapeutic decisions.

Physiological Bradyarrhythmias

Physiological bradyarrhythmias are caused by alterations of extracardiac factors usually secondary to systemic disease including, hypothermia, hyperkalemia, hypothyroidism, hypertension (via baroreceptor reflex activation), gastrointestinal/intra-abdominal disease, respiratory/intrathoracic disease, central nervous system disease, and ocular disease. Most physiological bradyarrhythmias are mediated by an increase in vagal tone and commonly manifest as sinus bradycardia, a pronounced sinus arrhythmia, or atrioventricular (AV) conduction abnormalities. The ECG of dogs and cats with hyperkalemia is classically accompanied by tall and narrow T-waves, low-amplitude or absent P-waves (atrial standstill), wide QRS complexes, or some combination thereof, depending on the magnitude of hyperkalemia.

Iatrogenic Bradyarrhythmias

Iatrogenic bradyarrhythmias result from the administration of drugs that slow sinus node depolarization rate,

decrease AV node conduction, or both. The majority of these drugs act to increase vagal tone or decrease sympathetic tone. Similar to physiological bradyarrhythmias, drug-induced bradyarrhythmias usually manifest as sinus bradycardia, a pronounced sinus arrhythmia, or AV conduction abnormalities. Commonly used drug classes that may induce a bradyarrhythmia include opioids, sedatives (e.g. alpha-2 agonists), antitachyarrhythmics (e.g. beta-blockers, diltiazem, sotalol), and anesthetics.

Pathological Bradyarrhythmias

Diagnosis of a pathological bradyarrhythmia implies that physiological and iatrogenic bradyarrhythmias are ruled out and a primary abnormality of the cardiac conduction system is present. Pathological bradyarrhythmias typically result in heart rates that are too low to meet the perfusion demands of the patient, thus resulting in clinical signs including syncope, collapse, lethargy, mental dullness, exercise intolerance, weakness, ataxia, respiratory difficulty and/or abdominal distension secondary to congestive heart failure (CHF). These clinical signs may occur despite compensatory mechanisms including hyperdynamic myocardial systolic function and generalized cardiac chamber dilation. Chamber dilation is a result of prolonged diastolic filling time and fluid retention (via renin-angiotensin-aldosterone system stimulation) in response to diminished cardiac output, which may lead to CHF. CHF is commonly manifest as ascites unless concurrent left-sided cardiac disease is present.

Pathological bradyarrhythmias usually result from abnormalities of cardiac impulse formation, impulse conduction, or both. Common pathological bradyarrhythmias in small animal patients include second-degree AV block (Mobitz type II), third-degree AV block, sick sinus syndrome, and persistent atrial standstill (Figure 60.1).

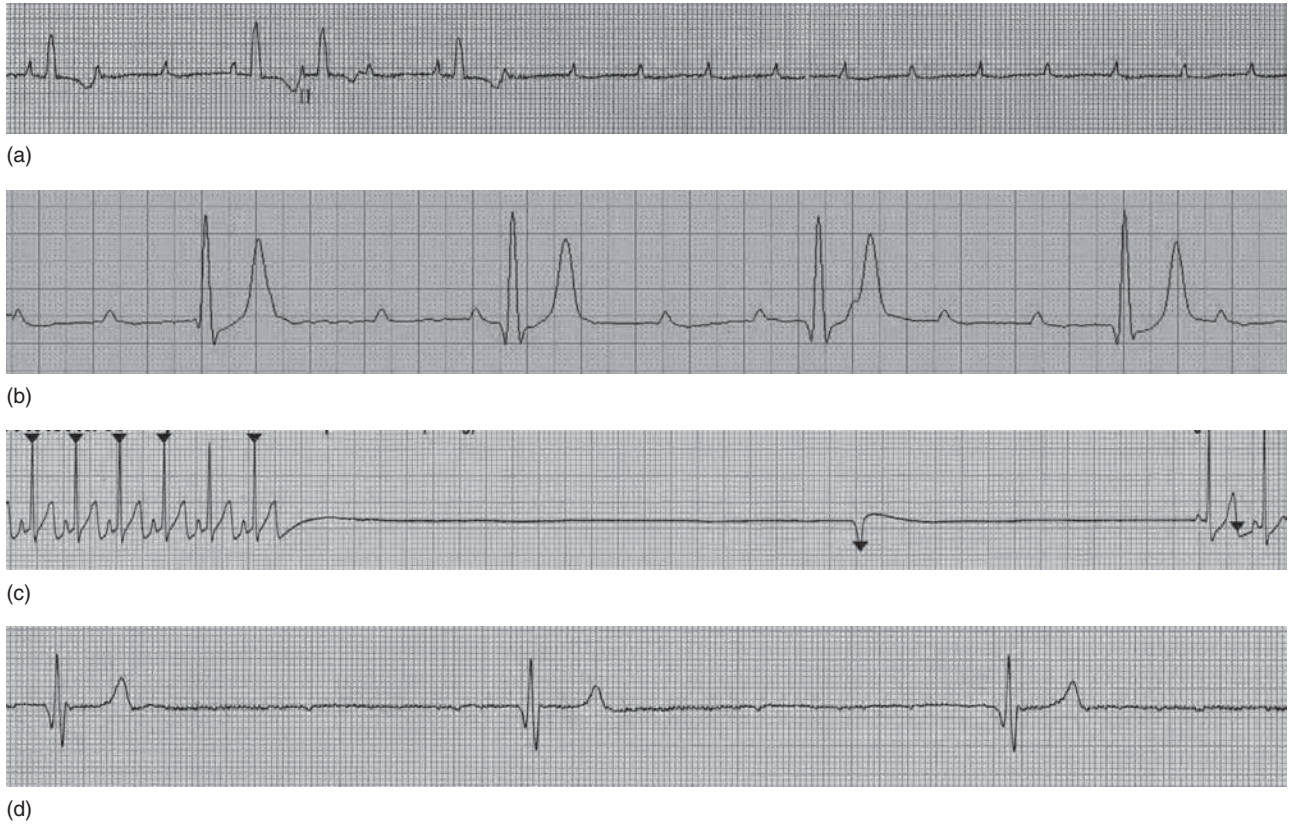


Figure 60.1 Common pathological bradyarrhythmias in small animal patients. (a) High-grade Mobitz type II second-degree atrioventricular block and left bundle branch block (QRS duration > 40 ms) in a cat. Note the abrupt lack of sufficient escape activity in this cat (lead II, 50 mm/sec, 10 mm/mV). (b) Third-degree atrioventricular block in a dog. Note the upright and narrow QRS complexes suggesting a junctional escape rhythm depolarizing at 50 bpm (lead II, 50 mm/sec, 10 mm/mV). (c) Sick sinus syndrome in dog. A supraventricular tachycardia is followed by an abrupt sinus pause lasting approximately 7 seconds. Escape activity of a subsidiary pacemaker is lacking and a motion artifact is apparent during the pause (lead II, 25 mm/sec, 10 mm/mV). (d) Persistent atrial standstill in a dog. Note the bradycardia (36 bpm) and lack of P-waves (lead II, 50 mm/sec, 10 mm/mV).

Atrioventricular Block (AVB)

Second-Degree Atrioventricular Block

Second-degree AVB is electrocardiographically diagnosed when a QRS complex does not follow every P-wave, implying that the AV conduction system intermittently fails to carry atrial depolarizations to the ventricles. Mobitz type I (Wenckebach phenomenon) occurs when a non-conducted P-wave is preceded by (progressively) delayed AV conduction (i.e. PR interval > 130 msec in dogs, > 90 msec in cats). Mobitz type II second-degree AV block is characterized by sudden failure of AV conduction that is without prior AV conduction delay. Mobitz type I second-degree AVB is generally viewed as a transient or benign condition, and is more properly classified as a physiological or iatrogenic bradyarrhythmia. Mobitz type II second-degree AVB is more commonly classified as a pathological bradyarrhythmia, especially when AV conduction failure is frequent or “high grade.” High-grade second-degree AVB

can be diagnosed when non-conducted atrial impulses (blocked P-waves) outnumber conducted atrial impulses or when consecutive non-conducted atrial impulses are noted (see Figure 60.1a).

Although both types of second-degree AVB may progress to third-degree AVB, Mobitz type II more commonly does so and is more commonly associated with clinical signs when high grade.

Third-Degree Atrioventricular Block

Third-degree AVB (also called complete AVB) is characterized by complete failure of AV conduction. Subsidiary (rescue) pacemakers below the level of the block usurp control of ventricular pacing in an attempt to maintain cardiac output. In most cases, the escape rhythm originates from Purkinje cells or ventricular cardiomyocytes, resulting in a wide QRS complex. Narrow and upright QRS complexes (in lead II) are occasionally observed and imply that the escape rhythm originates in the AV junction (see Figure 60.1b). Escape rates typically range from

20 to 60 bpm in dogs and 80 to 140 bpm in cats, with junctional escape rhythms demonstrating higher heart rates within this range. Feline escape rates are commonly 120–140 bpm, and auscultation of heart rates within this range must not be overlooked during the physical examination.

The ECG of dogs and cats with third-degree AVB typically displays P-waves and QRS complexes without any regular or consistent relationship. So-called atrio-ventricular dissociation is apparent with two independent pacemakers present: the atria are paced by the sinus node and still under the influence of the autonomic nervous system, and the ventricles are paced by a spontaneous escape rhythm at slower rates. Ventricular escape rhythms are usually regular and monomorphic. If this is not the case, and particularly if the escape rate is low, this likely implies the patient is more hemodynamically unstable and should promote more urgent therapeutic intervention.

An underlying primary cause of pathological AVB is rarely identified, and most commonly involves a fibrodegenerative disease of the AV conduction system. Other potential causes include infiltrative, neoplastic, infectious, inflammatory (myocarditis), ischemic, traumatic, and metabolic diseases with sporadic reports of each noted throughout the literature.

Labrador retriever, cocker spaniel, chow-chow, Afghan, Catahoula leopard dog, and German wire-haired pointer breeds appear to be predisposed to high-grade second- and third-degree AVB [1]. Cats with third-degree AVB do not commonly demonstrate clinical signs and appear to be very tolerant of this bradyarrhythmia [2]. Emergency clinicians should also be aware that cats are notorious for sporadic periods of high-grade second-degree AVB lacking sufficient escape activity (see Figure 60.1a) and may exhibit seizure-like clinical signs [3]. Unless a transient bradyarrhythmia is witnessed or considered, prompting ECG monitoring, cats may be misdiagnosed with a seizure disorder and undergo unnecessary diagnostic testing.

Sick Sinus Syndrome

Sinus node dysfunction (SND) is characterized by intermittent failure of the sinus node to depolarize and is usually manifest electrocardiographically as sinus bradycardia or sinus arrest. Sick sinus syndrome (SSS) indicates the SND is coupled with clinical signs such as weakness, lethargy, collapse, or syncope that may or may not be activity induced. SSS usually indicates the SND is severe and the ECG often reveals periods of asystole lasting 6–8 seconds interrupted by inadequate or delayed junctional escape complexes (see Figure 60.1c). Thus, SSS should not be thought of solely as a disease of the sinus node but also as a disease of the subsidiary pacemakers.

Intermittent bouts of supraventricular tachycardia may precede prolonged sinus pauses, which is referred to as overdrive suppression and denotes the so-called bradycardia-tachycardia syndrome (see Figure 60.1c). Occasionally, periods of AVB may also be observed.

It is important to note that abnormal ECG findings in dogs with SSS may not be readily apparent on a baseline/screening ECG. Therefore, prolonged ECG monitoring is encouraged. Even if syncope is not witnessed, sinus pauses >6–7 seconds in an awake dog suggest a diagnosis of SSS.

Sick sinus syndrome is most commonly encountered in older small-breed dogs, and predisposed breeds include miniature schnauzers, West Highland white terriers, dachshunds, and cocker spaniels. The cause of SSS is unknown but a genetic component is likely. Genetic mutations and sinus node ischemia or fibrosis have been identified in humans with SSS. Sick sinus syndrome is considered relatively rare in cats.

Persistent Atrial Standstill

Persistent atrial standstill (PAS) is a relatively uncommon bradyarrhythmia of dogs and cats where the atria fail to depolarize despite normal sinus node discharge. The surface ECG subsequently lacks P-waves as a result of an electrically and mechanically “silent atrium” and loss of conduction from the sinus node to the AV node (so-called “sinoventricular rhythm”) (see Figure 60.1d). The ECG may also demonstrate a junctional or ventricular escape rhythm secondary to concurrent sinoatrial or AV block. Upon close inspection of the ECG, disorganized atrial activity (atrial fibrillation) or low-voltage, non-conducted P-waves may be apparent. PAS must be differentiated from failure of atrial depolarization secondary to hyperkalemia, cardiac glycoside toxicity, or hypothermia (temporary atrial standstill).

Persistent atrial standstill may be a familial disease of English springer spaniels and is most commonly diagnosed in younger to middle-aged large pure-bred or mixed-breed dogs. PAS can be considered an idiopathic atrial cardiomyopathy classically characterized by progressive atrial dilation. In some cases, the disease may also affect the ventricles, leading to progressive global myocardial failure.

Clinical Management of Dogs and Cats with Bradyarrhythmias

Initial Stabilization

Upon recognition of a bradyarrhythmia via physical examination and ECG, urgent therapeutic intervention may be

required in dogs and cats that are hemodynamically compromised or exhibiting severe clinical signs, regardless of whether it is a physiological, iatrogenic, or pathological bradyarrhythmia. In rare cases, medical management will suffice but in the majority of symptomatic dogs, temporary pacing is required for optimal stabilization, as a bridge to permanent pacing, or frequently both.

Medical Management

Vagally mediated bradyarrhythmias and some cases of SSS may respond to parenteral parasympatholytic medications (atropine 0.04 mg/kg or glycopyrrolate 0.01 mg/kg). If a favorable response is noted (sinus tachycardia with heart rate usually > 140 bpm within 30 min), these parenteral parasympatholytic medications may be utilized as needed while hospitalized. A favorable response may suggest the patient will respond to oral pharmacological therapy. Popular choices in these cases, and in palliative cases where pacing is not an option, include bronchodilators/sympathomimetics (theophylline – dogs: extended-release 10 mg/kg PO q12h; terbutaline – dogs and cats: 0.1–0.2 mg/kg PO q12h) or the oral parasympatholytics (hyoscyamine – dogs: 0.003–0.006 mg/kg PO q8h; propantheline – dogs: 0.25–0.5 mg/kg PO q8–12h). Unfortunately, oral therapy is rarely effective long term and many of these medications possess several adverse effects. Further, they may induce or exacerbate any concurrent tachyarrhythmias.

Lastly, in a hospital setting when temporary pacing equipment is unavailable or when beta-blocker or calcium channel blocker toxicity is encountered, a constant-rate infusion of the non-selective beta-agonist isoproterenol (0.04–0.08 µg/kg/min IV) or dopamine (5–10 µg/kg/min IV) may be considered to increase heart rate and AV conduction.

Temporary Transvenous Pacing

Temporary transvenous pacing involves guiding a temporary pacing lead (usually 100–110 cm length, 4–6 Fr in diameter) into the right ventricular apex via the left jugular or a lateral saphenous vein. The right jugular vein should be preserved for permanent transvenous pacing.

Access to the peripheral vein is accomplished using standard aseptic technique and a percutaneous or cut-down approach (if necessary) with a vascular introducer large enough to accommodate the pacing lead. The lead is guided into the right ventricular apex, preferably via fluoroscopy or echocardiography, and connected to a battery-operated external generator (Figure 60.2). Some leads have an inflatable balloon at the tip that is intended to flow along with blood flow and allow atraumatic placement. The balloon is deflated once the lead is beyond the tricuspid valve and in contact with the right ventricular endomyocardium.

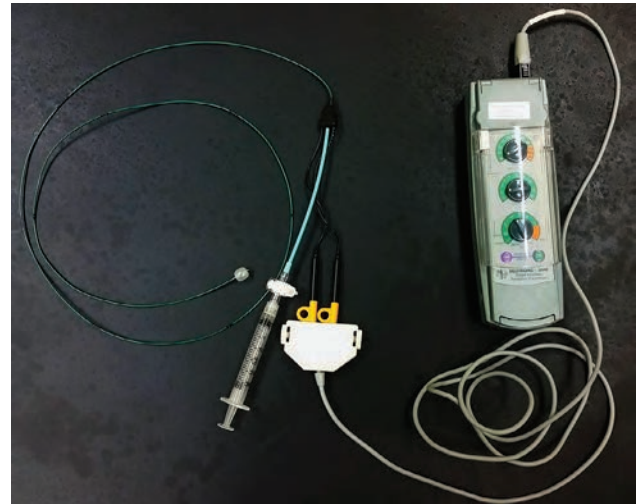


Figure 60.2 Temporary transvenous pacing system. Note the inflatable balloon at the tip of this lead.

Next, pacing can be initiated to the desired heart rate by gradually increasing the output (mA) until capture is noted on ECG. The temporary pacemaker operates in VVI mode (ventricle paced, ventricle sensed, pacing inhibited during a sensed event). The sensitivity setting must be adjusted to allow appropriate sensing of non-paced complexes and not sensing T-waves. Typical sensitivity settings range from 2 to 4 mV. If sensing of T-waves is noted on the ECG (“oversensing”), the sensitivity can be decreased by increasing the number value in mV, for example from 3 mV to 4 mV. Once pacemaker programming is sufficient for consistent capture, so that paced complexes stimulate myocardial contraction and a pulse is palpated accordingly, the lead must be secured to the introducer. This is usually accomplished by taping the lead to where it enters the introducer.

Temporary transvenous pacing may serve to stabilize the patient prior to permanent pacing and is a good option if permanent pacing may not be necessary. It is not painful and can be performed with (or sometimes without) mild sedation (usually an opioid and atropine). Following implantation, the patient is typically sedated to limit mobility and avoid lead dislodgment.

Temporary Transthoracic Pacing

Transthoracic pacing is an efficient way to achieve cardiac pacing in an emergency setting when permanent pacing is intended to follow shortly thereafter. It has been demonstrated to be an effective means of pacing in a relatively large number of dogs [4,5]. It involves applying commercially available human transthoracic pacing adhesive patches to the clipped skin directly over the palpated cardiac apex beat on each side of the thorax. The patches are typically secured to the patient by wrapping

bandage material around the patient's thorax. The patches are connected to an external generator and many commonly utilized external defibrillators can serve this purpose. Programming methods are similar to transvenous pacing. This method of pacing requires general anesthesia during pacing. It is painful and significant movement can be observed secondary to skeletal muscle contraction.

Indications for Permanent Pacing

In general, dogs that demonstrate clinical signs deemed secondary to a pathological bradyarrhythmia should be considered for permanent pacemaker implantation. Additionally, if high-grade second-degree or third-degree AVB is encountered in a reportedly asymptomatic dog, most cardiologists advise permanent pacing regardless due to their relatively high risk of sudden death [1]. Also, AV conduction disease appears to persist or progress in the vast majority of dogs [6]. Permanent artificial pacing in dogs, albeit with a transvenous or epicardial lead, has been demonstrated to be a relatively safe and reliable procedure that permits a favorable quality and quantity of life [7–10].

In contrast to dogs, many cats with third-degree AVB can exhibit a good quality of life without treatment of the AVB, regardless of whether structural cardiac disease or heart failure is present [2]. The benefits of permanent

cardiac pacing noted in dogs may not be as substantial in cats and are generally outweighed by the risks, complications, and costs of pacing, in addition to the already fair prognosis of untreated cats. Thus, permanent pacing in cats is typically reserved for those with severe/refractory clinical signs secondary to a pathological bradyarrhythmia. Epicardial leads are most commonly implanted in cats via a surgical transdiaphragmatic approach due to their small size [9].

Work-Up of Dogs and Cats with Bradyarrhythmias

If possible, a full diagnostic work-up is advised in patients with bradyarrhythmias, especially if they are being considered for permanent pacing. This is recommended for several reasons including ruling out the aforementioned systemic diseases that may be causing or contributing to the bradyarrhythmia, assessment of co-morbid conditions, and determining anesthetic candidacy. Particular care should be taken to assess the patient for any infectious processes that could predispose the patient to bacteremia and infection of the pacing system. Specific diagnostic tests are performed on a case-by-case basis but commonly include hematology, serum chemistry, urinalysis and culture, echocardiography, thoracic radiographs, abdominal ultrasound, infectious disease testing, troponin I, and atropine response test.

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Myocarditis

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Introduction

Myocarditis (MC) is defined as inflammation of the cardiac myocardium and can occur from a variety of causes including infectious, inflammatory, toxic, traumatic, and neoplastic etiologies. In most cases, dilated cardiomyopathy (DCM) and arrhythmias are the major sequelae of MC.

Infectious agents are one of the most common causes of MC in dogs. Major pathogens include viral (parvovirus, West Nile virus), protozoal (*Trypanosoma*, *Toxoplasma*, *Babesia*), bacteria (*Staphylococcus*, *Streptococcus*, *Bartonella*, *Borrelia*), fungi (*Cryptococcus*, *Coccidioides*), and helminths (*Toxocara*). Infectious agents cause MC via direct infiltration of inflammatory cells, injury from released toxins from the organisms, or a delayed type immune response.

Parvovirus

Parvovirus MC was one of the most common infectious causes of MC prior to widespread vaccination programs. If the puppy is infected either *in utero* or within the first several weeks of life, parvovirus can precipitate MC as the virus has a predilection for rapidly dividing cells which include cardiac cells. Many of these dogs will die suddenly with few preceding clinical signs. On histopathology of the infected puppies' hearts, parvovirus MC is characterized by a non-suppurative lymphocytic infiltrate with intranuclear viral inclusion bodies. Often the virus affects one organ system (cardiac, gastrointestinal, neurological) although a generalized form of infection can also occur. The prognosis for MC with parvovirus in neonates is grave. If they survive, puppies typically present at a young age with dilated cardiomyopathy, cardiac arrhythmias, and congestive heart failure.

Chagas' Disease

Chagas' disease, caused by the parasite *Trypanosoma cruzi*, is a common cause of MC and DCM in people and dogs in Latin America; it is rare in North America except in the southern states. *T. cruzi* is transmitted by the Mexican kissing beetle of the family Reduviidae and its natural hosts include dogs, people, cats, and armadillos. There have been no reports of feline cases of Chagas' disease in northern America. It is common in the acute form for there to be no echocardiographic abnormalities. The main cardiovascular findings are arrhythmias including atrioventricular block (AVB), right bundle branch block (RBBB), and sinus tachycardia. Following the acute phase, during which there is a risk of sudden death, a latent phase of a variable time frame occurs. Again, the echocardiogram may be normal during this phase. Once the chronic form develops, Chagas' disease is indistinguishable from DCM on an echocardiogram although it classically precipitates left- and right-sided ventricular failure.

Chagas' disease MC is diagnosed on the basis of consistent electrocardiograph and echocardiographic abnormalities and the identification of circulating antibodies to *T. cruzi* in the blood. Diagnosis of the disease in the acute stage is not only hampered by the lack of echocardiographic changes but also as the number of circulating organisms in the blood can be low in the early stage of disease. Unless diagnosed in the acute phase, treatment is similar to that for idiopathic DCM as antiparasitics have not been shown to be uniformly effective (see Chapter 55).

Lyme Disease

Lyme disease caused by *Borrelia* can cause MC in about 10% of human patients. Similarly, Lyme MC is a rare

cause of myocardial disease in canine Lyme disease patients. The most common manifestation of the disease is AVB and myocardial failure and it is believed that the spirochetes of *Borrelia* may produce toxins that damage the myocardium. Diagnosis of the disease is via antibody titers, echocardiogram, endomyocardial biopsy, or at postmortem. Most humans respond to antibiotic therapy for the bacteria with penicillins or tetracyclines, though a minority may require permanent pacemaker implantations for severe arrhythmias.

Bartonella

Bartonella species are being increasingly identified in the veterinary literature as a possible cause of MC in both dogs and cats. *Bartonella* is most common in the temperate states of northern America and may be associated with flea or tick infestations. Studies performed in animals with suspected MC from *Bartonella* infections showed the presence of *Bartonella henselae* in cardiac tissues. Many animals presenting with MC from *Bartonella* often have non-specific clinical signs including lethargy, anorexia, fever, and weakness. Cardiac symptoms may or may not be present although arrhythmias and heart murmurs are most commonly reported. Reported antibiotic treatment for the disease includes penicillins, macrolides, aminoglycosides, tetracyclines, and fluoroquinolones with concurrent flea and tick control. Although there are few case reports, the prognosis for MC with *Bartonella* appears guarded. Rare cases of fungal MC have also been reported.

Toxoplasmosis

One of the most common causes of infectious MC in cats is toxoplasmosis, though the heart is the focus of the infection in only a small minority of cats. In the literature, there is only one case of a suspected antemortem MC from toxoplasmosis in a cat. Similar to Chagas' disease, suspect diagnosis is made on the measuring of serum antibodies to *Toxoplasma gondii* and accompanying echocardiographic and electrocardiographic abnormalities. The one feline case report had increased serum antibodies, thickened ventricular walls, a nodular interventricular septum, and pericardial effusion; all improved following treatment for the parasite with clindamycin.

Traumatic Myocarditis

Traumatic MC is one of the most frequently encountered causes of MC in the emergency department. In people

with blunt chest trauma, traumatic MC may occur in 10–75% of patients, with most experiencing arrhythmias including ventricular premature complexes, ventricular tachycardia, AVB, atrial tachycardias, and bundle branch blocks. Retrospective veterinary studies evaluating presumed myocardial injury in dogs reported a range of 10–96% in cases of blunt thoracic trauma, with a minority of these animals experiencing arrhythmias. Pathological findings include edema, ecchymosis, and intramyocardial hematoma formation. Arrhythmias occur as trauma to the myocardium may lower the resting membrane potential and the effective refractory period in the damaged myocardial cells from alterations in sodium and calcium currents across the cell membranes. Usually, traumatic MC is a self-limiting process and most do not require antiarrhythmic treatment.

Diagnosis

The diagnosis of MC can be challenging. Biomarkers of cardiac injury such as troponins are only elevated in the minority of human patients; it is unclear if this also occurs in veterinary patients.

Cardiac troponins (CTn) help regulate excitation-contraction coupling in the cardiac sarcomeres. There are three major subunits: CTnI, CTnT, and CTnC. Elevated concentrations of CTnT and CTnI are associated with cardiac injury. Although sensitive, CTn are not very specific and can be increased by a variety of disease processes including primary cardiac diseases, cardiotoxicosis from drugs (i.e. doxorubicin) and extracardiac disease such as blunt chest trauma and gastric dilation volvulus. In experimental canine studies, CTn release has been reported for 4–5 days and peak release may occur 12–36 hours after the original insult.

As discussed, arrhythmias are common and an ECG should be part of the work-up though it may have a low sensitivity. For many of the causative agents of MC, the echocardiogram may be initially normal while in the late stages it may be indistinguishable from idiopathic DCM. In people, cardiac magnetic resonance imaging is being used with increasing frequency to help diagnose MC and is also used to localize sites on the myocardium for biopsy.

The gold standard for diagnosis of MC is an endomyocardial biopsy (EB). In humans, biopsies are recommended for unexplained, new-onset heart failure of 2 weeks to 3 months duration associated with ventricular dilation, hemodynamic compromise, and new ventricular arrhythmias or AVB. In dogs and cats, EB may be performed via the jugular vein under anesthesia with a fluoroscopy. Potential complications include cardiac tamponade (see Chapter 54), arrhythmias (see Chapter 53), and vascular damage.

Treatment

Treatment of MC is often supportive as the patient may be experiencing clinical symptoms from an arrhythmia or poor systolic myocardial function and potential congestive heart failure (CHF) (see Chapters 55 and 57). Treatment for CHF secondary to MC is similar to standard CHF treatment including diuretics, ACE inhibitors, and pimobendan. Only when an actual causative agent has been identified can more specific therapy be instituted, such as antimicrobial agents for infectious causes. However, for viral etiologies, as MC is often diagnosed many weeks after the initial viral infection, these are often not

beneficial. The use of non-steroidal anti-inflammatories has been associated with increased mortality in people and is not currently recommended. Immunosuppressive medications have also not been associated with an improved prognosis though may be of most use in those with lymphocytic MO. Studies have evaluated intravenous immune globulin (IVIG) and showed that those people did no better than those treated without IVIG.

For many people with end-stage MC, cardiac transplantation may be pursued. Prognosis for MC is guarded and depends on when in the disease course the MC is identified, the patient's cardiac function, and the underlying cause.

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Thromboembolic Disease

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Introduction

Hemostasis is a physiological phenomenon that leads to blood clot formation. Hemostasis has been divided into several steps, including endothelium vasoconstriction, primary hemostasis (i.e. platelet adhesion, activation, and aggregation), secondary hemostasis (i.e. thrombin formation leading to fibrin meshwork), and neoangiogenesis [1]. Those hemostatic steps were unified by the cell-based model [2]. Thrombosis is defined as a pathological hemostasis leading to occlusion of blood supply and ischemia [1]. Thrombus has been defined as an aggregation of platelets and fibrin with entrapped blood cells whereas thromboembolus is migration of the thrombus.

Pathophysiology of Thrombosis

In 1856, Rudolf Virchow described what became known as Virchow's triad [3]: blood stasis, hypercoagulability, and endothelial damage. It is generally believed that two factors have to be present, but one also influences the others [4].

Hypercoagulability is characterized by increased platelet activation, enhanced activation of coagulation factors, and reduction of natural anticoagulant or inhibition of fibrinolysis [4]. Hypercoagulability is described in conditions implicated in thrombosis, including canine immune-mediated hemolytic anemia (IMHA), canine protein-losing enteropathy (PLE), and feline cardiomyopathy [5–8]. Blood stasis can be caused by reduced or turbulent blood flow, and is often caused by vascular or heart valve or chamber anomalies. Decreased perfusion often leads to blood stasis, especially in sepsis and neoplasia [4]. Endothelial injury can be difficult to diagnose *in vivo*, but revolves around increased platelet

activation and increased concentration of activated clotting factors [4].

Venous or arterial thrombi are created under different endothelial wall stress conditions. At low shear stress rates ($0\text{--}1000\text{ s}^{-1}$), fibrin generation (i.e. secondary hemostasis) plays a major role [9]. Therefore, a venous thrombus is primarily composed of red blood cells embedded within a fibrin meshwork [10,11]. This is compared to arterial thrombosis, where high shear stress conditions (greater than 10000 s^{-1}) predominate, and platelet adhesion to the endothelium is the most important part of thrombus formation [9]. Therefore, an arterial thrombus is primarily composed of platelets.

Diagnosis of Thrombosis

Diagnosis is influenced by thrombus location, in terms of both organ as well as vessel type affected (i.e. vein or artery). Occlusion of an artery causes lack of blood supply to the downstream organ, leading to organ dysfunction if no collateral circulation develops. Occlusion of a vein usually creates increased congestion of the upstream organ. Clinical manifestations vary with the affected organ (e.g. portal vein thrombosis leads to ascites). Identification of risk factors is an important part of diagnosis, as thrombosis is never a disease on its own.

Diagnosis of thrombosis is challenging. Presence of active fibrinolysis (usually associated with active clot formation) can be suggested by decrease in platelet count, as well as measurement of fibrin and fibrinogen degradation products levels including D-dimers. A risk factor such as hypercoagulability can be suggested using viscoelastic testing such as thromboelastometry [5,12]. However, despite extensive work-up, the cause of the thrombus may remain cryptogenic.

General Aspects of the Treatment and Prevention of Thrombosis

The appropriate treatment for companion animal thrombosis is unknown, and will depend on location of thrombus, clinical signs, and chronicity of symptoms. The treatment for a specific patient with thrombosis includes thrombolysis (if applicable); treatment of the cause (if possible); prevention of further growth of the clot using antiplatelet medications and/or anticoagulant; and treatment of upstream or downstream organ damage (see Chapters 68 and 71).

Although acute thrombolysis is standard of care in several human medicine scenarios, the timing of presentation and the cost make it challenging in veterinary medicine. Thrombolysis should be done as soon as possible, and within 3–6 hours to secure a survival or functional outcome benefit (see Chapter 68) [13]. Tissue plasminogen activator (TPA) is the only licensed thrombolytic drug in the US but other thrombolytic agents such as urokinase are also used, although less frequently [14]. Streptokinase, another thrombolytic, is not now available in the US.

Aspirin and clopidogrel are two commonly prescribed antiplatelet medications. Both have been shown to decrease platelet function in small animals, although the dose regimen is controversial. An excellent review of treatment options can be found elsewhere [15]. In brief, aspirin acts on the arachidonic acid pathway and irreversibly inhibits the cyclo-oxygenase (COX) pathways. These enzymes (COX 1 and COX 2) catalyze the conversion of arachidonic acid to PGH₂, the precursor for several metabolites including thromboxane A₂ (TXA₂). As TXA₂ enhances platelet function and promotes platelet aggregation and vasoconstriction, aspirin is a platelet inhibitor. Furthermore, it produces a permanent defect in platelet TXA₂ synthesis during the entire life of the platelet (7–10 days). Aspirin pharmacodynamics in people, dogs, and cats are similar, and dogs have served as an animal model for many preclinical studies of the antiplatelet effects of aspirin [15]. The recommended dose of aspirin in dogs starts at a low dose (1–2 mg/kg orally once a day) moving up to a high dose (10 mg/kg orally once a day). However, low-dose aspirin does not consistently inhibit platelet function in every dog so its clinical efficacy has been questioned [16].

Feline aspirin pharmacokinetics, in contrast, are different because of a relative deficiency of glucuronate in cats. Aspirin has a prolonged elimination half-life of approximately 38 hours in the cat compared with 15–20 minutes in people and approximately 7 hours in dogs. Therefore, the main use of aspirin in cats is geared toward prevention of thromboembolic events and the

recommended dose is 20.25–81 mg/cat orally every 2–3 days [17].

Clopidogrel is a thienopyridine that selectively inhibits ADP-induced platelet aggregation but has no direct effects on arachidonic acid metabolism. It requires hepatic biotransformation to produce the active metabolite [15]. The clinical effects and pharmacodynamics of clopidogrel have been evaluated in cats; dosages ranging from 18.75 to 75 mg per cat orally q24h result in significant antiplatelet effects in this species [18].

Commonly used anticoagulants include warfarin, unfractionated heparin (UF), low molecular weight heparin (LMWH) and more novel direct antithrombin antagonists such as apixaban (see Chapter 71). Heparin complexes with and catalyzes the activity of the anticoagulant protein antithrombin. The heparin:antithrombin complex inhibits coagulation factors IIa (thrombin), IXa, Xa, XIa, and XIIa [15].

Unfractionated heparin is a mixture of glycosaminoglycan molecules with variable sizes, anticoagulant activities, and pharmacokinetic properties. The molecular weight of UF ranges from 3000 to 30000 daltons, with a mean of 15000. Only approximately one-third of UF molecules contain the binding site for antithrombin, and the remaining two-thirds have minimal anticoagulant activity. The clotting factors IIa and Xa are most sensitive to the activities of the heparin:antithrombin complex. By inactivating thrombin, heparin not only prevents fibrin formation but inhibits thrombin-induced platelet activation and continued activation of coagulation factors V and VIII. The biological effects and pharmacokinetics of UF are quite variable and depend on the proportion of heparin molecules large enough to bind thrombin. Larger heparin molecules are cleared from the circulation relatively rapidly, with a half-life of approximately 30 minutes [15]. Because of this high degree of variability in pharmacokinetics and biological activity, UF therapy must be monitored closely and titrated to effect to avoid undertreatment or bleeding complications. Most clinicians use the activated partial thromboplastin time (aPTT), with an accepted therapeutic target range of 1.5–2.5 times the normal control aPTT value [19].

Low molecular weight heparin is derived from UF by depolymerization and has been developed in response to some of the challenges associated with UF therapy. LMWH has a mean molecular weight of 4000–5000 daltons (approximately one-third that of UF) [15]. In general, LMWH has reduced anti-IIa activity relative to anti-Xa activity and also has better predictable pharmacokinetic properties. LMWH, like UF, binds to and catalyzes the activity of antithrombin; however, only 25–50% of the heparin molecules in LMWH are large enough to inhibit factor IIa, although all retain the capacity to inactivate factor Xa. LMWH at standard doses has a minimal effect

on aPTT, because the prolonged aPTT seen with UF therapy primarily reflects inhibition of factor IIa. Inhibition of factor Xa, in contrast, has little effect on aPTT. It should be noted that the available LMWH preparations (e.g. enoxaparin, dalteparin) are variable in their pharmacokinetic profiles and are not clinically interchangeable. One of the potential benefits of using LMWH is that it has a reduced affinity for binding to plasma proteins or cells compared with UFH, leading to a more predictable dose–response relationship and longer half-life [15]. LMWH preparations have a bioavailability after subcutaneous administration of nearly 100% at low doses, and peak activity consistently occurs between 3 and 5 hours after administration in people [20]. The predictability of LMWH pharmacokinetics in people allows administration at a fixed dose without routine monitoring of therapeutic efficacy [15].

Chromogenic assay of anti-factor Xa activity is the recommended laboratory method for monitoring LMWH therapy, although the relation between clinical effect and anti-Xa activity is not entirely clear. The pharmacokinetics of LMWH in dogs have been evaluated, and therapeutic anti-factor Xa levels can be achieved with doses of 0.8 mg/kg SC TID and 150 µ/kg subcutaneous TID for enoxaparin and dalteparin respectively [21,22].

Feline Aortic Thromboembolism

Feline aortic thromboembolism (FATE) or “saddle thrombus” is a well-described entity with a prevalence rate of 1 in 175 cases in a tertiary center [23]. The clinical syndrome of FATE is initiated by the sudden migration of a left atrial thrombus into the systemic arteries. This leads to an acute disorder characterized by pain, paralysis, and rhabdomyolysis in the affected limb(s). Both pelvic limbs are affected in 75% of cats [23–25]. The vast majority (90%) of cats have underlying cardiomyopathy of varying types and severity, which can lead to higher co-morbidity [23,24].

Age ranges from 1 to 21 years with a median 12 years. Male cats are predisposed. Both pelvic limbs are affected in 75% of cats. The vast majority of cats have underlying cardiomyopathy, but less than 10% are previously diagnosed with cardiac disease [23,24].

Diagnosis of FATE is mostly clinical. Clinicians use the “5P” rule, which comprises pallor (i.e. purple or pale toes), polar (i.e. cold extremities), pulselessness, paralysis, and pain. Lack of Doppler flow, direct visualization of the thrombus on ultrasound, and angiography are other diagnostic tools [25,26]. Additionally, a study showed that local blood glucose of affected limbs was 50 ± 25 mg/dL compared to central blood glucose which was 182 ± 89 mg/dL [27]. Similarly, local blood lactate

was 10.7 ± 2.7 mmol/L compared to central blood lactate of 2.1 ± 0.8 mmol/L [27].

Treatment usually involves treating the underlying cardiac disease, providing potent analgesia such as fentanyl, use of UF or LMWH and/or antiplatelets such as clopidogrel to prevent recurrence [23,24].

One of the largest and most recent studies used both UF and/or aspirin for treatment of 87 episodes of FATE, with 47% receiving UF only, 38% receiving a combination of both UF and aspirin and 15% receiving aspirin only [23]. The authors found no differences in survival between treatments, including between a high-dose aspirin group (>40 mg/cat PO q24–72h) and low-dose aspirin group (5 mg/cat PO q72h). Median survival time was 3.9 months and recurrence rate was 25% [23].

Another study recently investigated 68 cats with FATE (out of 250 originally presented) who received treatment besides analgesia and found that aspirin alone (dose unknown) was used most commonly (37%), followed by heparin (UF or LMWH; specifics including doses unknown) alone (31%) or in combination with aspirin and/or clopidogrel (15%), followed by a combination of aspirin and clopidogrel alone (15%) and clopidogrel alone (3%). In that study, median survival time was 3.1 months and the recurrence rate was 47% [24].

The FATCAT study investigated the difference in outcome between aspirin and clopidogrel in stable, treated (1–3 months after the episode) cardiogenic FATE and found recurrence rates of 75% and 49% with aspirin and clopidogrel respectively [28]. The authors concluded that clopidogrel was superior to aspirin, although recurrence rate in the aspirin group vastly differed from previous studies. Differences in outcome may be related to study population, but a treatment effect cannot be excluded.

Although uncommonly used, thrombolysis represents the standard of care for acute thrombotic or thromboembolism events in human patients with stroke or pulmonary thromboembolism [13,29,30]. Some preliminary data comparing standard of care and TPA use in cats presented with 6 hours of FATE seem encouraging for use in acute cases [31].

Overall, the prognosis for FATE is considered poor, with euthanasia rates as high as almost 90% reported [23,24]. When treated, survival is between 27% and 45%, with no real trends being identifiable due to the retrospective nature of available studies. There are no prospective studies in FATE and the retrospective studies available differ greatly regarding information available for in-hospital treatment, medications dispensed at discharge, and outcome data.

Some studies identified outcome factors such as number of limbs affected, motor function, or presence of heart failure. Cats with motor function or one limb affected have a better prognosis (70% survival to

discharge) than cats with bilateral pelvic limb paralysis (25% survival to discharge) [23,24]. Smith's study showed that other non-survivor baseline characteristics included lower rectal temperature, heart rate, phosphorus levels, and absence of motor function. Presence of congestive heart failure, elevated BUN, glucose and sodium levels were not part of non-survivor baseline characteristics, although the astute reader will notice that P values were 0.08 and 0.09 for presence of congestive heart failure and elevated BUN respectively [23].

However, the presence of congestive heart failure in that study was correlated with a shorter long-term follow-up. Interestingly, outcomes varied over the course of the study, with euthanasia rates ranging from 20% to 55% and survival rate being 0% early on in the study period (i.e. 1993 and 1994) with minimal cases seen, compared to 60% in 2001, at the end of the study, with more robust number of cases.

In the most recent British study by Borgeat, non-survivor baseline characteristics included lower rectal temperature and presence of congestive heart failure, as well as non-clinical characteristics such as being presented after-hours or to a specific study clinic [24]. Interestingly, after multivariable analysis, only lower rectal temperature and being presented to that clinic retained statistical significance. When that clinic was excluded, there were no differences between non-survivors and survivors [24].

In this author's opinion, those two studies show that recruitment bias exists in FATE, with the possibility that euthanasia can be driven by clinician perception of the disease process, and that each owner should be presented with a fair understanding of causes for FATE, long-term prognosis (especially with cardiac diseases) and treatment options, including natural course of the disease with thromboprophylaxis, thrombolysis or euthanasia.

Canine Aortic Thrombosis

Various case series on canine thrombosis (CATH) have been published [32–35]. There are numerous differences between canine thrombosis and FATE. Although acute paralysis has been described, most of the CATH cases have a more chronic history and subtler neurological findings. Some authors postulate that canine distal aortic thrombosis is more an *in situ* thrombus formation than a thromboembolism.

Several disease processes have been implicated in distal CATH, including protein-losing nephropathy (PLN) and protein-losing enteropathy (PLE), hyperadrenocorticism, diabetes mellitus, hypothyroidism, liver disease, neoplasia and infective endocarditis, as well as immune-mediated diseases where chronic or higher doses of steroids are required, such as IMHA, immune-mediated

thrombocytopenia (ITP) or Addison's disease. In a significant number of cases, the cause may be cryptogenic or multiple predisposing factors may be present.

The hypercoagulability associated with PLN and PLE was originally thought to be related to loss of antithrombin, but more mechanisms are probably involved [5,36]. Endocrine diseases such as hyperadrenocorticism and diabetes mellitus are believed to predispose to thrombosis through a combination of endothelial defects such as atherosclerosis and hypercoagulability [37,38]. Immune-mediated diseases such as IMHA are usually thought to be associated with hypercoagulability, but endothelial defects are also probably present, leading to increased risks for thrombosis [6,12,39]. The vast majority of cases are diagnosed using direct abdominal ultrasound visualization of the blood clot in the aorta. Glucose differentials between affected and normal limbs have been described in dogs [26]. In that study, a difference between affected and normal limb glucose above 30 mg/dL corresponded to a 100% sensitivity and specificity for CATH.

The prognosis of CATH varies based on presentation and clinical signs. Overall survival to discharge is 50–60%, patients with chronic and/or less severe neurological deficits having a better prognosis.

There is no recommended treatment of CATH at this time. Various treatments have been retrospectively described including UF, LMWH, warfarin, antiplatelet therapy, and combination therapy. From the retrospective cases published in the literature, it is extremely challenging to link a specific outcome to a specific treatment. It is probable that clinician decisions about specific treatments may have been dictated by clinical presentation and experience.

Portal Vein Thrombosis

The veterinary literature on portal vein thrombosis (PVT) is largely limited to three studies – two in dogs and one in cats [40–42]. In dogs, PVT is most common in older, larger dogs, with a median age of 7.3 years and a median weight of 29.6 kg [41]. In the feline study, the median age was 7.5 years (range 3–10 years). All cats were domestic short-hair and included three spayed females and three castrated males. No specific weight was provided [42].

Clinical signs depend on chronicity of the thrombosis, being in order of frequency hypovolemic shock (more acute presentation), vomiting (acute and chronic presentation), abdominal pain (more acute), diarrhea (acute and chronic), and abdominal distension (acute and chronic).

Causes of PVT are various, with approximately half of patients having hepatopathy. Other causes are non-hepatic neoplasia, immune-mediated diseases or

infection. Glucocorticoid administration was reported in 54% of animals in the two canine studies [40,41]. In addition, it is common that dogs with PVT have other sites of thrombosis, such as pulmonary, splenic or mesenteric veins [41]. All cats in the feline study had liver disease, with 50% having congenital portosystemic shunt, two having neoplasia and the last one having acute hepatic necrosis of unknown origin. No other sites of thrombosis were found in those six cats [42]. Antemortem diagnosis is made by abdominal ultrasound, surgery, or computed tomography (CT) angiogram [41,42].

Management ranges from supportive care, including anticoagulant or thrombolytic therapy, to surgical intervention. Aspirin, LMWH or UF were mostly used in one study [41].

Prognosis is variable, with an overall survival rate in the canine study of 57%. In that study, patients with an acute presentation, SIRS, or thrombi at >1 location were more likely to be non-survivors whereas those that received anticoagulant medications were more likely to survive to discharge [41]. Three out of six cats with PVT were discharged [42].

Splenic Thrombosis

Splenic vein thrombosis (SVT) is a relatively uncommon incidence in veterinary medicine, and usually an incidental finding. There is one case series, and several canine case reports [32]. There are no data on feline patients.

Splenic vein thrombosis primarily occurs in older, larger breed dogs, with medians of 9 years and 28.9 kg. The causes are (in order of frequency) neoplasia (54%), corticosteroid use (43%), inflammatory and immune mediated, PLN, hyperadrenocorticism, and PLE [43]. In humans, isolated SVT is primarily associated with pancreatic disease, particularly pancreatitis, with a reported incidence of up to 45% [44]. Splenic thrombi may have different inciting causes depending on whether they are isolated or associated with additional thrombi, specifically PVT.

Splenic vein thrombosis is usually asymptomatic and there is little evidence that isolated SVT leads to clinical disease in dogs. In human patients, isolated SVT is commonly asymptomatic and requires no treatment [43,45].

Mesenteric Thrombosis

Only two reports of mesenteric venous thrombosis (MVT) in companion animals exist, and only postmortem diagnoses were made [41,46]. Shahar described a 4-year-old cocker spaniel presented for 2 days' duration of anorexia and vomiting. The dog underwent exploratory laparotomy for a suspected intussusception and

had an intestinal resection and anastomosis. Mesenteric thrombus was diagnosed on histopathology. No apparent cause for thrombus formation was found [46]. MVT was found at necropsy in three dogs with PVT but no specific data were available [41].

In humans, MVT has been linked to vasculopathies, abdominal surgery, cirrhotic livers, and intra-abdominal infections. Multiple factors may be involved, but up to 37% of MVT cases are cryptogenic [47]. In humans, onset of signs range from peracute (i.e. shock and acute abdomen) to chronic (i.e. vomiting and abdominal discomfort) [47].

Contrast-enhanced CT angiography is the diagnostic test of choice, making the diagnosis in veterinary medicine more challenging due to the paucity of practices with CT capabilities.

In humans, initial treatment includes bowel rest, intravenous fluids, and parenteral anticoagulation with UF or LMWH. Advanced therapeutic options (i.e. fibrinolysis or surgery) are for patients with hemodynamic instability or refractory symptoms. In humans, acute MVT mortality may be up to 32.1%. Patients with chronic MVT have an 80% survival rate [47].

Caval Thrombosis

Vena cava thrombosis (VCT) is uncommon in companion animals. Thrombosis of the caudal vena cava is usually associated with adrenal tumors [4]. Caudal VCT is more common in patients with pheochromocytoma compared to adrenocortical tumor (54% versus 11% in one study) [48–50]. Most cases are diagnosed with abdominal ultrasonography, which has sensitivity and specificity of 80% and 90%, respectively [50]. However, it may be difficult to differentiate between local tumor invasion and actual thrombosis due to impaired flow and/or endothelial injury.

Presence of VCT does not lead to a poorer prognosis in humans with adrenocortical carcinoma [51]. However, there have been discrepancies between studies regarding the impact on outcome of VCT after adrenalectomy in dogs, with some studies associating presence of VCT with a poorer prognosis and some not [50,52].

Thrombosis of the cranial vena cava in veterinary medicine is limited to a few case reports and one retrospective study [53–56]. Clinical signs associated with cranial VCT were pleural effusion and dyspnea. Predisposing conditions identified were (in order of frequency) immune-mediated disease, corticosteroid use, sepsis, PLE, neoplasia, and cardiac disease [53]. All dogs in the retrospective study had central venous catheters placed and several cases of cranial VCT have been associated with pacemaker lead placement [53–55]. Placement of a large-bore catheter in the jugular vein may have

contributed to thrombus formation through disturbance of laminar flow or damage to the vascular endothelium.

Diagnosis can be made by physical examination finding such as palpation of jugular thrombi, and ultrasonography can be used to confirm the diagnosis.

There is no specific treatment for VCT, but prognosis is poor, with 20-day survival of approximately 10%, although it was unclear if the poor prognosis was related to the underlying disease or directly associated with the cranial CVT [53].

There are only a couple of case reports of vena cava thrombosis in cats [56,57]. The primary clinical sign was respiratory compromise and two cats had chylothorax. Two cats had a central venous catheter or a vascular access port placed within 3 weeks of presentation. Both cats' clinical signs resolved with medical management or thoracic duct ligation [56]. The third cat also had cranioventral (i.e. neck and jaw) swelling secondary to an invasive mediastinal lymphosarcoma diagnosed at post-mortem examination [57].

Cerebral Infarction

Stroke or cerebrovascular accident is broadly divided into ischemic and hemorrhagic [58]. Because the canine cerebral arterial circle receives blood supply from many alternative routes through contribution of anastomotic vessels derived from branches of the external carotid artery, it is considered that brain infarction is rare in dogs [59]. However, there are several retrospective studies and case reports [58,60]. In the largest study of 40 dogs, median age was 8 years. The main breeds affected were Cavalier King Charles spaniel, Greyhound and Labrador retriever.

Clinical signs varied according to the vascular territory affected. Most dogs suffered from cerebellum (45%) and telencephalon (28%) infarcts and had cerebral or vestibular ipsilateral ataxia or mild postural/cranial nerve deficits [58].

Clinical conditions associated with brain infarction in dogs were chronic kidney disease, hyperadrenocorticism, diabetes mellitus, aortic stenosis, and neoplasia, with 85% of dogs having systemic hypertension [60].

Diagnosis was obtained with magnetic resonance imaging and the main distribution of lesions (in order of frequency) was cerebellar, telencephalic, and thalamic/midbrain [58].

Treatment options depend on the suspicion of ischemic versus hemorrhagic strokes [61]. Most cases of ischemic stroke recover within several weeks with only supportive care. In the acute phase, maintenance of oxygenation and normotension is paramount. Although neuroprotection can be attempted, no neuroprotective agents (i.e. N-methyl-D-aspartate (NMDA) antagonists,

calcium channel blockers, sodium channel modulators) have proven their efficacy in human clinical trials. There is no evidence that glucocorticoids provide any benefit in stroke [61]. Intravenous recombinant tissue plasminogen activator (tPA) is used in human stroke patients if it can be given within the first 3–6 hours after onset, but no controlled studies in veterinary medicine have assessed thrombolysis [29,61].

In hemorrhagic stroke, the most important consideration is maintaining cerebral perfusion by treating hypotension and elevated intracranial pressure using mannitol (0.5–1 g/kg intravenously over 20 min) or hypertonic saline (7–7.5%, 3–5 mL/kg intravenously over 5–10 min), and treating any underlying cause such as thrombocytopenia or secondary hemostasis disorders [61].

Regarding the prognosis for brain infarction, one study reports that out of the patients that were discharged, two-thirds had a good to excellent long-term outcome with a mean follow-up time for all dogs of 18 months [60].

Reports of feline brain infarction are scarce [61,62]. One postmortem study identified 12 cats with brain infarction over 6 years [62]. Median age was 8 years. The presentation was usually acute and clinical signs depended on the affected vascular territory. Most cats had seizures, altered level of consciousness, circling, ataxia, blindness, and/or head tilt. Forebrain (five out of 12) and brainstem (five out of 12) were the most common lesion distributions in that study [62]. Causes associated in cats were hepatic lipidosis, cardiomyopathy, cerebrospinal cuterebriasis, hypoxia, and neoplasia [62,63].

Myocardial Thrombosis

Although a major health issue in humans, myocardial infarction is seldom reported in companion animals. One study found 37 cases over a 9-year period at the necropsy service at the University of Pennsylvania Veterinary Hospital. Median age was 7 years for dogs and 12 years for cats and the majority of canine patients were female (59%) whereas three out of five cats were male. Great Pyrenees were overrepresented in dogs. Initial signs of illness were non-specific, including lethargy, inappetence or gastrointestinal signs. Many dogs had predisposing factors leading to hypercoagulability and/or endothelial defects such as exogenous steroid administration, neoplasia, PLN, pancreatitis or IMHA [64]. Another study from Sweden confirmed the trend for older and larger dogs, with Newfoundland dogs being overrepresented in that patient population. In that study, approximately half of the dogs had chronic heart disease whereas others suffered sudden death (20%) or anesthesia-related death (15%) [65]. All diagnoses were postmortem [64,65].

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63

Systemic Arterial Hypertension

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Introduction

Systemic hypertension is defined as a sustained pathological increase in systemic arterial blood pressure (BP). Sustained or, if severe, even acute paroxysmal increases in BP are troubling because of the associated potential for injury to several target organs, referred to as end-organ or target organ damage (Table 63.1).

Definitions used to designate BP measurements as normal or as indicative of systemic arterial hypertension are somewhat problematic. First, differences in measurement techniques utilized among studies aimed at defining normal BP in dogs and cats make direct comparison of derived data difficult. Age, breed, and sex influences may also factor into BP interpretation; for example, normal sighthounds have consistently higher (by approximately 10–20 mmHg) BP than dogs of most other breeds [1], suggesting a potential need for the establishment of canine breed-specific normal ranges. Finally, as is true for human patients, there is likely a continuous relationship between BP and risk of target organ damage, making creation of a distinct cut-off between normotension and hypertension problematic.

Nonetheless, BP cut-off values are clinically useful to help simplify the decision-making process regarding

treatment of hypertensive patients. In 2007, a consensus group of the American College of Veterinary Internal Medicine issued guidelines for the definition and classification of systemic arterial hypertension based upon potential risk for target organ damage [2], generating cut-offs that have also been endorsed by the International Renal Interest Society [3]. These definitions have recently been revised [4], and provide guidance regarding assessment of patient risk and establishment of rational treatment goals.

Pathophysiology of Systemic Hypertension

Simply defined, blood pressure is the outward force exerted by the intravascular blood column against the blood vessel wall [5]. This force is determined by a number of factors, with both blood flow into the arterial system (i.e. cardiac output) and resistance to blood flow through the aorta and peripheral arterial system (i.e. aortic impedance and systemic vascular resistance) contributing directly to mean arterial pressure. In the normal system, mean arterial pressure is under close regulation, both in the short term (i.e. beat-to-beat) and intermediate to long term, so that rapid and/or wide swings in BP are avoided.

Table 63.1 ACVIM supported guidelines for the categorization of blood pressure based upon risk of target organ damage in dogs and cats.

ACVIM category	IRIS category	Systolic BP (mmHg)	Risk of target organ damage
I	Normotensive	<140	Minimal
II	Prehypertensive	140–159	Low
III	Hypertensive	160–179	Moderate
IV	Severely hypertensive	≥180	High

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Factors that favor increases in mean arterial pressure by augmentation of cardiac output (e.g. increases in intravascular volume/preload, heart rate, or myocardial contractility) and/or systemic vascular resistance (e.g. arteriolar vasoconstriction, increased blood viscosity) are typically balanced by autonomic, renal, and local vascular responses designed to restore BP to a normal setpoint. Therefore, systemic hypertension may develop in association with disease processes or pharmacological agents that overwhelm or interfere with these normal homeostatic mechanisms or with normal vascular responsiveness to these mechanisms.

Target Organ Damage Caused by Systemic Hypertension

Neurological Target Organ Damage

Hypertensive encephalopathy is recognized in both dogs and cats with systemic hypertension [6–11]. The reported prevalence of neurological signs in cats [8,10] and dogs [11] with systemic hypertension is 21–45% and 16%, respectively, and hypertensive encephalopathy occurs as a postoperative complication in 12–21% of cats undergoing renal transplantation [12,13]. The central nervous lesions of hypertensive encephalopathy may include white matter interstitial edema, hyperplastic vascular lesions, and/or parenchymal microhemorrhages [8,9].

Utilizing magnetic resonance imaging, lesions appear as multifocal white matter hyperintensities that may affect multiple regions of the cerebrum, a feature shared with human hypertensive encephalopathy, and consistent with vasogenic edema [6]. Cerebral infarction associated with systemic hypertension, although uncommon, has also been reported in dogs [14]. In human hypertensive patients, apparently asymptomatic brain damage, in the form of white matter hyperintensities and silent infarcts, is commonly identified on cerebral MRI, and is associated with an increased risk of cognitive decline and dementia [15,16]. It is unclear whether veterinary patients with systemic hypertension are at similar risk.

Ocular Target Organ Damage

The reported prevalence of ocular lesions in cats [8,17–19] and dogs [7,11,20,21] with systemic hypertension is 48–100% and 10–62%, respectively. Ocular changes in animals with systemic hypertension may include retinal hemorrhage, edema, retinal vascular tortuosity, vitreal hemorrhage, secondary glaucoma, and partial or complete bullous detachment that may be bilateral or unilateral (Figure 63.1) [10,22].

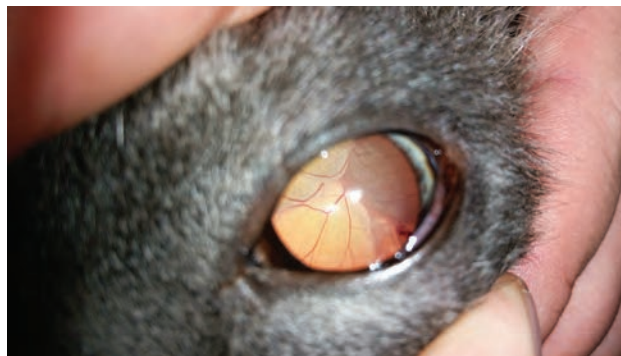


Figure 63.1 Photograph of the left eye from a hypertensive (systolic blood pressure 270 mmHg), 11-year-old cat that was presented for acute lethargy, ataxia, and altered mentation. Complete, bullous retinal detachment was noted bilaterally. Reproduced with permission of Dr. Kate Myrna.

Cardiovascular Target Organ Damage

Systemic hypertension may be associated with alterations in left ventricular geometry, most frequently characterized by concentric hypertrophy patterns that occur, at least in part, as a physiological response to the increased impedance to left ventricular ejection (afterload). Echocardiographic evidence of hypertensive cardiomyopathy is present in 74–85% of feline [8,19,23] and 47% of canine [11] patients with systemic hypertension. Clinically detectable cardiac physical examination abnormalities, including a systolic heart murmur, gallop sound, and/or dyspnea, are present in 69–74% of feline [19,23] and 66% of canine [11] hypertensive patients.

If systemic hypertension is severe and long-standing, cardiac dysfunction (primarily diastolic) may lead to left atrial enlargement, increased left-sided diastolic filling pressures, and left-sided congestive heart failure. Fortunately, congestive heart failure is a relatively uncommon sequel in cats and dogs with systemic hypertension. Aortic aneurysm and dissection, reported in cats [24,25] and dogs [26] with systemic hypertension, may be a rare but potentially life-threatening complication.

Renal Target Organ Damage

At present, it is unclear whether chronic systemic hypertension is able to induce *de novo* damage in the normal canine or feline kidney. However, in patients with chronic kidney disease (CKD), normal renal autoregulatory mechanisms – which maintain stable renal blood flow and glomerular filtration rate over a wide range of systemic BP – are impaired, even at relatively normal BP. Superimposition of systemic hypertension in these patients exacerbates glomerular capillary hypertension and contributes to the spontaneous progression

of CKD through a final common pathway of progressive glomerulosclerosis and tubulointerstitial fibrosis. Systemic hypertension also leads to the development of proteinuria, a negative prognostic indicator in both feline and canine CKD [7,27–29]. In veterinary patients, these effects are usually insidious, and rarely necessitate emergency intervention; instead, they are signaled by the presence of proteinuria, or documentation of progressive increases in serum creatinine concentrations or decreases in measured glomerular filtration rate.

Conditions Associated with Systemic Hypertension

In the majority of dogs and cats with increases in systemic BP that are not considered anxiety-induced (i.e. “situational” or “white coat” hypertension), systemic hypertension occurs secondary to an underlying disease or in association with drugs known to cause hypertension. Idiopathic hypertension (also referred to as primary or essential hypertension in human beings), which occurs in the absence of a potentially causative condition, is far less common in veterinary patients.

Of the conditions known to cause systemic hypertension, acute and chronic kidney disease (in dogs and cats), diabetes mellitus and hyperadrenocorticism (in dogs), and hyperthyroidism (in cats) are the most common. Primary hyperaldosteronism, pheochromocytoma, hypothyroidism, and polycythemia, which are also associated with secondary systemic hypertension, occur less frequently [2]. The prevalence of systemic hypertension in animals with these conditions varies widely both within and among disease groups and based on definitions utilized. Systemic hypertension has also been noted in animals treated with glucocorticoids, mineralocorticoids, erythropoietin, or phenylpropanolamine, and in patients suffering from stimulant drug intoxication (e.g. cocaine, amphetamine, methylxanthine) [30–32].

Clinical Recognition of Systemic Hypertension

In human medicine, acute or rapidly progressive target organ damage (e.g. evidence of hypertensive ocular disease or hypertensive encephalopathy) in the setting of an increased systemic BP is deemed a *hypertensive emergency*; conversely, the term *hypertensive urgency* is applied when severely increased systemic BP (SBP > 180 mmHg) is not accompanied by signs of progressive target organ damage, posing less of an immediate threat [33]. Because relatively prompt reductions in BP are advisable in those patients experiencing a hypertensive emergency,

recognition of systemic hypertension as the cause of a patient's clinical signs is critical, so that timely intervention to stop or reverse these complications may be performed.

Clinical Presentation

Systemic hypertension may be identified in apparently asymptomatic dogs and cats in which BP measurement is prompted by the diagnosis of disease known to cause systemic hypertension, or when the patient's history discloses prescription or accidental ingestion of substances known to cause systemic hypertension. Alternatively, patients may be presented with clinical signs referable to systemic hypertension, which motivate the attending clinician to measure BP.

The clinical manifestations of hypertensive urgencies and emergencies vary with the affected target organ, and may be severe. People with severe systemic hypertension frequently complain of headaches, blurred vision, and anxiety, symptoms that would be expected to result in relatively non-specific signs in veterinary patients. Affected animals may exhibit neurological signs consistent with involvement of the prosencephalon and/or caudal fossa, including altered mental status, seizures, ataxia, sudden-onset central blindness, and/or nystagmus [6,8,12,34]. Likewise, evidence of hypertensive retinopathy, manifest as sudden-onset or progressive partial or complete blindness, may be noted [10]. Although uncommon, respiratory signs attributable to cardiogenic pulmonary edema may be present. Epistaxis, which occurs relatively uncommonly in dogs and cats with systemic hypertension, represents hypertensive urgency if present as the sole clinical sign [8,10,35].

Blood Pressure Measurement

The diagnosis of systemic hypertension requires reliable and reproducible documentation of increased blood pressure. White coat hypertension, defined by BP increases that are present only when the patient is in the hospital setting, is commonly identified in veterinary patients and can be attributed to the excitement or anxiety caused by being in the hospital or by the measurement process itself [36,37]. Hypertension is less likely to be white coat in origin when BP increases are classified as severe and when target organ damage co-exists [38]. As a general rule, documentation of persistent hypertension (i.e. consistently present during multiple BP measurement periods, ideally performed on different days) is advisable to reduce the risk of falsely diagnosing “true” systemic hypertension. However, for patients presented to the emergency department with evidence of acute-onset, rapidly progressive signs that may be attributed

to systemic hypertension, detection of pathological increases in BP during a single measurement period is sufficient to warrant initiation of therapy.

Systemic BP may be measured via direct or indirect methods. Although considered the gold standard, direct methods that involve catheterization or needle puncture of a peripheral artery are more invasive and are utilized less frequently in the clinical setting. Instead, determination of indirect blood pressure with measurement devices that rely on Doppler ultrasonography or oscillometry is more common.

Clinically utilized non-invasive indirect BP measurement methods require placement of a circumferential air-filled cuff to temporarily occlude arterial blood flow by applying an external, compressive force. The Doppler ultrasonographic technique exploits the Doppler shift principle to detect red blood cell movement, creating an audible sound that allows the operator to identify the pressure (corresponding to mean or systolic BP) at which blood flow is restored distal to the compressed arterial segment. In contrast, oscillometric methods determine mean arterial pressure by detecting oscillations in the arterial wall that occur in response to incident pulse waves as the circumferentially placed cuff is slowly deflated; a proprietary algorithm is then used to calculate systolic and diastolic BP from this information.

Importantly, methods utilized for BP measurement should be standardized to avoid inaccuracies due to technical error; for example, selection of an appropriate cuff size is essential to prevent over- or underestimation of blood pressure if the cuff used is too small or too large, respectively. The reader is referred elsewhere for detailed guidelines on this subject [2].

Treatment of the Patient with Systemic Hypertension

The rationale for antihypertensive treatment is to reverse or limit ongoing target organ damage and to prevent future target organ damage. In general, initiation of antihypertensive therapy is indicated in dogs and cats with persistent systemic hypertension conferring moderate or severe risk of target organ damage (i.e. $SBP \geq 160$ mmHg). Unless there is evidence of target organ damage that is characterized by the potential for rapid progression (e.g. hypertensive retinopathy or encephalopathy), reduction of BP in patients with hypertension should be considered an intermediate- to long-term objective, with a goal of gradual BP decline over several weeks. In these patients, aggressive, dramatic reductions in BP should be avoided to prevent unsafe compromise of vital organ perfusion.

Conversely, for patients experiencing a hypertensive emergency, interventions designed to more rapidly reduce

BP are necessary. In general, decreases of no greater than 25% are recommended within the first hour of hospitalization, with cautious reduction to approximately 160 mmHg over the following 2–6 hours. Further, gradual reduction toward normotension (i.e. < 150 mmHg) may be targeted over the subsequent 24–48 hours [33]. Ideally, intravenous agents are preferred, as they allow prompt reductions in BP, and can be titrated to produce a gradual decline (Table 63.2). For these cases, continuous, and preferably direct, arterial BP measurement is advisable to monitor for hypotension.

Intravenous agents that may be used for this purpose include sodium nitroprusside (editors' note: this drug is no longer available) and hydralazine. Labetalol, a combined alpha- and beta-adrenergic antagonist, and nicardipine, a calcium channel blocker, are commonly used in human hypertensive emergencies [39] but veterinary experience with these drugs is limited. Oral antihypertensive drugs with a relatively rapid onset of action, such as amlodipine, a calcium channel blocker, or hydralazine, a direct arterial vasodilator, may also be used. The effects of these drugs are less predictable and titratable than those of parenteral antihypertensives, and the practice of administering repeated "loading" doses of oral antihypertensives should be undertaken with caution to avoid cumulative, difficult-to-reverse hypotensive effects.

Ideally, treatment for systemic hypertension should be tailored to the likely underlying mechanism. This information may not always be known in the emergency setting so the immediate goal in hypertensive emergencies is to lower BP to a safe level, with diagnostic work-up deferred until later.

An ideal long-term target BP has not been established for hypertensive dogs and cats. Reclassification to lower BP risk category should be considered at a minimum, and reduction of SBP to < 150 – 160 mmHg, which places the patient at minimal to mild risk for target organ damage, is a reasonable goal. Drug-induced *hypotension* ($SBP < 120$ mmHg) is rare with starting doses of most oral antihypertensive agents, but should be avoided. Table 63.2 lists drugs with oral antihypertensive effectiveness that may be prescribed for the treatment of systemic hypertension.

Every patient that is discharged with instructions to begin therapy with oral antihypertensive medications should leave with a clear plan for outpatient follow-up, generally within 1 week.

Prognosis and Long-Term Management

Treatment of systemic hypertension may reverse some alterations (e.g. hypertensive encephalopathy) or slow the progression of others (e.g. decline of renal function

Table 63.2 Parenteral and oral agents with antihypertensive efficacy.

Drug	Drug class	Dosage, route	Specific indications/notes
Intravenous antihypertensive drugs for use in hypertensive emergencies			
Nitroprusside	Inorganic nitrate	1–10 µg/kg/min IV (D) 0.5–5 µg/kg/min IV (C)	Start at low end of dose range, titrate by 0.5–1 µg/kg/min to effect
Hydralazine	Direct arteriolar vasodilator	0.5–2 mg/kg SC or IM q 8–12h OR 0.1–0.5 mg/kg IV q2–8h CRI: 1.5–5 µg/kg/min IV	Effects unpredictable; start at low dose and titrate up if necessary
Fenoldopam	Dopamine (DA ₁) antagonist	0.1–0.8 µg/kg/min IV (D)	Little experience in clinical veterinary medicine
Nicardipine	Calcium channel blocker	0.5–5 µg/kg/min IV (D)	Little experience in clinical veterinary medicine
Oral antihypertensive drugs			
Amlodipine	Dihydropyridine calcium channel blocker	Initially: 0.05–0.1 mg/kg PO q24h; increase to 0.4 mg/kg PO q12–24h if necessary (D) 0.625–1.25 mg per cat PO q24h (C)	
Enalapril	Angiotensin converting enzyme inhibitors	0.5–1.0 mg/kg PO q12–24h (D)	
Benazepril		0.5 mg/kg PO q12–24h (C)	
Hydralazine	Direct arteriolar vasodilator	0.5–3 mg/kg PO q12h (D) 2.5 mg per cat PO q12–24h (C)	Effects unpredictable; start at low dose and titrate up if necessary
Telmisartan	Angiotensin II, subtype 1 receptor antagonist	1.0 mg/kg PO q24h (D,C)	
Phenoxybenzamine	Alpha-1 adrenergic antagonist	0.25 mg/kg PO q8–12h or 0.5 mg/kg q24h (D) 2.5 mg per cat PO q8–12h or 0.5 mg/kg q24h (C)	Pheochromocytoma
Prazosin	Alpha-1 adrenergic antagonist	0.5–2 mg per dog PO q8–12h (D) 0.25–0.5 mg per cat PO q24h (C)	Pheochromocytoma
Atenolol	Beta-adrenergic antagonist	0.1–1.5 mg/kg PO q12h (D) 6.25–12.5 mg PO q12h (C)	Most frequently used in patients with hyperthyroidism, for which efficacy as a single agent is poor. Contraindicated in patients with active cardiogenic pulmonary edema
Spironolactone	Aldosterone antagonist	1–2 mg/kg PO q12h (D, C)	Primary hyperaldosteronism

C, cat; CRI, constant-rate infusion; D, dog; IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

in animals with CKD). Prompt treatment of systemic hypertension is usually associated with relatively rapid and complete reversal of neurological manifestations in patients with hepatic encephalopathy, with improvement appreciated within 24–48 hours in most cases. Conversely, partial or complete resolution of visual deficits may take weeks in patients with hypertensive ocular disease, if at all; in one study, despite successful BP reduction following initiation of amlodipine, 18/26 (69%) cats with hypertensive retinopathy had improved ocular signs

in one or both eyes, while only 4/30 (13%) eyes initially assessed as blind had some degree of visual recovery [10].

In the majority of dogs and cats with systemic hypertension, lifelong therapy – often with multiple oral agents that may require periodic dose adjustment – is required to achieve lasting BP reduction. For cases of secondary systemic hypertension in which the underlying disease can be treated definitively (e.g. hyperthyroidism, primary hyperaldosteronism, pheochromocytoma), hypertension may be partially or completely cured [40,41].

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D. Hematological and Oncological Disorders

64

Leukocytosis and Leukopenia

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Introduction

Neutrophils comprise the majority of leukocytes in circulation in both dogs and cats [1,2]. Neutrophilia and neutropenia therefore account for the vast majority of cases of abnormal leukocyte concentration in these species. Neutrophils are an integral component of the innate immune response and are a hallmark for inflammation. Interpretation of neutrophil responses is therefore essential in the emergency patient, and will be the major focus for this chapter.

Leukocytosis

Neutrophilia

Four mechanisms account for the vast majority of cases of neutrophilia: increased production (appropriate), increased production (inappropriate), demargination, and decreased egress from circulation.

Increased Production (Appropriate): Inflammation

Appropriate increased production of neutrophils occurs in times of increased demand (i.e. septic or non-septic inflammation). Dogs and cats have a large storage pool of mature neutrophils in their bone marrow, as well as marginated neutrophils along endothelial walls, which both serve as a buffer for fluctuations in peripheral demand. Dogs, for example, have up to a 5-day supply of neutrophils, based on normal rates of utilization, in the bone marrow storage pool [3]. Early stages of inflammation in these species are therefore most commonly associated with a neutrophilia that is independent of bone marrow production. Note that if the inflammatory nidus is acute and fulminant with rapid depletion of bone marrow neutrophil stores prior to any regenerative effort, a neutropenia may ensue (see Neutropenia section below).

The marginated and bone marrow storage pool of neutrophils may be sufficient to control the inflammatory nidus, and the neutrophil concentration will return to normal. Alternatively, if the inflammatory stimulus persists, *de novo* generation of neutrophils is required, and occurs via myeloid progenitor cell proliferation in the bone marrow in a complex response known as emergency granulopoiesis [4]. Major granulopoietic cytokines and growth factors responsible for this essential response include G-CSF, GM-CSF, IL-3, IL-6, and FLT3 ligand. This process takes time, and to tide over the lag period, previously produced band neutrophils, or even earlier granulocytic precursors, are released into circulation. This subsequent leukogram is referred to as left shifted. High neutrophil counts with a left shift suggest that the bone marrow is able to respond to an inflammatory stimulus. In contrast, left shifts with normal or low neutrophil counts suggest an inability of the bone marrow to meet increased demand. The progression of the neutrophil response can only be accurately appreciated with serial monitoring of the leukogram, sometimes every 24–48 hours due to the short half-life of neutrophils and the dynamic interplay between production and consumption.

A left shift confirms inflammation, but it says nothing about the source of the inflammatory stimulus. A plethora of infectious (bacterial, viral, fungal, protozoal), non-infectious (immune-mediated, pancreatitis), and neoplastic lesions can incite an inflammatory leukogram.

Degenerative Left Shift

A degenerative left shift (DLS) is present when granulocytic precursors outnumber mature neutrophils in circulation. The presence of a DLS, irrespective of the total leukocyte concentration, has been found to increase the risk of death or euthanasia in hospitalized dogs and cats [5,6]. In cats, not only the presence but also the severity of the DLS, as measured by a ratio of mature to immature

neutrophils (N/I index), predicts a higher risk of mortality. DLS is associated with a broad range of diseases in both species, including infectious and non-infectious etiologies, and intensive, directed therapy is warranted in such cases.

Leukemoid Response

A leukemoid response describes a marked leukocytosis due to a strong inflammatory stimulus that can mimic a neoplastic response. Dogs and cats with marked neutrophilic leukocytosis (mean absolute neutrophil concentrations of 53 798 cells/ μ L, and 59 046 cells/ μ L respectively) had high mortality rates [7,8]. Both dogs and cats with extreme neutrophilia secondary to neoplasia were more likely to die than other etiologies, and dogs with infectious etiologies had a reduced mortality risk.

Toxic Changes

Toxic changes in neutrophils are signs of dysplasia, associated with increased granulopoiesis and inflammation. They are mostly cytoplasmic, and include the presence of Dohle bodies, increased cytoplasmic basophilia, vacuolation of the cytoplasm, and rarely the presence of primary granules. Giantism of neutrophils and neutrophilic precursors is also a sign of toxicity. Recognition of toxic changes within neutrophils has both diagnostic and prognostic importance. They can be helpful in differentiating cases of inflammation (toxic changes often present) from corticosteroid/stress and epinephrine responses (toxic changes not present). The presence of toxic changes is associated with increased hospitalization time in both dogs and cats, and degree of toxicity is associated with risk of mortality in dogs [9,10].

Increased Production (Inappropriate)

Inappropriate increased production of neutrophils is rarely seen in dogs and cats and is due to neoplasia, which may be either primary neoplasia of the bone marrow (i.e. granulocytic leukemia – very rare) or may represent a paraneoplastic response secondary to release of growth factors (e.g. GM-CSF) from a wide array of different neoplasms: hemangiosarcoma, mast cell tumors, thymoma, ovarian carcinoma, pulmonary adenocarcinoma [11].

Demargination

As described previously, the intravascular pool of neutrophils comprises both circulating and marginated neutrophils. In cats, approximately 70% of total blood neutrophils reside in the marginated pool, compared to 50% in dogs [1,2]. As the marginated pool is not normally circulating, and hence not routinely part of the measured neutrophil concentration, demargination of these cells can dramatically increase the neutrophil concentration and WBC concentration. Two clinically important

scenarios where this phenomenon is seen are response to corticosteroids and epinephrine.

Corticosteroid Response

Also known as a “stress” leukogram, both endogenous and exogenous corticosteroids can cause demargination of neutrophils. Increased release from the bone marrow and decreased transit into tissues may also contribute to the neutrophilia from corticosteroids. The magnitude of the neutrophilia is variable, but is frequently 15 000–25 000 cells/ μ L in dogs and cats [12]. Experimental studies have shown neutrophilias up to 40 000 cells/ μ L due to steroid use only. Maximal response occurs within 8 hours, and if no further steroids are administered/released, the count will return to normal within 24 hours [12]. If prolonged exposure to steroids has occurred, it may require many days to normalize, as the recovery response appears to be time and dose dependent.

One of the hallmarks of a corticosteroid effect is a lymphopenia. The peripheral lymphocyte count is low due to redistribution of lymphocytes. The lymphopenia occurs more rapidly than the neutrophilia (approximately 4 hours) and may take longer to resolve [12]. Dogs are the only species in which a mild monocytosis is reliably seen.

Epinephrine Response

Release of epinephrine from excitement (common in cats and puppies) causes marginated neutrophils to be released into circulation. The effect is seen immediately, and resolves within 30 minutes. Conversely to corticosteroids, epinephrine normally results in a lymphocytosis, secondary to mobilization from the thoracic duct and blockage of entry into lymphoid organs.

Decreased Transit into Tissues

The most important cause of decreased transit of neutrophils into tissues is corticosteroids (see above). A rare genetic disorder of Irish setters (and single reports in a cat and mixed-breed dog) is seen called leukocyte adhesion deficiency (LAD) in which neutrophils lack surface receptors (CD18) to be able to bind to blood vessels and enter into tissues, and therefore accumulate in the blood [13]. Extremely high neutrophil concentrations occur (50 000–100 000+ cells/ μ L) and many hypersegmented neutrophils may be seen. Affected animals are susceptible to infections and invariably die at a young age.

Neoplasia

Circulating neoplastic cells can occasionally cause a leukocytosis in emergency patients. The prognosis for such patients is highly variable based on the underlying process. Chronic lymphocytic leukemia (CLL), for example, is common in middle-aged to older dogs (less common

in cats) and can present with marked leukocytosis ranging from 15 000 to 1 600 000 cells/ μ L [14]. Neoplastic cells comprise small, mature lymphocytes and the disease is indolent and slowly progressive. Conversely, acute leukemias (e.g. lymphoid, myeloid) are associated with large, immature circulating cells, and are aggressive, high-grade malignancies that carry a grave prognosis. Acute leukemias are mostly associated with concurrent cytopenias. The leukemic phase of lymphoma (small cell or large cell) can also cause a leukocytosis and have a variable prognosis with therapy. Neoplastic cells are not reliably identified by automated machines, and inspection of blood smears in patients with leukocytosis is essential. If neoplastic cells are suspected, inspection of the smear by a clinical pathologist is recommended, especially given the divergent prognoses associated with different neoplasms that can cause leukocytosis.

Other Cell Lines

Increases in eosinophils, lymphocytes, and monocytes can frequently give clues to underlying disease processes in emergency patients. These have been summarized in Box 64.1.

Treatment

In most patients with neutrophilia, inflammation (whether sterile or septic) is the underlying cause. The magnitude of the neutrophilia often correlates with the severity of the disease process [15]. Monoclonal therapies against neutrophils have been tested in lab animal models of inflammatory and immune diseases to prevent

neutrophil adhesion to the endothelium and to protect against sepsis or systemic inflammation [16,17]. These have not been carried out in domesticated animal species and are still experimental in humans. In essence, this therapy induces a leukocyte adhesion deficiency syndrome that may impose a risk for exacerbating sepsis. Clinical trials are ongoing to determine the disease process, bacterial species, time of therapeutic intervention, and overall effect of inhibition of neutrophil adherence.

There is argument against these therapies, as alterations in neutrophil morphology, mechanics, and motility occur commonly in experimental and clinical sepsis. Worse outcomes were noted in septic patients with neutrophils that were less granular and larger [18]. Neutrophils from septic patients have also been shown to have slower migration and chemotaxis as well as increased resistance to mechanical forces [19,20].

Neutrophilia is more likely to be associated with the disease than to be responsible for the patient's illness. Therefore, it is more appropriate to direct the treatment at the underlying disease rather than at the neutrophilia. With the variety of diseases that may cause neutrophilia, left shift, or toxic changes, diagnostic tests and specific treatments must be carried out to battle the primary disease. In most clinical patients, therapy to reduce the neutrophil concentration is generally not indicated.

Leukopenia

Neutropenia

Mechanisms of neutropenia include decreased production by the bone marrow, increased utilization, and destruction.

Decreased Production by the Bone Marrow

In a large retrospective study on neutropenia, non-bacterial infectious diseases were the most common etiology in both dogs and cats [21]. These agents mostly target progenitor cells in the bone marrow, resulting in decreased production of neutrophils and other cells. In dogs, parvovirus infection accounted for 53% of cases of neutropenia [21]. Importantly, evaluation of the leukogram in cases of parvoviral enteritis can give prognostic information, with increasing severity of leukopenia associated with increased mortality [22,23]. Conversely, a WBC concentration of $\geq 4.5 \times 10^3/\mu$ L at 24 hours post admission had a positive predictive value for survival of 100% [22]. In cats, FeLV and FIV accounted for 24% and 10% of neutropenic patients respectively [21]. Feline panleukopenia virus is also a potent cause of neutropenia in cats and, similar to canine parvovirus, increased severity of leukopenia is associated with increased risk of mortality [24].

Box 64.1 Diseases associated with eosinophilia, lymphocytosis, and monocytosis in dogs (D) and cats (C).

Eosinophilia

Allergic/hypersensitivity disease (D,C)
Parasitic disease (D,C)
Hypoadrenocorticism (D)
Eosinophilic inflammatory disease (D,C)
Paraneoplastic (especially T-cell lymphoma and mast cell neoplasia) (D,C)

Lymphocytosis

Antigenic stimulation (D,C)
Epinephrine response (C > D)
Hypoadrenocorticism (D)
Neoplasia (D,C)

Monocytosis

Acute and chronic inflammation (D,C)
Corticosteroid response (D)

Box 64.2 Drugs, hormones, and toxins associated with neutropenia in dogs (D) and cats (C) [21,26].*Chemotherapeutic agents (D,C)*

Carboplatin

Cisplatin

Cyclophosphamide

Doxorubicin

Antimicrobial agents (D,C)

Cephalosporin

Chloramphenicol

Trimethoprim sulfadiazine

Anticonvulsants (D)

Phenobarbital

Primidone

Cardiovascular drugs (D)

Captopril

Quinidine

*Albendazole (D,C)**Estrogen (D)**Griseofulvin (C)**Methimazole (C)**Phenylbutazone (D)*

Other diseases affecting the bone marrow and production of neutrophils include neoplasia, necrosis, myelofibrosis, radiation therapy, and drug toxicity [25,26]. Bone marrow toxicity secondary to drug, toxin or hormone exposure is a common etiology in neutropenic patients [21], and a list of the more common agents responsible for causing neutropenia is presented in Box 64.2. Many of these conditions are accompanied by anemia, thrombocytopenia or both (pancytopenia).

Increased Utilization

As mentioned previously, acute fulminant inflammation can deplete neutrophil numbers, resulting in neutropenia. Neutropenia secondary to increased demand from marked inflammation, bacterial sepsis or endotoxemia accounted for 17% of feline cases and 10% of canine cases in one study [21]. Although leukocytosis secondary to neutrophilia is most commonly observed in dogs with naturally occurring sepsis [27,28], it is important to recognize that the early stages of sepsis can be associated with neutropenia [21,29]. In experimental models of endotoxin-mediated sepsis in dogs, severe leukopenia is observed 3 hours after induction of sepsis [29]. The leukopenia is due to neutropenia, with lymphocyte and monocyte concentrations remaining relatively constant. By 24 hours, a rebound leukocytosis secondary to neutrophilia was seen. This finding is likely due to transient margination of neutrophils secondary to endotoxin-mediated upregulation of adhesion molecules on neutrophils [30].

Neutropenia may also be persistent in severe cases of sepsis where there is a lag between fulminant consumption of neutrophils and increased production by the bone marrow. Serial monitoring of the leukogram is recommended to ensure an appropriate bone marrow response.

Destruction

Immune-mediated destruction of neutrophils is rarely seen in dogs, and even more rare in cats. Dogs with corticosteroid-responsive, idiopathic neutropenia are more likely to be younger (<4 years), and have lower neutrophil concentrations than patients with known causes of the neutropenia [31].

Lymphopenia

Lymphopenia may in some cases be severe enough to cause a mild leukopenia. Most cases of lymphopenia are due to the presence of endogenous or exogenous corticosteroids and are a hallmark of a “stress” leukogram (see previous section). Other causes of lymphopenia include lymph losing diseases, viral disease (including parvoviral enteritis), and other infectious diseases.

Treatment

Management of the clinical veterinary patient with neutropenia relates to the underlying cause and severity. Most veterinarians do not initiate treatment until the neutrophil concentration drops below 2500 cells/ μ L. Human guidelines suggest that the propensity to develop an infection is significant at neutrophil concentrations below 1000 cells/ μ L whereas fever may be common and managed on an outpatient basis between these measures [32].

The goal of management is to prevent infection. Well described in the human literature is the management of febrile neutropenia secondary to chemotherapy [33,34]. Patients expected to have a short nadir in neutrophil concentrations may be easily managed as outpatients without the inherent risks of hospitalization. If the expected duration of neutropenia is unknown, the management decisions may be less clear.

Therapy with antimicrobial agents should be based on the degree of fever, magnitude of leukopenia/neutropenia, and patient characteristics. Important information to determine and weigh into the clinical decision for treatment includes the following points.

- Has the patient been on previous or current antimicrobial therapy?
- What are the results of a culture (if submitted/completed)?

- What pathogen is most likely?
- What are the regional susceptibility patterns?

Broad-spectrum antimicrobial agents should be initiated in all febrile neutropenic patients (see Chapter 200). A potentiated penicillin or fluoroquinolone has the spectrum and route of delivery desired. If the patient has more signs of systemic inflammation or sepsis, combination of an aminoglycoside with a beta-lactam antimicrobial is preferred. Antimicrobial therapy should be changed based on culture and susceptibility testing when available. The decision for hospitalization should be based on consideration of the clinical severity of the patient as well as the abilities and compliance of the owner and patient at home. The risks involved with hospitalization (e.g. percutaneous/urinary catheterization, nursing care, barrier precautions, hand hygiene) and proximity to animals with other infections must also be considered.

In any patient with organ dysfunction (severe sepsis), hospitalization is essential as the therapy is more

intensive than antimicrobials alone. Patients suspected of septic shock should have their effective circulating volume established early and their perfusion and flow maximized using any combination of fluids and vaso-pressors as indicated (see Chapter 155). The antimicrobial selection cannot wait for a culture, and an empiric choice must be made as early in the course of treatment as possible.

Granulocyte-colony stimulating factor (G-CSF) has also been recommended to aid in the earlier increase of neutrophils from bone marrow that has the potential to produce more leukocytes. In a common septic model in clinical veterinary medicine, treatment with recombinant human G-CSF in parvoviral enteritis puppies has unfortunately been ineffective at increasing neutrophil concentrations and survival [35]. A canine recombinant G-CSF has been shown, however, to improve neutrophil concentrations in neutropenic patients, making this an interesting option if/when clinical available [36].

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65

Non-Regenerative Anemia

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Introduction

Early, accurate characterization of anemia as being regenerative or non-regenerative is a vitally important step when assessing anemic patients. Regenerative anemia is caused by blood loss (i.e. hemorrhage or hemolysis) while non-regenerative anemia reflects ineffective erythropoiesis. Dyserythropoiesis occurs because of primary bone marrow pathology or systemic disease causing bone marrow suppression. The peracute development of anemia also appears non-regenerative initially (i.e. prerenal), since insufficient time has elapsed to mount a regenerative response. The differential diagnoses, diagnostic plan, therapeutic interventions, and prognosis all vary depending on the presence or absence of regeneration.

Erythropoiesis

Pluripotent hematopoietic stem cells in the bone marrow give rise to all adult stages of erythrocytes, leukocytes, and platelets [1]. The red cell line undergoes successive mitoses through several stages [2]. This process is characterized by each successive cell division being smaller than the last with increasing hemoglobin content [3]. Upon achieving a critical hemoglobin concentration, reticulocytes are released into the peripheral circulation via diapedesis. Within 48 hours, any residual basophilic material in the reticulocyte is lost, forming mature erythrocytes [1]. Erythropoietin is a glycoprotein produced primarily by the kidney in response to hypoxia and is the primary regulator of erythropoiesis [1]. Other substances (e.g. thyroxine, cortisol) augment erythropoiesis [3], while sufficient iron stores are essential for hemoglobin function. Erythrocytes persist for approximately 104 days in the periphery of the dog [4] and 73 days in the cat [5]. Aged erythrocytes are cleared by

the erythrophagocytic system, with subsequent replenishment of the peripheral pool with new reticulocytes.

Pathophysiological Response to Non-Regenerative Anemia

The symptoms of non-regenerative anemia may be non-specific (e.g. lethargy) and typically are milder than for regenerative anemia. Some historical clues (e.g. pica) are suggestive of chronic anemia. Chronic anemia typically is met with some degree of physiological compensation. This compensation includes increasing cardiac output via nitric oxide-mediated vasodilation [6,7], as well as rheological changes promoting lower systemic vascular resistance [8]. The downstream effects of this “relative hypovolemia” include increased sympathetic discharge and renin-angiotensin-aldosterone system activity, risking hypervolemia and cardiac remodeling over time. Volume overload is considered a risk, therefore, in chronic anemia, especially in cats [9]. Compensatory increased synthesis of 2,3-DPG with a rightward shift of the oxygen dissociation curve may also occur in dogs [10].

Diagnostic Approach

The erythron refers to all mature and immature erythrocyte stages. An estimation of the peripheral erythron is a core component of the minimum laboratory database. A spun packed cell volume (PCV) with concurrent estimation of total solids is an invaluable diagnostic test. Alternatively, the hematocrit may be calculated from the red blood cell count and mean cell volume (MCV) using automated hematology analyzers, potentially increasing the likelihood of error compared to PCV [11]. Traditionally, EDTA anticoagulated blood samples are preferred for hematology analysis due to superior leukocyte

Table 65.1 Expected characteristics of regenerative and non-regenerative anemia.

Characteristic	Regenerative anemia	Non-regenerative anemia
Reticulocyte count	Increased	Low-normal
Anisocytosis	Present	Absent
Polychromasia	Present	Absent
MCV	Increased	Normal
MCHC	Low	Normal
RDW	Increased	Normal

MCHC, mean corpuscular hemoglobin concentration; MCV, mean cell volume; RDW, red cell distribution width.

staining, but EDTA and lithium heparin samples are both acceptable for emergency PCV estimation [12]. Institution-specific reference ranges are used preferentially but adult dogs are considered anemic when PCV < 35% and adult cats < 30% [13].

The expected characteristics of regenerative and non-regenerative anemia are listed in Table 65.1. A complete blood count (CBC) performed by a clinical pathology laboratory should be undertaken in all anemic patients but this may not be available for emergency veterinarians. Maximizing the utility of in-house diagnostics is therefore wise.

Helpful information can be gleaned from peripheral blood smears but the limitations of this technique compared to specialist pathologist review should be remembered [14]. Characteristics of regeneration present on a blood smears stained with standard Romanowsky stains (e.g. Diff-Quik) include polychromasia, anisocytosis, and nucleated red cells (Figure 65.1). Polychromatophils

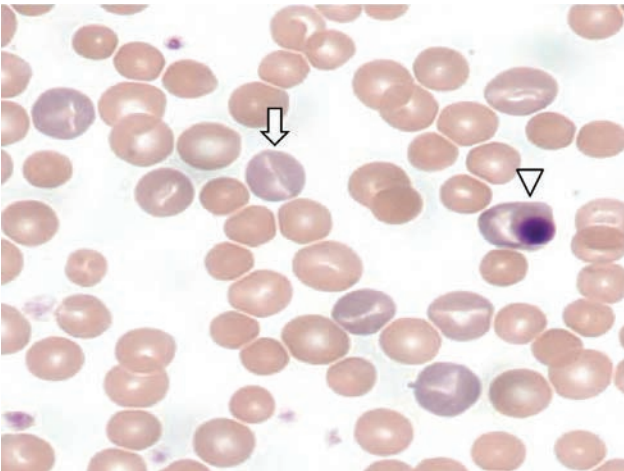


Figure 65.1 A blood smear from a dog illustrating key characteristics of regenerative anemia, including anisocytosis, polychromasia (arrow indicates polychromatophil) and a nucleated red cell (arrowhead).

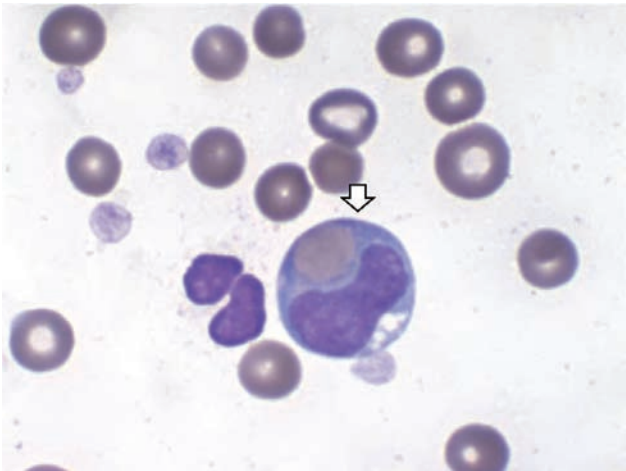


Figure 65.2 A peripheral blood smear from a dog with non-regenerative IMHA with evidence of erythrophagocytosis (arrow).

represent reticulocytes that are basophilic due to the staining of their nuclear material. While all polychromatic cells represent reticulocytes, not all reticulocytes are polychromatic [15]. One veterinary study reported a diagnostic accuracy of 77% for identifying regeneration based solely on polychromasia [16]. Accurate reticulocyte enumeration from flow cytometry or examination of smears stained with supravital stains (e.g. new methylene blue) is the gold standard for assessing regeneration [3]. An added challenge in cats is the recognition of two varieties of reticulocytes: the aggregate and punctate forms. The former is used for assessment of recent regeneration since they are shorter lived than the punctate form. Additional information that may be gleaned from blood smear evaluation includes the presence of parasites (e.g. feline hemoplasmas), spherocytosis, schistocytosis, and erythrophagocytosis (Figure 65.2).

Erythrocyte indices obtained from automated hematology analyzers also aid in identifying regeneration. The MCV indicates the average erythrocyte size, while mean corpuscular hemoglobin concentration (MCHC) indicates hemoglobin content. Non-regenerative anemia is typically normocytic and normochromic (i.e. normal MCV and MCHC), while regenerative anemia is classically considered macrocytic (high MCV) and hypochromic (low MCHC). Iron deficiency anemia is microcytic (low MCV) and hypochromic (low MCHC), associated with additional mitoses occurring in the bone marrow before the critical hemoglobin content required for diapedesis is reached [3]. The most common reason for iron deficiency anemia in small animals is chronic blood loss, typically of gastrointestinal origin, that becomes non-regenerative over

time. The diagnostic accuracy of MCV and MCHC for identifying regeneration has been reported as 70% and 66% respectively [16]. However, other diseases can result in macrocytosis (e.g. feline leukemia virus, FeLV) [17] and microcytosis (e.g. portosystemic shunts) [18] which limits the sensitivity of MCV as the sole indicator of regeneration.

The red cell distribution width (RDW) indicates variation in erythrocyte size, with regenerative anemia being associated with a high RDW and non-regenerative with a low RDW. The RDW helps identify regeneration in dogs [16,19] with a reported diagnostic accuracy of 69% [16]. The combination of RDW and polychromasia improved diagnostic performance (79%) compared to either value being assessed alone [16].

The integrity of other cell lines should be assessed whenever anemia is identified. The presence of pancytopenia suggests primary bone marrow pathology, while preservation of other cells lines may represent either bone marrow or extramarow disease. Additional diagnostic tests may be recommended in specific cases, including, but not limited to, serum chemistry analysis, urinalysis, fecal examination, infectious disease testing (e.g. FeLV, ehrlichiosis), thoracic and abdominal imaging, endocrine testing, and gastrointestinal endoscopy.

Bone Marrow Sampling and Analysis

Once extramarow disease has been ruled out definitively, assessment of the erythron localized to the bone marrow via aspiration or biopsy may be recommended. Bone marrow samples should always be analyzed by clinical pathologists given the inherent complexity of their interpretation. Cytological analysis of aspirates has a faster turnaround time than core biopsy and may provide a definitive diagnosis (e.g. neoplastic infiltration). It is recommended that aspirates and biopsy, however, always be submitted concurrently to characterize the pathology as accurately as possible. For instance, if an aspirate is considered to have a low cellularity, this could reflect a non-diagnostic sample or a truly hypoplastic process. Concurrent interpretation of a biopsy would help interpret the aspirate and may avoid further, potentially unnecessary, bone marrow sampling. A CBC should also be submitted along with the bone marrow sample to guide interpretation.

Animals undergoing bone marrow sampling should be deeply sedated or anesthetized with provision of analgesia given the pain associated with the procedure [20]. A variety of anatomical locations could be used for sampling, including the proximal humerus, iliac crest, and trochanteric fossa of the femur. Sternal marrow aspiration using hypodermic needles has been

described in beagles, which provided good-quality diagnostic samples [21] and was associated with lower pain scores [22]. The specific bone marrow needle chosen depends on patient size but generally Illinois sternal needles are preferred for smaller patients and Jamshidi needles for larger.

When performing a bone marrow aspirate, only small volumes of marrow (e.g. <0.5 mL) are required, with larger samples risking inadvertent hemodilution of the sample. The aspirated sample should be promptly transferred to glass slides and should contain visible spicules of bone marrow. A core biopsy can then be obtained by repeating this same technique but with removal of the stylet from within the bone marrow needle. A blunt probe within the marrow needle kit is then used to exteriorize the collected core sample before carefully transferring it to formalin. Further detailed information on bone marrow sampling is described elsewhere [23].

Primary Bone Marrow Disorders

Primary bone marrow disorders tend to produce more severe anemia than extramarow suppression. A definitive diagnosis may only be possible with bone marrow sampling but a strong index of suspicion of toxicity or infection may allow the clinician to omit that diagnostic step in some cases. If bicytopenia or pancytopenia is identified, aplastic anemia is considered likely, where hematopoietic marrow space is replaced with adipose tissue [24]. Neutrophils have the shortest half-life and neutropenia may be evident within 5 days, followed by thrombocytopenia after 8–10 days, and lastly anemia weeks later [3]. Dogs with aplastic pancytopenia may have idiopathic disease [25] but secondary pancytopenia associated with infections (e.g. *Ehrlichia canis*, parvovirus), toxins/drugs (e.g. azathioprine, procarbazine, estrogens, phenylbutazone) or immune-mediated diseases are reported [26]. Some dogs can regain marrow function with supportive care and discontinuation of myelotoxic drugs but the prognosis is guarded. Theoretically, bone marrow transplantation could offer a cure but is not routinely performed in veterinary medicine. Idiopathic aplastic anemia has also been reported in cats, along with secondary causes including FeLV infection, renal disease, and drug reactions [27].

Pure red cell aplasia (PRCA) [28,29] and non-regenerative IMHA (NRIMHA) represent two variants of immune-mediated erythrocyte precursor destruction [30]. In these situations, white cell and platelet count are unaffected. The absence of all red cell precursors on bone marrow samples is consistent with

PRCA, while NRIMHA classically involves destruction of later stages of erythrocyte development with a distinct maturation block [3]. In NRIMHA, there may be a compensatory erythroid hyperplasia [31]. In contrast to peripheral IMHA, spherocytosis is uncommon, icterus is not observed, and Coombs positivity is rare [31]. Both conditions are managed with long-term immunosuppressive agents, with glucocorticoids being the mainstay, but additional immunosuppressives (e.g. cyclosporine, mycophenolate) may be considered in some cases. Response to therapy has been reported in 61–77% of dogs with PRCA, and 88% of cats were alive at 60 days after diagnosis [32]. The time to recovery is slow (weeks to months) in both dogs [28,30,32,33] and cats [29,32,34] with the potential necessity for multiple transfusions during this period. In comparison to peripheral IMHA, thromboembolic sequelae appear rare and thromboprophylaxis is not routinely employed [31]. Secondary PRCA and NRIMHA have been described associated with FeLV in cats [35], parvoviral infection [36], adverse effects of human recombinant erythropoietin therapy [37], and estrogen toxicity [38].

Neoplasia should also always be considered in non-regenerative anemia cases. Leukemia involves the neoplastic proliferation of one hematopoietic cell line in the marrow with secondary suppression of other cell lines [39]. Similar to dogs with aplastic pancytopenia, anemia develops later than leukopenia and thrombocytopenia. Disseminated lymphoma may cause a non-regenerative anemia, as can the invariably fatal diagnosis of malignant histiocytosis (MH). In MH, both regenerative and non-regenerative anemia may occur due to erythrophagocytosis by malignant histiocytes and marrow crowding by neoplastic cells respectively [3]. Myelodysplastic syndromes represent a group of disorders characterized by dysplastic rather than neoplastic hematopoietic precursor development in the marrow. Normocytic normochromic non-regenerative anemia is typically noted, although macrocytosis may be identified in cats [24]. Bone marrow sampling is required to distinguish myelodysplastic syndromes from neoplasia. Primary forms of the disease may occur although secondary myelodysplasia associated with lymphoma, IMHA, and drug reactions has been reported [40]. Replacement of hematopoietic tissue with fibroblasts is also described (myelofibrosis) and can be a primary or secondary disease entity. Bone marrow aspiration would be acellular (i.e. dry tap) and biopsy is necessary to definitively diagnose this condition [3].

Secondary Extramarrow Disorders

Anemia of renal disease is common [41,42] and contributes to overall morbidity. This anemia is likely multifactorial in nature, with erythropoietin deficiency considered the major cause [37]. Increased concentrations of cytokines in uremia may also inhibit erythropoiesis [43] and shorten erythrocyte lifespan [44]. A functional iron deficiency has been reported in cats with renal disease [45]. Uremic gastropathy causing ulceration appears to be an uncommon cause of anemia in dogs [46] and cats [47], however. Recombinant human erythropoietin analogues (e.g. darbepoietin) are the mainstay of chronic therapy [37,38], although iron and B vitamins may be supplemented also [49]. Since thyroxine augments the effects of erythropoietin, mild non-regenerative anemia may be seen in dogs with hypothyroidism [50,51]. Anemia has also been reported to occur in some dogs with hypoadrenocorticism [52,53], reflecting the supportive role of cortisol in normal erythropoiesis, but this is an inconsistent finding since volume depletion could interfere with its recognition. Concurrent gastrointestinal hemorrhage in these patients could also plausibly contribute to anemia [54].

Anemia of inflammatory disease, also termed anemia of chronic disease, is usually mild, normocytic, and normochromic. Inflammatory cytokines including interleukin-6, interleukin-1, and tumor necrosis factor- α may result in upregulation of the acute phase protein, hepcidin [55]. Hepcidin promotes a state of relative iron deficiency, blunting erythropoiesis [56] and therefore promoting a low-grade insidious anemia.

Therapies for Non-Regenerative Anemia

The judicious use of blood products and hemoglobin oxygen-carrying solutions may be required in animals with hemodynamic compromise due to their anemia (see Chapter 176). In addition to disease-specific considerations like immunosuppression or exogenous erythropoietin administration, other non-specific therapies could be considered to promote marrow function. Anabolic steroids (e.g. nandrolone) may be considered in chronic non-regenerative anemia, especially renal disease [57], although proven efficacy in small animals is lacking. Theoretically, the psychiatric medication lithium could have applications for aplastic pancytopenia [58,58], although veterinary data are unavailable.

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Hemolytic Anemia

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Introduction

Hemolytic anemia results from increased erythrocyte destruction and shortened red blood cell (RBC) lifespan. Hemolysis is usually extravascular, with macrophagic erythrocyte destruction occurring in spleen, liver, and bone marrow; splenomegaly is frequently present. Intravascular hemolysis is less common, leading to hemoglobinemia and hemoglobinuria. With either process, the rate of erythrocyte destruction can exceed hepatic clearance, resulting in hyperbilirubinemia and icterus.

History and Physical Examination

Clinical signs are similar to those seen with other causes of anemia, namely lethargy, weakness, exercise intolerance, and inappetence. Some owners may also note pigmenturia. The history should include detailed enquiries into medications, diet, travel, and past illnesses. Dietary indiscretion (e.g. onions, zinc) may result in hemolysis, while travel to certain locations should alert the clinician to the possibility of tick-borne disease or erythroparasites.

Common physical examination findings in patients with hemolytic anemia include tachycardia, tachypnea, cardiac murmur, gallop heart sounds, “snappy” pulses, pallor, jaundice, splenomegaly, and pigmenturia. Physical examination should aim to rule out hemorrhage, to look for further evidence of a hemolytic mechanism, and identify any clues regarding etiology.

Laboratory Assessment

Anemia is confirmed via demonstration of a decreased packed cell volume (PCV), or decreased hematocrit and hemoglobin concentration on complete blood

count (CBC). A reticulocyte count is essential. Hemolytic anemias are almost always regenerative, defined as an absolute reticulocyte count $>60\,000/\mu\text{L}$ in the dog or aggregate reticulocyte count $>50\,000/\mu\text{L}$ in the cat [1]. Hemolytic anemias may be non-regenerative early in the disease process, prior to the bone marrow's response to increased erythropoietin levels. Some cases of immune-mediated hemolytic anemia are non-regenerative if the disease targets RBC precursors (see Chapter 65).

The evaluation of patients with hemolytic anemia should always include blood smear examination and saline agglutination test. Morphological abnormalities highly suggestive of an etiology can be detected on smear examination, such as spherocytes, Heinz bodies, eccentrocytes, erythroparasites, and schistocytes.

Differential Diagnoses for Hemolytic Anemia

Immune-Mediated Hemolytic Anemia (IMHA)

Immune-mediated hemolytic anemia is the most common cause of hemolysis in dogs, and occurs due to immune targeting of and damage to the erythrocyte membrane [2]. Resultant hemolysis is most commonly extravascular, but can be intravascular. IMHA may occur secondary to an inciting cause or underlying condition, or it may occur as part of a systemic immune disease [2–9]. In many cases, however, an underlying condition is not discovered, also known as autoimmune hemolytic anemia (AIHA). American cocker spaniels, miniature schnauzers, English springer spaniels, Old English sheepdogs, and poodles are overrepresented, as are spayed females [2,10,11]. IMHA is less common in cats.

Immune-mediated hemolytic anemia is thrombophilic [12–14]. The incidence of thromboembolism is significant and a frequent cause of mortality [15–17] (see Chapter 62).

The diagnosis of IMHA requires demonstration of immune-mediated RBC destruction by one or more of the following: the presence of spherocytes on a blood smear, a positive saline agglutination test, and/or a positive direct Coombs test [2,18]. Spherocytes result from phagocytosis of a portion of the RBC membrane. They are recognized as microcytic, spherical erythrocytes without central pallor. Because they are hard to distinguish from normal erythrocytes in cats, spherocytosis is not a reliable test for IMHA in this species [2]. Autoagglutination is assessed by the saline agglutination test. A drop of blood is mixed with an equal or greater volume of physiological saline on a slide. Macroagglutination can be grossly visualized. Microscopic evaluation of a fresh wet mount enables detection of microagglutination and differentiation from rouleaux formation. True autoagglutination will persist following saline addition [2]. The direct Coombs test detects antibodies or complement on the erythrocyte surface. Reported sensitivity is 60–70% with significant variability between laboratories [19,20].

Once a diagnosis of IMHA is established, a primary cause should be aggressively sought. Diagnostic testing will depend on the clinical findings and geographic location, and may include thoracic radiography and abdominal ultrasonography to identify possible neoplasia or infectious disease, urine culture to rule out the presence of a urinary tract infection, and tick-borne pathogen testing via serology and/or polymerase chain reaction (PCR).

Assessment for hypercoagulability has clinical merit, but is only reliably achieved via thromboelastography [12,21,22]. Elevated D-dimer concentrations have been demonstrated to occur in dogs with IMHA, but their reliability as an indicator of hypercoagulability or thromboembolic risk is uncertain [23,23] (see Chapter 62).

Treatment of IMHA includes immunosuppression to decrease the rate of erythrocyte destruction, treatment of any known underlying disease processes, and prophylactic antithrombotics (see Chapter 71). Transfusion (preferably with packed RBCs) is indicated for patients showing significant clinical signs referable to their anemia (see Chapter 176).

Immunosuppression is essential, and corticosteroids are the mainstay of immunosuppressive therapy. Prednisone or prednisolone is initiated at 1–2 mg/kg q12h. In large dogs, the low end of the dosage range should be used or the dose based on body surface area (not exceeding 50 mg/m² or 40–60 mg/day). In cats, prednisolone is preferred, resulting in higher plasma concentrations than prednisone. In patients that cannot tolerate oral therapy,

dexamethasone can be administered at 0.15–0.3 mg/kg IV or SC q12h. Most patients show a response to corticosteroids within 2–10 days as evidenced by a stabilization or increase in RBC parameters. This is not the case, however, in patients with non-regenerative IMHA in which response may take weeks or months [25] (see Chapter 65). Corticosteroids are usually continued at the initial dose for 3–4 weeks. Thereafter, doses are slowly tapered over subsequent weeks to months, based on response as determined by monitoring of red cell parameters. More rapid tapering is possible when an underlying cause can be removed or reversed.

Adjunctive immunosuppressive therapy is frequently initiated together with corticosteroids if there is perception of severe disease (aggressive hemolysis) or intent to more rapidly taper corticosteroids. Adjunctive agents include azathioprine, cyclosporine, mycophenolate, human intravenous immunoglobulin (IVIg), cyclophosphamide, danazol, and leflunomide [10,26–28]. Unfortunately, there is a paucity of high-quality evidence as to which of these agents are superior or indicated [29]. One small study demonstrated a possible benefit of mycophenolate mofetil in combination with corticosteroids in dogs with IMHA, but there was significant increased gastrointestinal toxicity [28]. Other studies have shown a lack of benefit of both azathioprine and IVIg as adjunctive therapy with corticosteroids [23,30]. Cyclophosphamide is no longer recommended based on studies that have shown either no benefit or increased mortality [31,32].

Optimal antithrombotic prophylaxis remains controversial (see Chapter 71). There is much disagreement regarding which, if any, antithrombotic medications should be used in patients with IMHA. A study in dogs with IMHA suggested improved survival when ultra-low-dose aspirin (ULDA) (0.5–1.0 mg/kg q24h) was included in the treatment regimen [10]. One study showed improved survival with individually adjusted dosing of unfractionated heparin based on anti-factor Xa activity versus fixed low-dose unfractionated heparin administration [33].

Splenectomy has been described as a treatment option for patients who are non-responsive to combination drug therapy [2,34]. The successful use of plasmapheresis has been described in one patient, but remains to be more fully evaluated [35].

The reported mortality rate for canine IMHA ranges from 40% to 70% [2,10,17,26,31,36,37]. Numerous negative prognostic indicators have been proposed, including thrombocytopenia, serum bilirubin concentration >5 mg/dL, increased blood urea nitrogen (BUN) concentration, the presence of band neutrophils, prolongation of PT or PTT, evidence of a hypocoagulable state via TEG, hypoalbuminemia, increased serum alanine

aminotransferase (ALT) concentration, and increased serum alkaline phosphatase (ALP) concentration [10,17,22,26,36,38]. There is little agreement between studies, however, in this regard [39].

Alloimmune Hemolytic Anemia

Alloimmune hemolytic anemia, as occurs with hemolytic transfusion reactions (see Chapter 176) and neonatal isoerythrolysis, is caused by alloantibodies directed against non-self erythrocyte antigens [2]. Alloantibodies can occur naturally, or following sensitization.

Neonatal Isoerythrolysis

Neonatal isoerythrolysis (NI) is the acute hemolysis that occurs in a neonate due to incompatibility between maternal and neonatal blood types. It is usually seen in cats when a type A or type AB kitten is born to a type B queen. NI does not occur *in utero* because cats have endotheliochorial placentation. However, type B queens secrete anti-type A antibodies in their colostrum and milk, which can be absorbed by neonatal kittens for the first 16 hours of life. Kittens are born healthy but develop hemolysis at a few days of age, and rarely live more than 1 week [2]. NI treatment is seldom successful. NI can be avoided by blood typing queens and toms to ensure compatible coupling. Following incompatible matings, kittens born of a type B queen and type A tom can be placed with a type A queen for the first 24 hours of life, or they can be fed a commercial milk replacer for 24 hours, and 1–3 mL of serum from a type A cat can be administered orally or subcutaneously to transfer passive immunity [2,40].

Oxidative Hemolysis

Oxidative injury leads to denaturation of hemoglobin, resulting in Heinz body formation, to RBC membrane damage, or to oxidation of ferrous iron to the ferric form, resulting in methemoglobinemia. Feline erythrocytes are more susceptible to oxidative injury than other species due to a greater number of reactive sulfhydryl groups and reduced ability to metabolize oxidative agents [2,41].

Heinz bodies (HB) result in erythrocyte rigidity and resultant shortened lifespan (Figure 66.1). Causes of HB formation include *Allium* species (onions, garlic), methylene blue, DL-methionine, phenacetin, and compounds which also cause methemoglobinemia (acetaminophen, benzocaine, and phenazopyridine) [2,41–43]. HBs are also associated with several diseases in cats, including diabetic ketoacidosis, hyperthyroidism, and lymphoma [44,45]. Commercial foods and drug preparations containing propylene glycol are associated with HB formation, but do not generally result in clinical anemia.

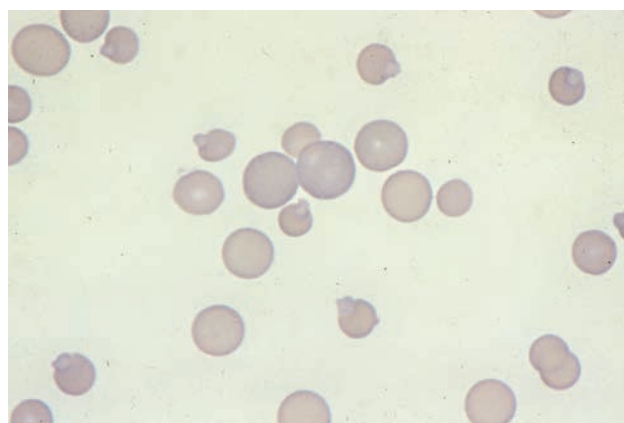


Figure 66.1 Feline heinz bodies on a peripheral blood smear. Reproduced with permission of Tracy Stokel, Cornell University.

Heinz bodies are best identified on blood smear examination with new methylene blue staining. In the dog, HBs are usually small, occur in multiples and, when large, may be seen as clear “blebs” protruding from the cell surface; they are frequently accompanied by eccentricities. In the cat, HBs are typically single.

Some oxidative agents, such as naphthalene, cause hemolysis via direct peroxidation of the erythrocyte membrane [2].

The diagnosis of overt HB anemia requires a history of exposure and visualization of HBs in many erythrocytes together with convincing evidence of hemolysis. Management includes removal of the oxidant agent, antioxidant therapy (e.g. *N*-acetylcysteine or *S*-adenosylmethionine), and supportive care.

Zinc and Copper Toxicity

Zinc toxicity results from the ingestion of zinc-containing objects, including US pennies minted after 1982, bolts screws, or topical skin protectants [46]. Toxicity is manifested as severe intravascular hemolysis, gastrointestinal signs and, occasionally, pancreatitis [46,47].

Zinc toxicity should be suspected in any patient with acute hemolytic anemia in the absence of autoagglutination, prompting abdominal radiography. Diagnosis is based on radiographic evidence of metallic foreign objects and/or possible exposure. The diagnosis can be confirmed by documenting elevated zinc blood levels [2,46]. Treatment should not be delayed pending zinc blood levels, which may take several days to return.

Copper toxicosis is a less common cause of hemolysis resulting from the ingestion of copper-containing foreign bodies or severe hepatocellular necrosis in dogs with copper storage disease [48]. The mechanism by which copper toxicosis induces hemolysis is incompletely

understood, but lipid peroxidation is suspected to play a role [49].

Treatment focuses on patient stabilization and prompt removal of the metal objects via endoscopy or laparotomy. Appropriate fluid therapy is essential due to the potential for renal injury caused by hemoglobinemia (see Chapter 167). Blood transfusion is administered as necessary (see Chapter 176). Antacids are recommended to reduce gastric acidity and “leaching” of metal from the source. Chelation therapy is rarely necessary if the source can be removed. If removal is not possible and chelation is required, calcium disodium EDTA is typically recommended (25 mg/kg IV q6h). The prognosis for recovery is excellent with timely and aggressive intervention.

Erythroparasites

Mycoplasmosis

Mycoplasma haemofelis (Figure 66.2) causes acute hemolytic anemia in cats, whereas a causative role of other *Mycoplasma* species is less clear [50,51]. Diagnosis can be achieved by visualization of the organism via blood smear examination, or on confirmation of the presence of parasite DNA via PCR. Cats with mycoplasmosis should be tested for underlying immunosuppressive disease. Treatment is with doxycycline (5 mg/kg PO q12h) or tetracycline (20 mg/kg PO q8h) for 3 weeks.

Cytauxzoonosis

Cytauxzoon felis causes severe, fulminant hemolysis, disseminated intravascular coagulation, and organ dysfunction in cats, and is associated with a very high mortality rate [2,52]. Diagnosis is achieved via visualization of the protozoa in erythrocytes or by PCR testing. The latter may facilitate earlier diagnosis. Treatment includes supportive care and administration of azithromycin and

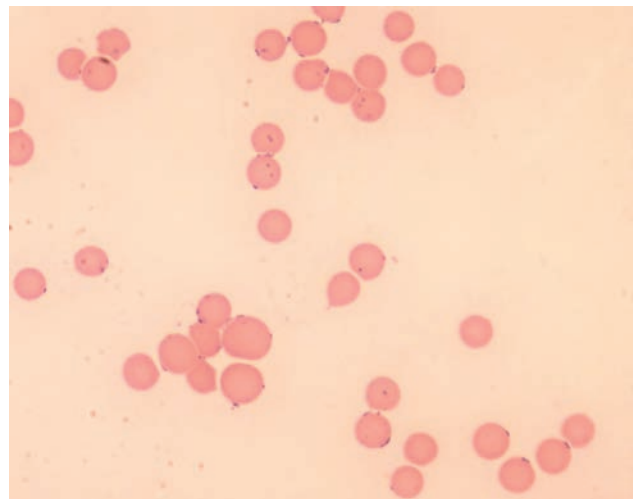


Figure 66.2 *Mycoplasma haemofelis* on a peripheral blood smear. Reproduced with permission of Tracy Stokel, Cornell University.

atavaquone or Diminazene (not available in the United States) [52,53]. Prognosis is guarded.

Babesiosis

Babesia spp cause hemolytic anemia in dogs. *B. canis* affects all breeds, with greyhounds most commonly reported [2]. *B. gibsoni* (Figure 66.3) is associated with recent dog bites, and is most commonly seen in American pit bull terriers [54]. Clinical manifestations range from acute disease with severe intravascular hemolysis to subacute or chronic disease with mild or moderate anemia. IMHA appears to occur frequently and, dependent on geographical location, concurrent infection with *Ehrlichia canis* is not uncommon. Complicated cases may manifest as DIC or systemic inflammatory response syndrome [55] (see Chapter 159).

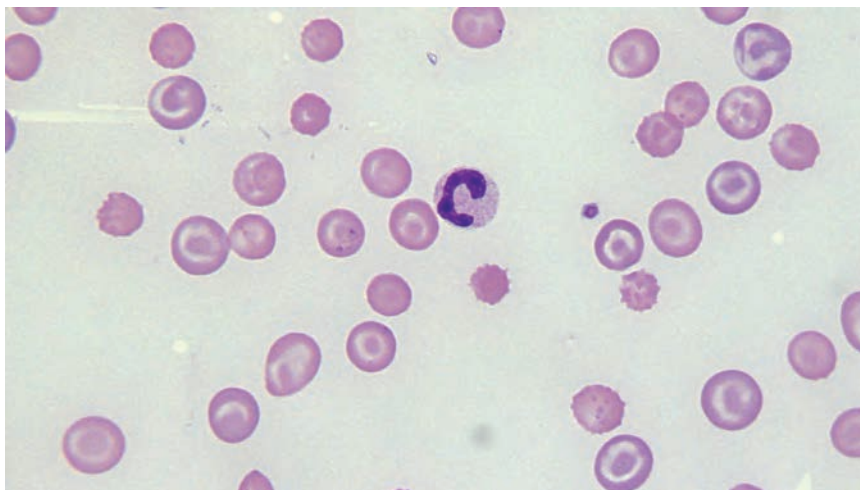


Figure 66.3 *Babesia gibsoni*, as visualized on a peripheral blood smear. Reproduced with permission of Tracy Stokel, Cornell University.

Diagnosis of babesiosis is achieved by identification of intraerythrocytic pyriform bodies on blood smear evaluation (best achieved by smear preparation from an ear stick), serology, or PCR. Work-up should also include evaluation for IMHA and testing for ehrlichiosis.

Babesia canis is treated with diminazine or imidocarb dipropionate, as well as a short, tapering course of corticosteroids [2]. Effective treatment of *B. gibsoni* has been described with a combination of metronidazole, enrofloxacin, and doxycycline, or a combination of clindamycin, diminazine, and imidocarb dipropionate [56,57].

Inherited Erythrocyte Defects

Erythroenzymopathies

Pyruvate kinase (PK) deficiency PK deficiency has been reported in several dog breeds (basenjis, beagles, dachshunds, toy Eskimos, West Highland white terriers, and cairn terriers) and in cats [2,58,59]. The disease typically has a chronic course, with mild clinical signs. Dogs, but not cats, with PK deficiency frequently develop myelofibrosis and osteosclerosis, and will usually die from hemosiderosis-induced hepatic failure or bone marrow failure [2,59]. Genetic tests are available for several breeds [2,58,59]. There is no specific therapy. Packed RBC transfusions are administered as needed, but should be utilized sparingly because they contain iron and can facilitate hemosiderosis. Prednisone therapy and splenectomy are potentially beneficial in cats, but not in dogs with PK deficiency [2,59].

Phosphofructokinase (PFK) deficiency has been documented in cocker spaniels and English springer spaniels [2,59–61]. It is characterized by chronic, well-compensated hemolysis with acute bouts of hemolytic anemia associated with exertion. The hyperventilation and alkalemia that accompany exertion or stress result in accelerated hemolysis of the alkaline-fragile erythrocytes. PFK deficiency is suspected based on breed and clinical course, and confirmed via genetic testing. Prognosis is excellent with environmental modification. Acute hemolytic episodes can generally be managed supportively; transfusion is rarely required.

Erythrocyte Membrane Defects

Inherited membrane defects, described in both dogs and cats, are characterized by hemolysis of variable severity that is associated with erythrocyte osmotic fragility but not with immune-mediated RBC targeting.

Hereditary stomatocytosis has been described in standard and miniature schnauzers, Alaskan malamutes, and Drentsche patrijshounds. Stomatocytes are overhydrated, “bowl”-shaped RBCs. Hemolysis ranges from mild and well compensated in schnauzers to severe in patrijshounds; subclinical stomatocytosis is also

described [2,62]. There is no specific treatment; management focuses on palliative treatment for anemia.

Severe osmotic fragility with resultant hemolytic anemia and splenomegaly (in the absence of immune-mediated disease) has been reported in Somali, Abyssinian, and Siamese cats [2,63]. PCV determined from fresh blood is significantly higher than that of EDTA-stored blood due to progressive lysis of the osmotically fragile erythrocytes. Diagnosis is confirmed via osmotic fragility testing. Optimal treatment has yet to be determined, but corticosteroid therapy and splenectomy are reportedly beneficial [2].

Microangiopathic Hemolysis

Microangiopathic hemolysis results from the mechanical fragmentation of erythrocytes traversing vessels narrowed by intimal fibrin deposition. It is recognized by the presence of schistocytes (sheared erythrocytes) on blood smear examination (Figure 66.4). Causes include DIC, hemolytic uremic syndrome, dirofilariasis, and splenic torsion [64,65]. Typically, anemia is subclinical, but overt anemia can develop in severe cases.

Hypophosphatemia

Severe hypophosphatemia (<1.5–2.0 mg/dL) causes hemolysis via depletion of erythrocytic ATP and DPG. It is most commonly associated with refeeding syndrome, insulin therapy in patients with diabetic ketoacidosis, and excessive administration of phosphate-binding drugs [2]. Hypophosphatemia is treated by supplementation of potassium phosphate (0.03–0.06 mmol/kg/h by CRI over 4–6h) until a serum phosphorus concentration in the low-mid normal range is achieved.

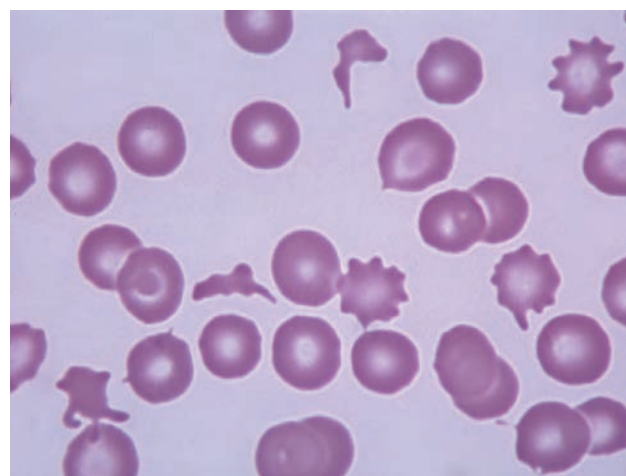


Figure 66.4 Schistocytes on a canine peripheral blood smear. Reproduced with permission of Tracy Stokel, Cornell University.

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67

Thrombocytopenia

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Platelets

The normal platelet count in dogs and cats ranges from 200 000 to 500 000/ μ L. Greyhound dogs have a lower reference range ($\sim$ 150 000/ μ L) and Cavalier King Charles spaniels can have hereditary macrothrombocytopenia with platelet counts of 25 000–100 000/ μ L and are asymptomatic for the thrombocytopenia [1].

Platelets are anuclear cell fragments produced by megakaryocytes in the bone marrow. They circulate in the bloodstream and play a vital role in hemostasis, inflammation, and cellular repair. The hormone thrombopoietin is a major regulator of platelet production. Thrombopoietin is primarily synthesized by the liver at a basal rate and the concentration in circulation is regulated by its binding and uptake by platelets. With decreasing platelet numbers, less thrombopoietin can be bound and as a result there is a greater concentration of the hormone unbound and able to stimulate megakaryocyte activity in the bone marrow [2].

The major clinical consequence of thrombocytopenia is bleeding, classically manifest as petechiae and/or ecchymoses (bruising), although life-threatening hemorrhage can occur. Petechiae and ecchymoses are due to red blood cells leaking out of blood vessels and into the tissues. Platelets have an important role in endothelial cell maintenance. Trophogens (platelet-derived growth factor, vascular endothelial growth factor, fibroblast growth factor, stem cell factor, sphingosine-1-phosphate) are released from platelets and are responsible for keeping the endothelial cell junctions tight [3]. When platelet numbers are low ($<20\,000$ – $25\,000$ / μ L), extravasation of red blood cells can occur through the normally tight endothelial cell junctions. Interestingly, this does not seem to happen with platelet dysfunction (thrombocytopathia) as long as platelet numbers remain above the threshold limit.

Petechiae tends to be a manifestation of inadequate platelet numbers, whereas ecchymoses (bruising) occurs with both thrombocytopenia and thrombocytopathia.

Endothelial tight junctions in the brain are not dependent on trophogens, which is why, in the absence of trauma, bleeding into the brain is rare even with severe thrombocytopenia [3].

Thrombocytopenia Etiology

Thrombocytopenia is due to decreased production, consumption, sequestration or increased destruction of platelets (Box 67.1) [1]. Decreased production can occur through drugs that suppress the bone marrow (chloramphenicol, chemotherapeutic agents, estrogens, and others), and from numerous other causes (inflammation, infection, neoplasia). Consumption of platelets can occur during persistent bleeding, in particular in association with other coagulation defects such as vitamin K antagonist intoxication [4]. Systemic activation of coagulation as occurs in disseminated intravascular coagulation (DIC) can also lead to consumption of platelets. Sequestration of platelets can occur with any cause of splenomegaly, neoplasia, and severe hypothermia. Sequestration usually causes a mild decrease in the platelet count.

Increased destruction of platelets is associated with immune-mediated mechanisms and can be primary (idiopathic; immune-mediated thrombocytopenia, ITP) or secondary to another cause. Idiopathic ITP is more common in female dogs, and Cocker Spaniel, Old English Sheepdogs, German Shepherds and Poodles are overrepresented [1]. Causes of secondary ITP include neoplasia, numerous drugs, toxins, infectious agents, inflammatory conditions, and possibly vaccines. Tick-borne diseases (Rocky Mountain spotted fever, ehrlichiosis, babesiosis) frequently cause thrombocytopenia along with other clinical signs. Other infectious causes such as leishmaniasis, leptospirosis, *Bartonella*, heartworm disease, anaplasmosis, and viral diseases (e.g. feline leukemia virus,

Box 67.1 Causes of thrombocytopenia.**Decreased production**

- Drugs:
 - Chloramphenicol
 - Chemotherapeutic agents
 - Estrogens
- Infection
- Inflammation
- Neoplasia

Consumption

- Disseminated intravascular coagulation
- Severe hemorrhage

Sequestration

- Splenomegaly
- Neoplasia
- Hypothermia

Increased destruction

- Primary immune-mediated disease
- Secondary immune-mediated disease:
 - Drugs
 - Toxins
 - Infections (tick-borne diseases in particular)
 - Neoplasia

Congenital

- Hereditary macrothrombocytopenia: Cavalier King Charles spaniels

feline infectious peritonitis, feline immunodeficiency virus) need to be considered. Immune-mediated thrombocytopenia is uncommon in cats.

Heparin-induced thrombocytopenia (HIT) is a well-recognized complication of heparin therapy in human patients but has not been reported in animals. Mechanisms of HIT vary and immune-mediated mechanisms are associated with thrombosis, not bleeding [5].

Clinical Signs

Clinical signs in patients with thrombocytopenia vary significantly depending on primary cause, co-morbidities, and actual platelet count. Many animals with thrombocytopenia may have no clinical signs referable to the platelet count. Spontaneous bleeding only occurs in association with severe thrombocytopenia. In human medicine, patients are considered at risk of spontaneous bleeding with platelet counts less than 10 000/ μ L and at risk of hemorrhage in association with an invasive procedure in patients with platelet counts <20 000/ μ L [6].

Bleeding can occur at higher platelet counts if there are other concurrent coagulation abnormalities present.

Bleeding associated with thrombocytopenia is most commonly manifested as petechiae, ecchymoses, and mucosal bleeding such as epistaxis, melena, hematochezia, and hematuria. Gastrointestinal hemorrhage can be severe in thrombocytopenia and was associated with decreased survival in dogs with ITP [7]. Hyphema and bleeding from venipuncture sites are also common. Bleeding into the lungs or the brain is not as common but can be rapidly fatal.

Diagnosis

As automated platelet counts are often inaccurate in the evaluation of thrombocytopenia, a manual platelet count on a blood smear should always be performed to confirm the diagnosis [8]. On a high-powered field, each platelet represents approximately 15 000/ μ L. Ten high-powered fields should be counted and averaged and the number should be multiplied by 15 000 to get an estimate of the platelet count. It is important to look at the feathered edge for clumps as these can falsely lower the count. Large platelets (macrothrombocytes) may represent increased production (regenerative response by the bone marrow). The plateletcrit estimates the packed cell volume of the platelet component and may be a more accurate marker of the platelet count [9]. Reticulated platelets signify a regenerative response but this test is only available at some centers.

Initial diagnostic tests for the thrombocytopenic patient in the emergency room will depend on the history and clinical signs. Relevant tests may include a CBC, biochemistry panel, coagulation panel (with PT, aPTT, fibrinogen, D-dimers or FDPs if DIC is suspected), tick-borne disease titers, thoracic and abdominal radiographs, abdominal ultrasound, infectious disease tests relevant to the geographic region (e.g. leptospirosis titers, *Leishmania* titers), and a free catch urinalysis (cystocentesis should not be performed on animals with low platelet counts).

Treatment

General principles of stabilization of the emergency patient apply. Underlying diseases that may be causing the thrombocytopenia should be treated as indicated. In patients with active bleeding believed to be due to thrombocytopenia, platelet transfusion is indicated. Platelet transfusion options include fresh whole blood, platelet-rich plasma (PRP), platelet concentrates (PC), and preserved/lyophilized platelet products (see Chapter 176). Platelet collection is difficult and there are numerous protocols on collection techniques without a clear consensus [10,11].

The half-life of PRP and PC is less than 5 days during optimal conditions. Due to the impractical nature (very short storage time, complicated collection techniques, sophisticated equipment, expense) of PRP and PC, these are rarely available in veterinary medicine. Cryopreserved platelets in dimethylsulfoxide (DMSO) have a much longer half-life (approximately 6 months at -20°C) but a significantly lower activity *in vivo* than fresh platelets [12]. Freeze-dried (lyophilized) platelets have a very short half-life (minutes) and may not be effective in veterinary patients [13]. Platelet transfusion reactions can occur as a result of transfusion with any of these products.

Other therapies to support hemostasis that can be of benefit in thrombocytopenia include red blood cell transfusion to maintain an adequate hematocrit, DDAVP administration and antifibrinolytic therapy (see Chapter 68).

Immunosuppression is an essential aspect of treatment of ITP. Glucocorticoids are the mainstay of initial therapy. Glucocorticoids downregulate the Fc receptors on macrophages, decrease proinflammatory cytokines (IL-1, IL-6), antibody adhesion, and T-cell function. Prednisone at 2–4 mg/kg/day divided q12h is the first line of therapy. Due to side-effects of glucocorticoids

(polyuria, polydipsia, polyphagia, panting, weight gain, muscle weakness, behavior changes), additional medications are frequently added in an attempt to enable faster weaning. Secondary immunosuppressive agents such as cyclosporine, azathioprine, and mycophenolate mofetil have also been used in the treatment of ITP.

Intravenous immunoglobulin (IVIG) is used in human children with ITP. In one study, dogs were treated with prednisone or prednisone and IVIG, with the IVIG group showing faster platelet recovery and shorter hospitalization time [14]. It is given at 0.5 g/kg IV q24h for 1–3 doses. As this is a foreign protein, patients should be closely monitored during administration and the likelihood of reactions is increased with repeat doses. Vincristine stimulates the release of platelets from megakaryocytes and impairs immune-modulated phagocytosis of opsonized platelets. A small randomized trial comparing vincristine to IVIG reported similar results with both products [15]. Vincristine is extremely toxic if extravasation occurs and careful precautions are warranted. It is given at 0.02 mg/kg IV once.

The prognosis of thrombocytopenia depends on both the severity and the underlying cause. In the absence of platelet transfusions, hemorrhage can be challenging to control.

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Fibrinolysis and Antifibrinolytics

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Introduction

Coagulation disorders are common in veterinary emergency patients and encompass abnormalities of platelet number and function and alterations in the balance between pro- and anticoagulant factors [1]. In the final stage of the hemostatic process, the fibrinolytic system is responsible for clot dissolution and the removal of fibrin from thrombi [2]. Under normal physiological conditions, the fibrinolytic system is well regulated since imbalances between fibrinolytic activity and inhibition can lead to hemorrhage or thrombotic tendency [3]. Disorders of fibrinolysis are increasingly recognized as contributors to prothrombotic [4] and coagulopathic phenotypes [5], and the fibrinolytic process has become a therapeutic target [6].

Physiology of Fibrinolysis

The fibrinolytic system is responsible for restoring vessel patency once the processes of hemostasis and wound healing have sealed the defect and restored vessel wall integrity. Plasmin, a serine protease, is the key fibrinolytic enzyme (Figure 68.1) [3,7]. Plasmin is derived from plasminogen, an inactive liver-derived protein that circulates in the plasma, through the activity of trypsin-like serine proteases named plasminogen activators (PA) [7].

There are two types of plasminogen activators: tissue-type (tPA) and urokinase-type (uPA) [3]. Plasminogen activators cleave consensus sequences in plasminogen to convert the zymogen to its active form. The principal source of tPA is the endothelium, while uPA is produced by many cells including fibroblasts, epithelia, monocytes, and the endothelium. Release of tPA by the endothelium is triggered by bradykinin, histamine, acetylcholine, alpha-adrenergic agonists, and platelet-activating factor [8]. Both tPA and uPA have short half-lives of 1–4 minutes and 8 minutes, respectively.

During clot formation, plasminogen binds to fibrin and is incorporated into the thrombus. Tissue-type PA binds fibrin at the site of clot formation and catalyzes the transformation of plasminogen to plasmin, placing the degradation enzyme adjacent to its target molecule, which enhances the rate of degradation and limits the diluting effects of blood flow. In contrast, uPA is able to activate plasminogen in the absence of fibrin. Plasmin-mediated breakdown of fibrin is indistinguishable from the breakdown of fibrinogen, unless the fibrin has been cross-linked by factor XIII. Cross-linking of fibrin slows the enzymatic breakdown of fibrin by plasmin and yields different degradation products, which has relevance for clinical diagnosis. Plasmin cleavage of fibrin generates fibrin degradation products (FDPs), a term that denotes any type of breakdown product (from fibrinogen, fibrin, or cross-linked fibrin), while D-dimers arise specifically from degradation of fibrin cross-linked by factor XIII [9,10].

Balance between plasminogen activators and protease inhibitors is essential for regulation of the fibrinolytic system [7]. Various proteins act to inhibit the activity of tPA, uPA, and plasmin. Plasmin can be inhibited by two plasma proteins, alpha-2-antiplasmin and alpha-2-macroglobulin, both of which are derived from the liver. The PAs can be inactivated by several serpin inhibitors, including plasminogen activator inhibitor-1 (PAI-1) and protease nexin [11]. Thrombin-activatable fibrinolysis inhibitor (TAFI) is also an important regulator of fibrinolysis [9,10,12]. The thrombin-thrombomodulin complex and plasmin are the two major activators of TAFI [9], which acts to inhibit fibrinolysis by eliminating carboxyl-terminal lysine residues from fibrin. This reduces the ability of plasminogen to bind fibrin, consequently reducing plasmin generation and hence limiting fibrin breakdown [9]. Significantly increased TAFI activity has been identified in dogs with bacterial sepsis [13].

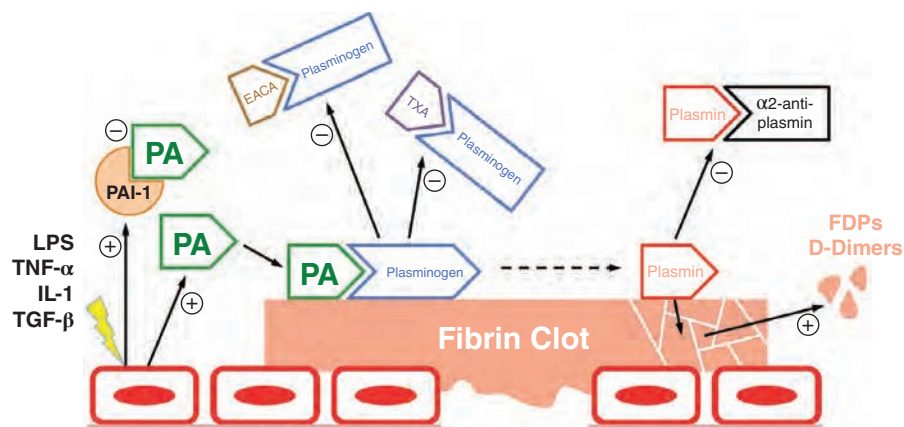


Figure 68.1 A schematic representation of the fibrinolytic system and the sites of action of endogenous and exogenous inhibitors of the fibrinolytic pathway. Plasminogen binds to fibrin. Plasminogen activator catalyzes the transformation of plasminogen to plasmin. Plasmin cleaves the fibrin thrombus and this leads to the formation of fibrin degradation products and D-dimers. Plasmin is inhibited by alpha-2-antiplasmin. Plasminogen activator (PA) is inactivated by plasminogen activator inhibitor-1 (PAI-1). The lysine analogues epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA) block the lysine binding sites for tPA on plasminogen, thus inhibiting plasmin generation.

Disorders of Fibrinolysis

From the above discussion, it follows that excessive activity of the PAs or plasmin may lead to hyperfibrinolysis and bleeding, which may also result from inadequate inhibition by PAI-1. Inadequate PA activity or excessive inhibition by TAFI and PAI-1 may contribute to thrombosis through inadequate clot breakdown. Numerous conditions have now been described in people and small animals in which disorders of fibrinolysis are proposed to contribute to their pathogenesis (Table 68.1).

Hyperfibrinolysis

Hyperfibrinolysis occurs when the activity of the fibrinolytic system exceeds the rate of fibrin formation and results from imbalances between fibrinolytic activators and inhibitors [14]. Hyperfibrinolysis reduces clot lifespan and disturbs clot integrity, increasing the risk of hemorrhage. It can also affect other aspects of hemostasis – for example, excessive plasmin activity diminishes platelet adhesion and aggregation [14].

Hyperfibrinolytic disorders can be primary or secondary. Primary hyperfibrinolysis occurs in the absence of a thrombotic state [15]. Inherited primary hyperfibrinolysis has been well described in people but is rare. Inherited hyperfibrinolytic disorders in people include alpha-2-antiplasmin deficiency, PAI-1 deficiency, increased plasma tPA concentration, factor XIII deficiency, and Quebec platelet disorder [16]. To date, no inherited fibrinolytic disorders have been reported in veterinary medicine. Primary hyperfibrinolysis can also be seen in chronic liver failure secondary to increased concentrations of tPA [17].

Table 68.1 Diseases associated with disorders of fibrinolysis in small animals.

Diseases associated with hyperfibrinolysis	Diseases associated with hypofibrinolysis
Disseminated intravascular coagulation	Disseminated intravascular coagulation
Trauma	Systemic inflammatory response syndrome/sepsis
Spontaneous hemoperitoneum	Trauma
Snake envenomation	Surgery
Liver diseases	Post cardiac arrest
Systemic inflammatory response syndrome/sepsis	Diabetes mellitus
Neoplasia	Hypothyroidism

Secondary hyperfibrinolysis is more common and describes the increased fibrinolytic activity associated with activation of coagulation [15]. Secondary hyperfibrinolysis has been reported in several disease processes. Disseminated intravascular coagulation (DIC) is the classic example of a dysregulated fibrinolytic system, associated with an imbalance between procoagulant and anticoagulant factors [18]. The acute coagulopathy of trauma-shock (ACOTS) is characterized by hypocoagulation and hyperfibrinolysis [19]. In patients with severe trauma, endothelial damage, catecholamine release, and hypoperfusion commonly ensue. Tissue injury with concomitant catecholamine release leads to endothelial thrombomodulin release. This thrombomodulin binds the available thrombin, thereby accelerating protein C activation and subsequent degradation of FV, FVIII, and

PAI-1. Hyperfibrinolysis may then result from induced tPA release without the appropriate concomitant increase in PAI-1 [8]. It is not clear if this phenomenon occurs in dogs following trauma [20–22] but recently, secondary hyperfibrinolysis has been demonstrated in dogs with spontaneous hemoperitoneum [5].

Some people with carcinoma and acute promyelocytic leukemia exhibit hyperfibrinolysis in conjunction with DIC [23], potentially through production of tPA and factors such as elastase that inactivate alpha-2-antiplasmin. Hyperfibrinolysis has been associated with snake envenomation, particularly by eastern and western diamondback snakes, whose venom contains tPA-like substances. Use of antifibrinolytic agents is not currently recommended in these patients, however, owing to the risk of DIC [24].

Hypofibrinolysis

Hypofibrinolysis may contribute to the development of thrombosis by prolonging the presence of a fibrin clot and enabling thrombus propagation. As with hyperfibrinolysis, disorders of hypofibrinolysis can be primary or secondary. Few primary hypofibrinolytic disorders are described in people and none have been identified in small animals to date. Inherited plasminogen deficiency has been described in people associated with thrombosis, but complete deficiency of plasminogen may be asymptomatic [25]. Inherited tPA deficiency has also been reported but again may be subclinical, which suggests that concurrent disease may be required to cause thrombosis in these individuals [26].

Compared with heritable forms, acquired hypofibrinolysis is more commonly associated with microvascular or macroscopic thrombosis. Acquired hypofibrinolysis may occur due to increased PAI-1 concentrations and/or decreased tPA production [27]. Endothelial PAI-1 synthesis is induced by inflammatory mediators such as LPS, TNF-alpha, TGF-beta, and IL-1. The combination of these mechanisms is the proposed cause of hypofibrinolysis in septic patients and following surgery or cardiac arrest [28–30]. Acquired hypofibrinolysis is particularly problematic in sepsis since thrombin generation is simultaneously increased [31]. The resulting propensity for thrombus formation likely contributes to the generation of microthrombi and multiple organ dysfunction syndrome [32]. Decreased TAFI activity may contribute to the thrombotic risk associated with diabetes mellitus [33] and hypothyroidism [34].

Evaluation of the Fibrinolytic System

Commonly available tests of coagulation, including the prothrombin time and activated partial thromboplastin

time, are of no value in assessing the fibrinolytic system. Although commonly available tests, such as FDPs and D-dimers, will enable clinicians to identify the downstream effects of fibrinolysis, these assays do not evaluate the balance of pro- and antifibrinolytic factors present in individual patients. As such, specific tests are required to quantify the fibrinolytic potential in individual patients. Options include individual fibrinolysis factor assays, *in vitro* clot lysis tests, and viscoelastic assays. Fibrinolytic activity is influenced by multiple factors and accurate functional assays require standardized blood collection. For certain assays (e.g. FDPs), specific blood collection tubes should be used. Consult your reference laboratory or the Cornell Comparative Coagulation laboratory (<https://ahdc.vet.cornell.edu/sects/Coag/>) for further information.

D-dimers

When cross-linked fibrin is cleaved by plasmin, neo-epitopes called D-dimers are released. Increased concentrations of D-dimers indicate that both generation of thrombin and fibrinolysis have occurred. D-dimer measurement does not allow evaluation of the balance between pro- and anti-fibrinolytic factors, however, and hence cannot identify hypo- or hyperfibrinolytic states. Numerous D-dimers assays are available, but all use antibodies directed against D-dimer neo-epitopes [35]. Increased D-dimer concentrations have been reported in people, dogs, and cats with DIC [36,37]. Increased D-dimer concentrations are sensitive for the diagnosis of DIC in dogs [37] but specificity is limited. Increased D-dimers have been reported in people with deep venous thrombosis, venous thromboembolism, cancer, and pulmonary embolism [38]. Similarly, elevated D-dimers have been identified in dogs with right-sided heart failure and ascites [39], cancer and distant metastatic diseases [40], spontaneous hemoperitoneum [5], and thromboembolic diseases [41]. Some cats with hypertrophic cardiomyopathy have increased D-dimer concentration [42].

Euglobulin Clot Lysis Time (ECLT)

The euglobulin fraction of plasma forms following cold, acetic acid precipitation and contains plasminogen, tPA, and fibrinogen. The ECLT is a simple test in which this euglobulin fraction of plasma is clotted with thrombin and then its dissolution monitored. The endpoint of the test is the time taken for lysis to occur, typically 90–240 minutes in people. This test reflects the overall fibrinolytic activity of plasma, but has largely been replaced by specific functional and immunological assays [43,44]. Thromboelastography and thromboelastometry provide equivalent information to the ECLT but are easier and

more rapidly performed and hence have largely supplanted it.

tPA Assays

Plasminogen activator antigen concentrations can be measured by ELISA. These assays are not affected by the interaction of tPA with inhibitors such as PAI-1. Functional tPA assays are also possible and are based on indirect determination through a plasmin-mediated reaction with chromogenic detection [45,46]. In these assays, plasminogen and a chromogenic plasmin substrate are added to the sample at 37°C. The degree of color change is calibrated using standard curves created using pooled plasma and is proportional to the tPA activity present. Typically the plasma is acidified to prevent interference from PAI-1. Presence of heparin or other agents that lyse plasminogen interferes with the test. In the single canine study to date, measurement of tPA activity did not perform as well as plasminogen or alpha-2-antiplasmin assays for detection of alterations in fibrinolysis after surgical trauma [46].

Plasminogen

Plasminogen can be measured by immunological assays using antiplasminogen antibodies and by functional assays that employ activation of plasminogen by urokinase or streptokinase. Plasmin activity can then be measured using a chromogenic substrate, which correlates with the concentration of plasminogen in the parent sample [47].

Plasminogen Activator Inhibitor-1

Several assays including ELISA, latex agglutination, and chromogenic assays are available to quantify or evaluate PAI-1 in people. Unfortunately, the antibodies in commercially available ELISA assays do not cross-react with dog PAI-1. Recently, a functional PAI-1 assay has been developed for dogs [48]. This two-stage assay is based on a chromogenic principle whereby a known excess quantity of tPA is incubated with patient plasma, enabling tPA/PAI-1 complexes to form. The sample is then incubated with a chromogenic plasmin substrate. The color change is proportional to the amount of residual tPA activity, which in turn is inversely proportional to the PAI-1 activity in the test sample.

Thrombin-Activatable Fibrinolysis Inhibitor

Thrombin-activatable fibrinolysis inhibitor is an important regulator of fibrinolysis, whose deficiency or dysfunction can lead to aberrant fibrinolysis and bleeding

[49]. The role of TAFI in thrombotic diseases is unclear but in one study, increased plasma concentration of TAFI was associated with venous thrombosis [27]. TAFI can be measured using ELISA methods that assess levels of the protein antigen. Two TAFI functional assays based on TAFI inhibition of tPA-induced fibrinolysis or using a specific hippuryl-arginine substrate to identify TAFI activity have been described. Analysis of TAFI activity in dogs has also been reported using a modified chromogenic assay [13].

Alpha-2-Antiplasmin

Analyses of alpha-2-antiplasmin can be performed by ELISA or by functional assays based on inhibition of plasmin. In one such assay, a known excess of plasmin is added to the sample such that all of the alpha-2-antiplasmin is consumed. The residual plasmin activity is inversely proportional to the concentration of alpha-2-antiplasmin in the original sample [45].

Viscoelastic Testing

Viscoelastic coagulation tests, such as thrombelastography (TEG), thromboelastometry (ROTEM) and the Sonoclot assay, offer graphical representations of the formation and dissolution of fibrin over time [50]. The three technologies share assay principles but are not interchangeable [51,52]. In all the assays, coagulation in blood or plasma is initiated and the interaction between the forming fibrin strands and a detector is monitored and transduced to produce characteristic tracings [53]. Modification of the standard assays through the addition of activators of both coagulation and fibrinolysis enhances their ability to interrogate the fibrinolytic system. Clot lysis *in vitro* occurs slowly, likely due to the absence of endothelial tPA, lack of activated protein C, degradation of TAFI and PAI-1, and the presence of plasma fibrinolysis inhibitors such as alpha-2-antiplasmin. In healthy cats the degree of fibrinolysis measured by TEG is 0–4% at 30 minutes and 0–9% at 60 minutes [54]. To address this, tPA-augmented modifications of the assay have been reported to accelerate fibrinolysis, allowing measureable lysis to occur within the assay timeframe [55].

The TEG 5000 system contains two channels and a limited number of proprietary assays but is easily manipulated to focus the assay on fibrinolysis [5,56]. The recently released TEG 6s system uses preloaded cartridges that provide four simultaneous assays and may reduce assay variability. However, this new system does not include a fibrinolysis assay and does not appear to be amenable to assay modification [57]. The ROTEM Delta and Gamma devices have four channels

and multiple proprietary assays designed to evaluate both the coagulation and fibrinolytic systems. The INTEM and EXTEM assays use ellagic acid and tissue factor, respectively, to evaluate the intrinsic (contact) and extrinsic pathways. In the APTTEM assay, aprotinin is used to inhibit fibrinolysis, enabling an assessment of the degree to which hyperfibrinolysis is contributing to the hemostatic disorder identified with other assays. ROTEM have also recently released the Sigma machine that, like the TEG 6s, is cartridge based but unlike the TEG system incorporates a fibrinolysis inhibition assay (APTEM). Both TEG and ROTEM assess the rate and extent of clot lysis at two standardized timepoints, 30 and 60 minutes after maximum clot strength is reached. The percentage clot strength remaining (CL30, CL60) and the percentage reduction of the maximum clot area (LY30, LY60) are the principal parameters used to identify hyperfibrinolysis, although there is currently no universally agreed viscoelastic test definition for hyperfibrinolysis.

Management of Hyperfibrinolysis

In people, inhibition of fibrinolysis is used to manage hemorrhage associated with cardiac, liver and neurosurgery, as well as patients with severe trauma or obstetric hemorrhage [58]. The serine protease inhibitor aprotinin was previously widely used in coronary artery bypass grafting (CABG) surgery in people, but was withdrawn in 2008 for safety reasons [59,60]. It was subsequently reintroduced and is currently available for prophylactic use to reduce perioperative blood loss in CABG surgery but has an FDA “blackbox warning” due to the risk of anaphylaxis. Although it has been demonstrated to reduce perioperative blood loss in a canine cardiopulmonary bypass model [61], there are no published reports on the use of aprotinin in clinical veterinary patients.

The two principal agents used for inhibition of fibrinolysis are tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA) (Table 68.2) [62]. Both TXA and EACA are lysine analogues that suppress fibrinolysis by reversibly blocking the lysine binding sites for fibrin on plasminogen, thus inhibiting fibrin degradation. In people, the potency of TXA is approximately 8–10 times greater than that of EACA [62]. In 2010, the CRASH-2 trial showed a reduction in mortality with early administration of TXA to trauma patients, without an increased risk of thrombotic events [63]. In this study, TXA was administered as a loading dose of 1 gram over 10 minutes, followed by 1 gram infused over 8 hours. However, when TXA was given more than 3 hours after injury, the risk of death due to bleeding appeared to increase,

Table 68.2 Reported dosages of antifibrinolytic agents in small animals. The dosages currently recommended by the authors are indicated in bold.

Drug	Dosage
Tranexamic acid (TXA)	10–15 mg/kg IM, SC, or slow IV followed by 1 mg/kg/h CRI for 5–8 h [67] 10 mg/kg/h over 3 h [68] 10 mg/kg IV q3–4h Or Initial loading dose of 10 mg/kg IV then 30–50 mg/kg PO q3–4h
Epsilon-aminocaproic acid (EACA)	15–40 mg/kg or 500–1000 mg IV, then 500–1000 mg PO q8h [71] 100 mg/kg IV slow followed by 10–15 mg/kg/h CRI [98] 50–100 mg/kg IV or PO q6h [99] 100 mg/kg IV or PO q6h

CRI, constant-rate infusion; IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

prompting the authors to recommend early administration [64]. TXA is also used in human surgical patients with or at risk of hemorrhage to reduce blood loss and the need for transfusion [58,65]. Use of TXA has been reported in dogs for treatment of clinical bleeding secondary to various conditions including neoplasia, immune-mediated thrombocytopenia, trauma, surgery, anticoagulant intoxication, and liver failure [66]. Data regarding the effectiveness and safety of TXA in veterinary medicine are limited, however.

Suggested dosages for TXA in dogs are 10–15 mg/kg SC, IM, or slow IV, followed by 1 mg/kg/h CRI for 5–8 hours [67]. This dosage was extrapolated from human literature, but recent studies indicate that dogs are hyperfibrinolytic compared to humans, suggesting higher dosages may be needed to inhibit fibrinolysis [56]. A recent study evaluating the use of TXA in healthy dogs showed that a dose of 10 mg/kg IV bolus followed by 10 mg/kg/h CRI over 3 hours was safe. However, this study was not able to evaluate the efficacy of TXA for inhibition of fibrinolysis. The only side-effect noticed in this study was vomiting; this was seen with higher initial dose of TXA (15–20 mg/kg) [68]. In another study, TXA was shown to induce vomiting in a dose-dependent manner in healthy beagles, but a single dose of 50 mg/kg of TXA given intravenously did produce a relatively short duration of antifibrinolysis (<24h) [69].

Epsilon-aminocaproic acid has also been used in veterinary patients, especially in greyhounds in which there is an approximately 25% rate of delayed postoperative bleeding, possibly due to enhanced fibrinolysis [70]. In

greyhounds undergoing limb amputation or gonadectomy, administration of EACA at a dose of 15–40 mg/kg IV bolus followed by 500–1000 mg PO q8h significantly decreased the incidence of bleeding [71,72].

Administration of antifibrinolytic agents to patients with prothrombotic diseases is controversial and the risks are uncertain at this time [67,73,74]. It is tempting to consider antifibrinolytic administration to patients with DIC and hyperfibrinolysis but the hyperfibrinolysis seen in DIC is a response to uncontrolled thrombin generation. In this context, antifibrinolytic agents may be detrimental and are therefore contraindicated [75]. Antifibrinolytic drugs may also be contraindicated in patients with hypercoagulable diseases such as immune-mediated hemolytic anemia, protein-losing enteropathy or nephropathy due to the risk of thromboembolic events [76].

There is limited information regarding the fibrinolytic system or the use of antifibrinolytic drugs in cats. Some experimental studies have reported adverse effects in cats administered TXA, including seizures and myocardial injury [77,78]. However, these studies described administration of this drug in ways that do not reflect its clinical use. Nonetheless, caution with the use of antifibrinolytic agents in cats is advised until more information regarding safety and efficacy is available.

Therapeutic Fibrinolysis

Thrombolysis is the administration of supraphysiological doses of plasminogen activators systemically or directly at the thrombus site to accelerate plasmin generation and induce thrombus dissolution. Several different thrombolytic drugs are available, including urokinase and the recombinant tPA products alteplase, reteplase, and tenecteplase. These thrombolytic drugs have distinct pharmacokinetics, thrombolytic activities, and fibrin specificities [79]. The tPA products are fibrin specific, activating fibrin-bound plasminogen more rapidly and more effectively than plasminogen in circulation. At pharmacological concentrations, however, a systemic lytic state can still occur and all tPA products are associated with a risk of hemorrhage [80]. Alteplase has the shortest half-life of the available recombinant thrombolytics [81], followed by reteplase and then tenecteplase, which have been modified to prolong their half-lives and alter their affinity for fibrin.

Risk stratification of patients with thrombosis underpins safe and successful thrombolysis and should be based on the location, size, and duration of thrombosis and through clinical, cardiovascular and neurological assessment and biomarker measurement. Thrombolysis is most effective early in the disease course. Decision

making is challenging and there is limited consensus on the best strategy for these patients. In some human centers, the formation of multidisciplinary clinical teams has enhanced safe and effective thrombolysis [82]. In veterinary medicine, no consensus on their administration exists and clinicians must determine the potential benefits and risks of administration for individual patients [83]. Recent advances in small animal interventional radiology may provide novel methods or routes for thrombolysis in the future [84].

For humans with PTE and an increased risk of bleeding, catheter-directed thrombolysis is preferred. However, in order to be effective, the local thrombolysis catheter must be placed within or beside the thrombus, since placement immediately proximal to the thrombus is likely to be no more effective than systemic thrombolysis [85]. If a patient with suspected or known PTE should suffer cardiopulmonary arrest (CPA), aggressive cardiopulmonary resuscitation (CPR) and administration of thrombolytic agents during the CPR efforts should be considered. In human patients, the typical CPR dose of alteplase is 50 mg (~0.6 mg/kg) [86].

Veterinary experience with thrombolytics is limited and is predominantly in the field of feline arterial thromboembolism (ATE) [87,88]. In feline ATE, thrombolysis has been associated with a high rate of complications, including hemorrhage and reperfusion injury, and is not currently recommended [89]. Alteplase has been successfully used in a dog with ATE [90], and experimentally induced canine PTE has been treated with tPA therapy [91,92]. Alteplase has also been effectively used in cases of device-associated thrombosis in cardiology and dialysis settings [93–95].

In appropriate cases, fibrin-specific drugs with short half-lives like alteplase are preferred [83], using the lowest effective dosage to optimize the risk–benefit ratio. Evidence from people with PTE suggests that low-dose tPA may be effective and safe [96]. One potential strategy for PTE is to administer half the maximum dose, that is, 0.2–0.5 mg/kg IV, over the first 30–60 minutes followed by a planned reassessment at the 1-hour mark. If the patient appears to be more hemodynamically stable, the full dose may not be necessary. If there appears to be limited response, administration of the second half-dose over the next 30–60 minutes is reasonable. This planned reassessment approach may ultimately reduce the dose administered on average, which may reduce bleeding complications, the risks of which are likely dose related. Reported protocols in small animals include locally infused tPA at 0.2 mg/kg [93], a locally infused CRI of 0.03 mg/kg/h (maximum 1 mg/kg) [94], and systemic administration of 0.2 mg/kg IV bolus, then 0.7 mg/kg IV over 30 minutes, then 0.5 mg/kg IV over 1 hour (total 1.4 mg/kg over 90 min) [97].

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Congenital Coagulopathy

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Introduction

Inherited coagulopathies are occasionally seen in dogs and rarely seen in cats. From an emergency point of view, the two major areas are, first, animals presenting with bleeding signs which may be consistent with an inherited coagulopathy and second, animals with a known inherited coagulopathy that have another disease that requires urgent management. The goal of this chapter is to provide an overview of the approach to both scenarios.

Inherited coagulopathies reflect deficiencies in clotting factor concentration or activity, or platelet function. Additionally, alterations in fibrinolysis may also result in rebleeding or excessive bruising. The emergency clinician should be especially concerned about coagulopathy in Doberman pinschers and greyhounds undergoing surgical procedures.

Dogs

Pure-bred dogs are more commonly identified with inherited coagulopathies, with von Willebrand's disease (vWD) being the most common deficiency detected, with hemophilias a distant second [1,2]. Hemophilias are X-linked bleeding defects characterized by deficiency of the clotting activity of factor VIII or IX [3–5]. Factor VIII deficiency, or hemophilia A, is far more common than factor IX deficiency (hemophilia B) although the two are clinically indistinguishable without factor analysis. Factor VII deficiency has also been described in dogs, and in an ER setting is most commonly associated with misidentification as anticoagulant rodenticide toxicity [6]. Factor XI deficiency has been reported in Kerry blue terriers, and was associated with operative bleeding [7].

A number of platelet function defects separate from vWD have also been reported, including Scott syndrome (German shepherds), Glanzmann's thrombasthenia

(otterhounds and Great Pyrenees), and P2Y₁₂ receptor gene mutation (Great Swiss Mountain dogs) [8–11]. Greyhounds have been recognized to have delayed post-surgical bleeding due to altered fibrinolysis, which may be mitigated with aminocaproic acid [12].

Cats

Cats are less commonly appreciated with inherited coagulopathies but they certainly occur as well. Devon rex cats have been found to have a vitamin K-responsive coagulopathy associated with a defective vitamin K-dependent carboxylase [13]. A clowder of British short-hair cats was shown to have hemophilia B, and factor XI deficiency was found in a domestic short-hair cat [14,15]. Finally, a cat with severe vWD was identified after multiple bouts of epistaxis [16].

A common inherited defect in cats is factor XII deficiency (Hageman trait), which is associated with prolongation of the aPTT but no clinical signs of hemorrhage. It is an important defect to be aware of as failure to recognize it may result in an overzealous evaluation for disseminated intravascular coagulation or other systemic disease.

Animals Presenting with Unexplained Hemorrhage

Unexplained hemorrhage is most often acquired coagulopathy (see Chapter 70), with anticoagulant rodenticide, immune-mediated thrombocytopenia, liver failure, heat stroke, and disseminated intravascular coagulation being commonly observed. Inherited coagulopathy usually presents in young animals although there is one report of hypothyroidism unmasking vWD in a Shetland sheepdog [17].

From an emergency perspective, hemophilia typically presents with bleeding from a small wound,

subcutaneous hematomas or bleeding following the loss of deciduous teeth. Platelet defects present with mucosal or surface bleeding. More subtle defects will more commonly present to primary care veterinarians or internists for evaluation rather than on an emergency basis. More common acquired causes should be excluded by routine coagulation testing (PT, aPTT, platelet count) before specialized testing. Some hemophiliacs will have moderately prolonged aPTT but in other cases, the results will simply be the upper limit of normal. Dogs with vWD will have a normal platelet count.

If a coagulopathy is suspected or confirmed, transfusion to correct the deficiency is warranted. A citrated plasma sample should be collected *before* transfusion for analysis of factors and vWF as clinically warranted. For animals with inherited disease, the prognosis depends on the extent of the defect and individual animal characteristics [4]. Clinicians should refine from prognosticating until the extent of the defect is appreciated, and even then with caution. Clinicians are encouraged to consult with specialized centers for more advice regarding diagnosis and treatment of coagulopathy. The Cornell Coagulation Laboratory and the University of Pennsylvania Genetics laboratory are particularly useful resources. For platelet disorders, Auburn University is an additional resource. Platelet defects often require that the patient be on site for testing as platelet function testing is not amenable to shipping.

Animals with Known Inherited Defects

Animals with known defects may present to the emergency service for treatment of other conditions, such as foreign bodies in Dobermans. Animals with inherited diseases may require treatment of coagulopathy in addition to whatever other disease or injury they may have. Owners of hemophilic dogs in particular tend to be very astute and may be far more familiar with treatment of hemophilic than some clinicians. Women with hemophilic sons similarly express frustration with human healthcare providers who appear unfamiliar with hemophilia [18]. Hemophilic dogs should be assumed to be bleeding; correction of factor defects should be prompt and complete, even if an apparent site of bleeding is not present. Hemophilic dogs will bleed in many places, including into the wall of the GI tract, chest cavity, and retroperitoneum, in addition to the more traditional joints and subcutaneous tissues. Dogs with vWD may have less obvious hemorrhage unless stressed by surgery or other invasive procedures.

In dobermans, the presence of cropped ears and docked tails without evidence of bleeding is not adequate to exclude vWD. Policies for the standard approach to common defects are helpful; one example is shown in Box 69.1.

Box 69.1 Protocol for Doberman pinschers with potential vWD used at one hospital with the ability to run vWF in-house. In ER cases, it may be hard to determine the result in a timely fashion.

SOP Checklist for Dobermans Requiring Surgery

Descriptions and details for each step are provided over.

1. Run vWF activity
2. Faculty members (surgery, ECC and anesthesia) to evaluate vWF results
3. Record vWF activity on this checklist
If vWF >50% no prophylactic therapy required.
STOP checklist
4. If vWF activity <50%, diagnose vWD requiring prophylactic and proactive management (continue with checklist)
5. Prepare owner for special considerations of vWD:
Increased cost of prophylactic therapy
Risk of transfusion reaction (low)
Risk of bleeding despite prophylactic therapy – and hence need for additional blood products (and increased cost)
Risk of death from perioperative bleeding despite aggressive therapy
Ensure that this discussion is logged in the client comm log
6. Prepare for potential blood transfusion needs
Blood type dog
Speak to blood bank technician
Ensure adequate stores of cryoprecipitate
Ensure adequate stores of type-specific blood
Ensure adequate back-up FFP
7. In the hours prior to surgery:
Give DDAVP (see instructions and complete dose form over)
Give cryoprecipitate (see instructions and complete dose form over)
ERR ON THE SIDE OF CAUTION WITH CRYO DOSE
Repeat vWF activity just prior to surgery
8. Anesthesia faculty member to ensure that this checklist is complete prior to anesthesia induction
IF FORM COMPLETE PROCEED TO SURGERY
9. If bleeding (confirmed or suspected) occurs at any time, repeat DDAVP and a full dose of cryoprecipitate as quickly as possible (as above)
10. Return dog to ICU post-op. All vWD will recover in ICU overnight.
Monitoring:
TPR at least every 4 hours, and
PCV/TS/Lactate post-op and q 6 hours (×3)
11. ECC and surgery faculty to regroup on first day post-op to assess patient status and approve dog moving to step-down ward

Factor transfusions are widely employed in people but are not currently available in dogs or cats. Human products, similar to albumin, are highly immunogenic in dogs and cats and should not be used. Due to a small market size, it is very unlikely that species-specific individual factor commercial products will be available.

For hemophilia A, gene therapy has long been considered to provide the greatest potential for improving quality of life and limiting clinical signs in affected animals. It is not commercially available, although a recent report documented the beneficial effects of gene transfer on two pet dogs with hemophilia; however, it is unclear when this option might exist routinely for dogs or even for people [19].

Specific therapies for recommended inherited diseases include DDAVP, vitamin K and blood transfusions (also shown in Box 69.2).

Von Willebrand's Disease

Desmopressin (DDAVP) can be useful in the treatment of vWD to prevent or control hemorrhage associated with surgery. DDAVP results in the release of stored vWF from the endothelium. There is a preferential increase in the larger, more hemostatically active multimers with DDAVP treatment. DDAVP onset of action is about 30 minutes and its duration of action is about 2 hours. The intranasal product may be used subcutaneously at a dose of 1–4 µg/kg 1 hour before surgery [20]. Cryoprecipitate (cryo), fresh frozen plasma (FFP), and fresh whole blood (FWB) are all effective. Cryoprecipitate is preferred due to smaller volume, but if bleeding is present with associated blood loss, FFP or FWB are equally effective. It is wise to recall that one unit of FWB is used to make one unit of FFP, which is then used for one unit of cryo; the advantage of cryo is smaller volume, not a more effective product.

Hemophilia A

Cryoprecipitate, FFP, and FWB are all effective. In people, specific factor products are widely used but these are not available in veterinary medicine. Hemophilics will bleed spontaneously and for most severely affected dogs, frequent transfusions are the norm. In dogs with

Box 69.2 Guidelines for dogs with suspected or documented inherited disease.

Von Willebrand's disease

DDAVP 1–4 µg/kg SC 30 minutes before procedure.

Cryoprecipitate 1 unit/10 kg IV

FFP 1 unit/10 kg IV

FWB 1 unit/15 kg IV or as indicated by hematocrit, volume of blood loss and perfusion parameters

Hemophilia A

Cryoprecipitate 1 unit/10 kg IV until bleeding stops; a large volume may be required

FFP 1 unit/10 kg IV

FWB 1 unit/15 kg IV or as indicated by hematocrit, volume of blood loss and perfusion parameters

Hemophilia B

Cryo-poor plasma 1 unit/10 kg IV until bleeding stops

FFP 1 unit/10 kg IV

FWB 1 unit/15 kg IV or as indicated by hematocrit, volume of blood loss and perfusion parameters

Platelet defects

Platelet concentrate 1 unit/10 kg IV

Platelet-rich plasma 1 unit/10 kg IV

FWB 1 unit/15 kg IV or as indicated by hematocrit, volume of blood loss and perfusion parameters

DDAVP, desmopressin; FFP, fresh frozen plasma; FWB, fresh whole blood; IV, intravenous; SC, subcutaneous.

very low activity, it is possible for them to develop inhibitors of FVIII, which can be very hard to overcome with transfusions [21].

Hemophilia B

Cryo-poor plasma, FFP, and FWB are all effective [22].

Conclusion

While uncommon, inherited defects are occasionally seen in the emergency room. Clinicians should be comfortable identifying and treating affected pets. An adequately stocked blood bank is mandatory for success in treating these patients.

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70

Acquired Coagulopathy

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General Approach

A systematic physical examination and detailed history are crucial in establishing differential diagnoses as many underlying conditions associated with acquired coagulopathy (AC) produce similar clinical signs and laboratory results. For instance, minor bleeding such as petechia and ecchymosis can be due to either DIC or liver failure. When time and patient condition permit, a detailed history should be taken to identify any co-morbid conditions. Drug history should be acquired, including current medications, prophylactic anthelmintics, vaccinations, and potential exposure to anticoagulants and toxins. For animals receiving anticoagulants, the dose and time of the most recent drug administration should then be documented. This information is particularly important in patients receiving injectable anticoagulants since dosing error can lead to overdose.

The first principle of management is the recognition and treatment of life-threatening conditions such as shock, intracranial hypertension, and respiratory distress. Hemorrhages in the eyes, joints, lungs, and brain manifest as clinical signs related to the respective body systems. Intrapulmonary and cerebral hemorrhages can rapidly progress with life-threatening consequences if they are not promptly identified and reversed. Figure 70.1 outlines the basic principles of emergency management of AC. Most AC can be identified by point-of-care coagulation tests such as prothrombin time (PT), activated partial prothromboplastin time (aPTT), activated clotting time (ACT), fibrinogen, D-dimer, and complete blood count with examination of a blood smear.

Although evidence pertaining to hemostatic resuscitation with blood products is lacking in veterinary medicine, they should not be administered merely to correct laboratory abnormalities. Instead, such decisions should be made based on clinical presentation, underlying disorders, and risk factors for bleeding. According

to the Society of Thoracic Surgeons guideline, major risk factors for bleeding include age, anemia, chronic co-morbidities (chronic renal failure, liver disease), and dual antiplatelet therapy [1]. Similar risk factors may also exist in dogs and cats.

Anticoagulant-Associated Coagulopathy

Anticoagulant rodenticide intoxication is the most frequently seen and treated anticoagulant-associated coagulopathy in small animals. Diagnosis and treatment of anticoagulant rodenticide toxicity are detailed in Chapter 130.

Heparins

Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are commonly used in hypercoagulable animals. However, evidence supporting the efficacy of anticoagulants in veterinary patients is limited (see Chapter 71). Optimal dosing of heparin requires hemostatic monitoring such as anti-Xa activity in order to achieve and sustain therapeutic anticoagulation. Due to the limited availability of these assays in veterinary practice, UFH or LMWH is often administered empirically in dogs and cats. Since their doses are based on pharmacokinetic data derived from healthy animals, standard doses may have unpredictable effects in hypercoagulable animals.

Low molecular weight heparin such as dalteparin and enoxaparin is considered superior to UFH due to its predictable dose response and longer duration of action. In two separate clinical studies examining the use of dalteparin and enoxaparin in dogs, the prevalence of bleeding complications was about 9% [2,3]. The most common complication was subcutaneous hemorrhage associated with injection sites. One dog that received

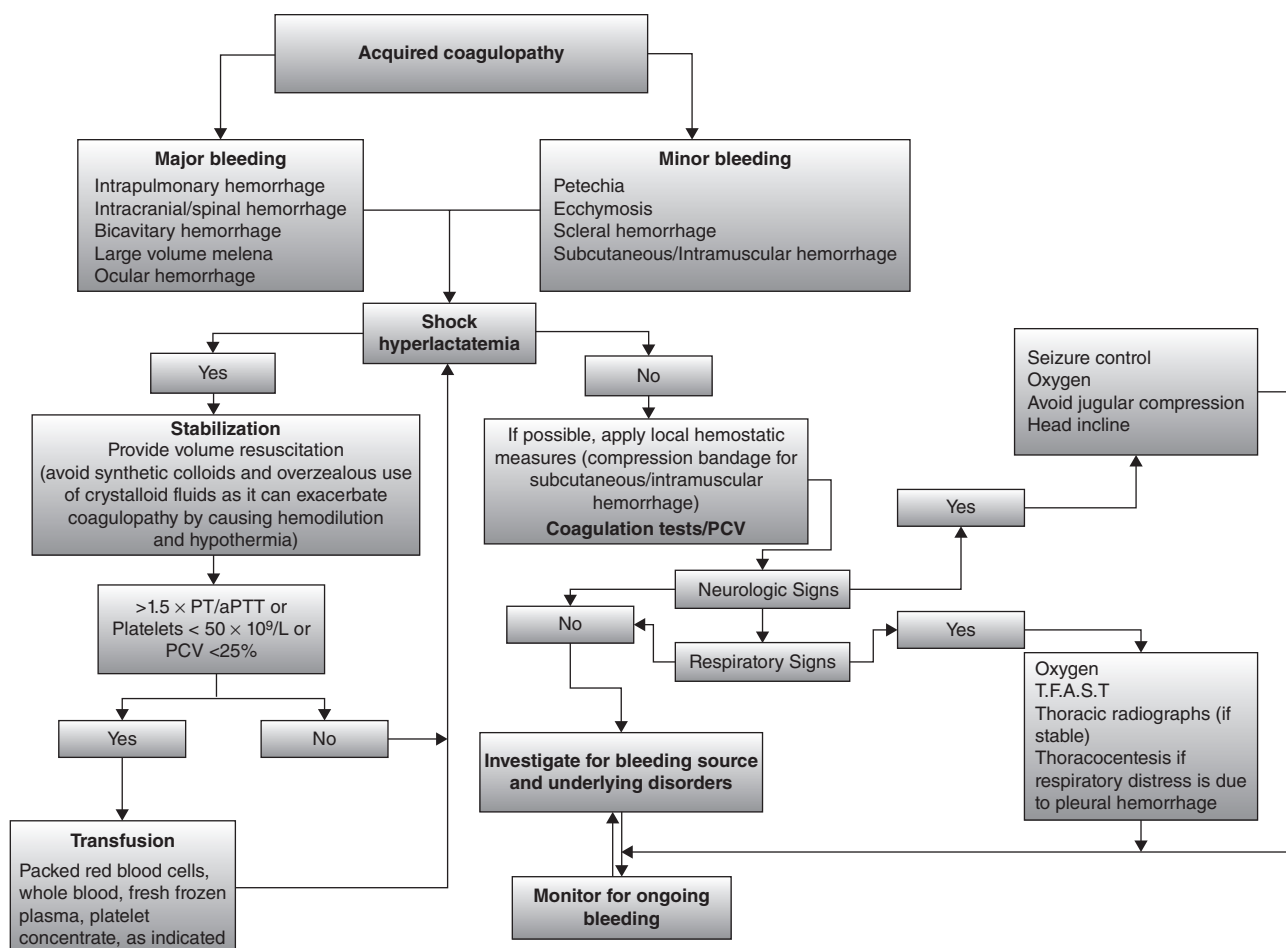


Figure 70.1 Basic principles of emergency management of acquired coagulopathy. aPTT, activated partial thromboplastin time; PCV, packed cell volume; PT, prothrombin time; tFAST, thoracic-focused assessment with sonography for trauma.

10 times the recommended dose of dalteparin was reported to have significant cutaneous bleeding and hemoperitoneum [2]. Cats, in general, absorb and eliminate LMWH more rapidly than dogs [4,5]. A retrospective study in cats receiving dalteparin reported a complication rate of 8.5%. Complications included ecchymosis, hematuria, and gingival bleeding [6].

Antiplatelet Drugs

Platelet inhibition by aspirin and clopidogrel, which are commonly used in dogs and cats, is irreversible. Inhibited platelets are gradually replaced by new platelets via thrombopoiesis. In general, bleeding due to platelet inhibition is rare but their adverse effects are dose dependent. In one retrospective study, high-dose aspirin (≥ 40 mg PO q24–72h) was associated with hematemesis, anorexia, and vomiting in cats. None of the cats on low-dose aspirin (5 mg per cat q72h) exhibited any signs of hemorrhage [7]. In another study, the

use of ultra-low-dose aspirin (ULDA) (0.5 mg/kg PO q12–24h) in dogs with immune-mediated hemolytic anemia (IMHA) did not lead to any bleeding complications [8]. In human medicine, combination therapy of aspirin and clopidogrel is associated with increased risk of bleeding. However, this was not the case in a study of IMHA dogs that received a combination with ULDA and clopidogrel [9]. No bleeding complications associated with clopidogrel therapy have been reported in cats [10,11].

Novel Oral Anticoagulants

The US Food and Drug Administration have approved three novel oral anticoagulants (NOACs): rivaroxaban, dabigatran, and apixaban. NOACs do not require frequent monitoring, dose adjustments, or dietary restrictions, making them favorable replacements for warfarin. With the increased availability of NOACs, pets may have increased exposure to these drugs.

General Management

The American Society of Hematology and the American Society for Chest Physicians created guidelines to assist physicians in managing anticoagulant-associated bleeding. The general principles of management are based on a six-step algorithm (HASHTI) that facilitates prompt recognition, reversal, and patient stabilization (Figure 70.2). For patients requiring invasive procedures or surgeries, please refer to Figure 70.2. The mechanisms of action, pharmacokinetics, and specific antidotes are summarized in Table 70.1.

Specific Management

Heparin

Since most bleeding complications associated with UFH/LMWH are minor, discontinuation of drug administration should be sufficient to reverse coagulopathy.

Patients should then be monitored for ongoing bleeding. Severe hemorrhage due to UFH should be reversed with protamine, which binds to heparin to form a biologically inactive complex. The reversal by protamine should take place in 5–15 minutes, and can be monitored via activated partial thromboplastin time (aPTT) and activated clotting time (ACT). Unlike UFH, the anticoagulant effect of LMWH is longer than UFH and cannot be fully reversed by protamine. LMWH reversal by protamine is also difficult to monitor without anti-factor Xa assays. Whole-blood viscoelastic hemostatic assays such as thromboelastography (TEG) may be helpful in assessing heparin reversal by protamine [12,13].

Rapid intravenous administration of protamine can lead to histamine release and anaphylactic reaction. Hemodynamic alterations such as systemic hypotension and pulmonary arterial hypertension were reported in a canine experimental study [14]. Adverse reactions were minimized when protamine was administered via

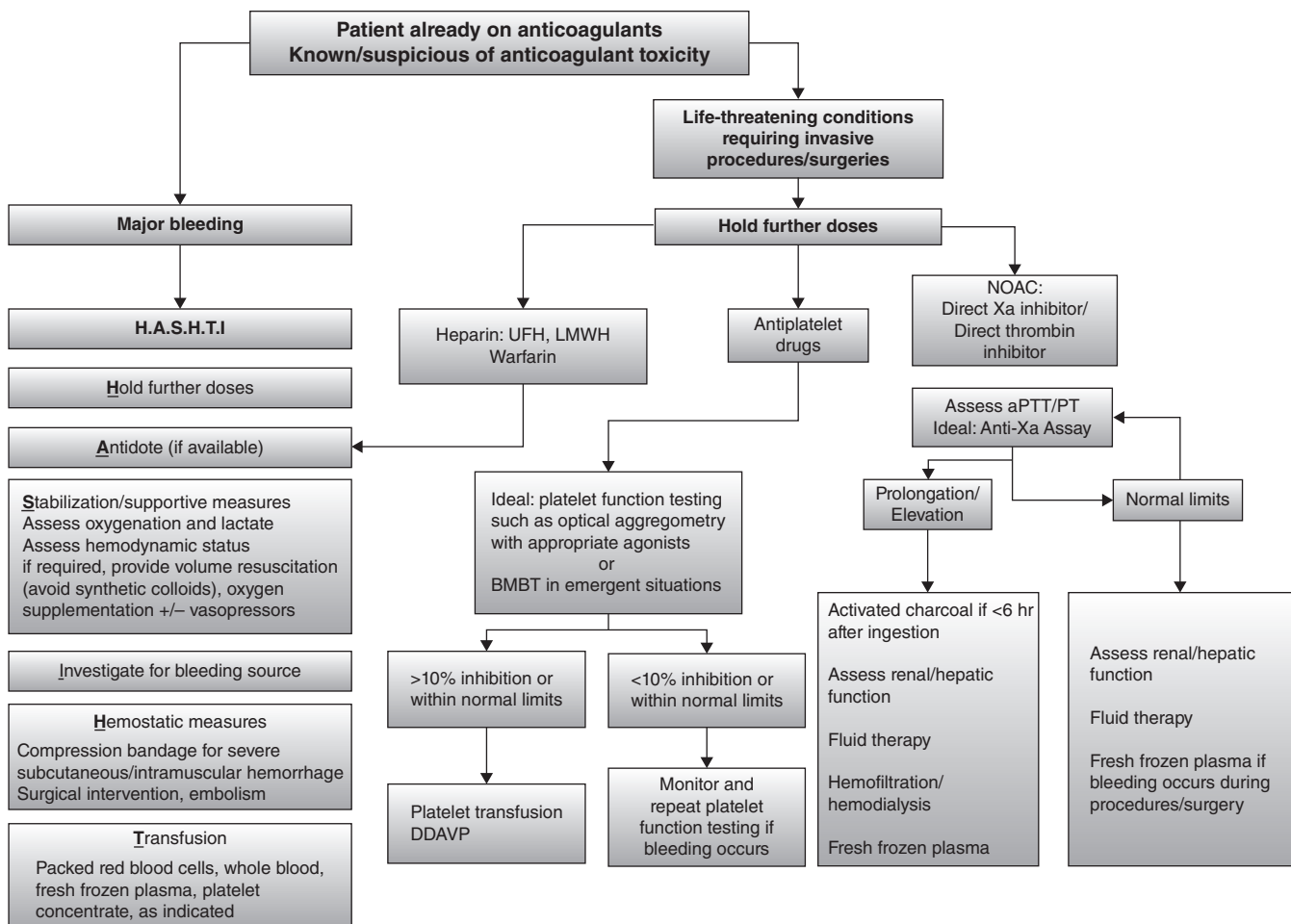


Figure 70.2 Algorithmic approach to patients with anticoagulant-associated coagulopathy. aPTT, activated partial thromboplastin time; BMBT, buccal mucosal bleeding time; LMWH, low molecular weight heparin; NOAC, novel oral anticoagulants; PT, prothrombin time; UFH, unfractionated heparin.

Table 70.1 Common anticoagulants, mechanisms of action, and therapies in dogs and cats.

	Mechanism of action	Half-life	Therapy/antidote
Antiplatelets			
Aspirin	Irreversible inhibition of cyclo-oxygenase and conversion of arachidonic acid to thromboxane A ₂	37.5h in cats 8.5h in dogs (irreversible platelet inhibition)	Desmopressin (DDAVP) in patients requiring invasive procedures/surgeries Consider platelet transfusion (platelet concentrate) and DDAVP and in actively bleeding patients
Thienopyridines (clopidogrel)	Irreversible blockade of ADP purinergic receptor, P2Y ₁₂ , thus inhibition of cell signaling for platelet secretion, shape change and integrin activation	Unknown in cats (low dose 18.75 mg PO – antiplatelet effect returned to normal in 14 days) [10]	No bleeding complications reported in the literature Consider DDAVP in patients requiring invasive procedures/surgeries Consider platelet transfusion and DDAVP in actively bleeding patients
Heparins			
Unfractionated heparin	Binds with and potentiates the activity of antithrombin III and inhibits factors IIa, IXa, Xa, XIa, and XIIa	Dogs: 20–40 min (IV)* 3.5 +/- 2.5h (SC)* Cats: Unknown but 250 IU/kg SC maintained anti-Xa activity at 4 h after treatment	Protamine (1–1.5 mg) per 80–100 units of unfractionated heparin. Decrease dose by 50% if drug was administered more than 30 min ago. Max dose: 50 mg Repeat dose in 1 h if aPTT is prolonged or subcutaneous dose of heparin given
Low molecular weight heparin (dalteparin, enoxaparin)	Exerts anticoagulant effects by primarily binding to FXa	SC injection: Cats: Dalteparin – ~2h [5] ⁵ Enoxaparin ~2.5h [4] Dogs: *Dalteparin 1.3–3h *Enoxaparin unknown	Protamine reverses its effect partially. 1 mg per 100 units of anti-factor Xa units (~1 mg enoxaparin) Consider FFP if hemorrhage does not resolve
Novel oral anticoagulants			
Rivaroxaban	Direct Xa inhibition	Dogs: Rivaroxaban 1h [17], apixaban 5.6h [16]	No specific antidote
Apixaban			Activated charcoal up to 6h after ingestion
Edoxaban		Unknown in cats	FFP +/- therapeutic plasma exchange
Dabigatran	Direct activation by plasma and hepatic esterases causing direct inhibition of free and fibrin-bound thrombin causing decreased platelet activation/aggregation, and amplification of FV, VIII, XI, XIII	Unknown	No specific antidote FFP +/- hemodialysis or continuous renal replacement therapy

*Dose-dependent.

aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; IU, international unit; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

the cephalic vein at a slow rate (5 mg/min). Protamine should also be used with caution in thrombocytopenic patients [15].

Severe hemorrhage due to enoxaparin overdose has been effectively reversed by fresh frozen plasma [2]. Other measures to reverse heparin such as extracorporeal heparin removal, heparinase and platelet factor-4, have not been evaluated in veterinary medicine.

Novel Oral Anticoagulants

Because no specific antidote exists for NOACs, managing a bleeding event due to these agents can be challenging. Apaxiban undergoes extensive enterohepatic recirculation in dogs. Activated charcoal is therefore effective at reducing peak plasma concentration and intestinal excretion at 2–4 hours after ingestion [16]. Activated charcoal may also be an effective therapy in dogs with rivaroxaban toxicity. Dabigatran, a direct thrombin inhibitor, is predominantly excreted by the kidney following hepatic activation in humans. Dabigatran is low protein binding and hence can be removed by hemodialysis.

Antiplatelet Drugs

In general, bleeding complications may occur in patients concurrently receiving heparin or dual antiplatelet therapy. There is no evidence in veterinary medicine that either supports or refutes perioperative discontinuation of antiplatelet agents. However, because most antiplatelet agents used in veterinary medicine are irreversible, discontinuation of these drugs has little impact on reducing perioperative bleeding in an emergency setting (see Figure 70.2). Clinicians should therefore evaluate the risk factors for bleeding in each individual patient before administering reversals and/or transfusions.

Disseminated Intravascular Coagulation

In veterinary medicine, DIC is a recognized syndrome that is associated with a number of underlying disorders (Table 70.2). DIC was traditionally classified as non-overt (early-stage) and overt (late-stage). Non-overt DIC is a compensated dysfunction of the hemostatic system. Overt DIC occurs when extensive intravascular thrombosis overwhelms the anticoagulant pathways, resulting in consumptive and decompensated coagulopathy [18,19]. In recent years, these definitions of DIC have been challenged as our understanding of DIC evolves. DIC can thus be further classified based on the activation of fibrinolysis: enhanced-fibrinolytic type and suppressed-fibrinolytic type DIC [20].

Table 70.2 Reported disorders associated with disseminated intravascular coagulation in dogs (D) and cats (C).

	Species
Infectious/inflammatory disorders	
Sepsis	D/C
Heat stroke	D
Babesiosis	D
Cytauzoonosis	C
Toxoplasmosis	C
Feline infectious peritonitis	C
Feline panleukopenia virus	C
Feline leukaemia virus	C
IMHA (primary/secondary)	D/C
IMTP	D
Pyelonephritis	C
Pyometra	D
Pancreatitis	D/C
Meningitis	D
Pneumonia	D
Polytrauma	D/C
Gastrointestinal disorders	
Gastric dilation volvulus	D
Hemorrhagic gastroenteritis	D
Hepatic disorders	
Acute liver failure	D/C
Cholangiohepatitis	C
Malignancy	D/C
Severe toxicosis or adverse reactions	
Snake bites	D
Diazepam	C
Metaldehyde	D
Methamphetamine	D
Acute hemolytic transfusion reactions	D/C
Urinary disorders	
Uroabdomen	C
Renal medullary amyloidosis	C

IMHA, immune mediated-hemolytic anemia; IMTP, immune-mediated thrombocytopenia.

Pathogenesis

Regardless of the underlying disorders, the cross-talk between inflammation and coagulation results in a vicious cycle [21]. Recognition of pathogen- or danger-associated molecular patterns such as

lipopolysaccharides, nucleic acids and high mobility group box 1 by pattern recognition receptors (toll-like receptors, nod-like receptors) initiates intracellular signaling that promotes the production of inflammatory cytokines [22]. Cytokines in turn upregulate tissue factor (TF) expression by monocytes and vascular endothelium, causing activation of coagulation. Thrombin and activated factor X, in turn, promote inflammation via protease-activated receptors (PARs) [23]. Thrombin-induced platelet activation not only generates additional thrombin, but also promotes platelet–leukocyte interaction. Binding of platelet P-selectin to P-selectin glycoprotein ligand-1 (PSGL-1) on monocytes and neutrophils further upregulates TF expression and generation of thrombin [24].

Activation of coagulation is countered by anticoagulant pathways such as tissue factor pathway inhibitor (TFPI), antithrombin (AT), and protein C (PC), which are decreased during DIC due to excessive consumption [25]. As a result of ongoing activation of the coagulation system, subsequent exhaustion of platelets and coagulation proteins may ultimately lead to consumptive coagulopathy.

Advanced DIC usually presents as hemorrhage or multiple organ failure. Whether hemorrhage or thrombosis occurs is highly dependent on the underlying disorders. The suppressed-fibrinolytic type DIC occurs most commonly in sepsis. Fibrinolysis is inhibited while widespread fibrin deposition leads to microvascular thrombosis and, ultimately, multiple organ failure and death [26]. This type of DIC was first characterized in a murine septic model that demonstrated increased activity of plasminogen activator inhibitor-1 (PAI-1), a serine protease inhibitor that suppresses tissue and urokinase plasminogen activators (tPA and uPA), in the vascular endothelium and organs [27]. Subsequent studies in human septic patients demonstrated that low fibrinolytic activity is associated with microvascular thrombosis and multiple organ failure [8,28].

Enhanced-fibrinolytic type DIC is associated with enhanced thrombosis and augmented fibrinolytic activity resulting in hemorrhage [20]. In humans, enhanced-fibrinolytic type DIC is associated with neoplasia such as acute promyelocytic leukemia, metastatic prostate cancer, and hemangioma [29,30]. Augmented fibrinolysis was reported in a dog with concurrent hemangiosarcoma and DIC, suggesting that this type of DIC also may occur in dogs [31].

Diagnosis

The diagnosis of DIC warrants a multidisciplinary approach in identifying coagulation abnormalities and clinical conditions consistent with DIC. In general,

diagnosis relies on recognition of predisposing conditions, activation of coagulation, consumption of coagulation proteins, activation and inhibition of fibrinolysis and organ dysfunction. In human medicine, the most referenced scoring scheme is the DIC score developed by the International Society of Thrombosis and Hemostasis (ISTH) [18]. The ISTH scoring system is specific at identifying the bleeding type or enhanced-fibrinolytic type DIC. Newer coagulation markers such as PAI-1 and plasmin-alpha-2 plasmin inhibitor complex (PIC), a fibrinolysis activation marker, are currently being evaluated.

In veterinary emergency medicine, the biggest challenge in diagnosing DIC is the availability of precise and accurate POC coagulation tests. For instance, soluble fibrin and AT assays are not readily available in most veterinary emergency rooms. Because the diagnostic criteria proposed by a number of studies were largely dependent on the coagulation assays that were available to the respective institutions, it is difficult to establish a scoring scheme that is universally applicable. Hence there is no consensus on the diagnostic criteria for DIC. To date, the most robust scoring system for the diagnosis of DIC in dogs is that proposed by Wiinberg et al. [32]. This model was validated to have a diagnostic sensitivity and specificity of 83.3% and 77.3%, respectively. Because standardized coagulation assays are lacking in veterinary medicine, this scoring scheme may not be relevant across institutions.

Suggested diagnostic criteria for DIC include the following [33–36].

- Underlying disorder(s) known to be associated with DIC
- Prolongation in PT or APTT (>25% to 50%)
- Thrombocytopenia
- Decreased fibrinogen concentrations
- Evidence of red cell fragmentation (schistocytes, acanthocytes)
- Increased in fibrin degradation products (FDP), D-dimers

Treatment

The cornerstone of DIC treatment is prompt identification and vigorous treatment of the underlying disorders. In some cases, DIC resolves following reversal of the underlying disorders [19]. However, patients with signs of hemorrhage or at risk of bleeding may require blood component therapies that aim at correcting coagulation abnormalities (see Chapter 176). Several human DIC guidelines recommend transfusion of platelets in actively bleeding patients with a platelet count of $<50 \times 10^9/L$ or $<20 \times 10^9/L$ in those with high

risk of bleeding [19]. Since fresh platelet products are not readily available in most veterinary emergency rooms, fresh whole blood (FWB) is a practical option to provide platelets in actively bleeding DIC animals. The additional advantage of FWB is the replacement of red blood cells, coagulation factors, and anticoagulant proteins that are depleted during DIC.

The use of fresh frozen plasma (FFP) in DIC patients is controversial. The decision to administer FFP based on abnormal coagulation tests is no longer recommended. A meta-analysis showed no benefit of prophylactic or therapeutic use of FFP in humans with a number of clinical conditions, including DIC [37,38]. In human medicine, FFP administration is recommended in actively bleeding patients with either $>1.5\times$ prolonged PT/APTT or decreased fibrinogen (<1.5 g/dL). FFP is also recommended in humans requiring invasive procedures with similar laboratory abnormalities [19]. In veterinary medicine, there is also little evidence supporting the use of FFP in critically ill patients [39]. A retrospective study found that FFP significantly decreased PT and aPTT but was not associated with outcome [40]. Clinicians should tailor their therapies based on the requirements of the individual animal and availability of blood products. For more details in transfusion, see Chapter 176.

Since DIC is initiated by extensive activation of coagulation, anticoagulants such as UFH or LMWH theoretically would be beneficial. Despite promising experimental results, heparin therapy in human DIC patients remains controversial as there is no randomized clinical trial that demonstrates the efficacy of heparin therapy for improving clinical outcome in DIC patients. Other anticoagulants such as activated protein C, AT, and TFPI all failed to demonstrate reductions in mortality in major randomized clinical trials in people.

Acute Traumatic Coagulopathy

Acute traumatic coagulopathy (ATC) occurs in approximately 15% of dogs following traumatic events and is associated with increased mortality and transfusion requirement [41]. The lethal triad of trauma (hypothermia, metabolic acidosis, and hemodilution) was once viewed as the contributing factor to trauma-associated coagulopathy. Because the lethal triad occurs mostly during or after resuscitation efforts, ATC is now considered a separate syndrome that takes place shortly after trauma [42]. The pathophysiology of ATC encompasses the dynamic interactions between the endothelium, platelets, anticoagulants, endocrine, and fibrinolytic systems [43]. For more details on the pathophysiology, diagnosis, and treatment of ATC, please refer to Chapter 163.

Hepatobiliary Disorders

Bleeding diatheses due to hepatobiliary disorders (HD) in small animals are mainly induced by invasive procedures. However, spontaneous hemorrhage such as epistaxis, petechia, and gastrointestinal hemorrhage have been reported in dogs with fulminant acute liver failure (ALF) (see Chapter 90) [44,45]. Dogs with advanced chronic hepatitis or cirrhosis may be more prone to gastrointestinal bleeding but the underlying pathology is likely secondary to portal hypertension-associated enteropathy and gastropathy. Cats with cholangiohepatitis and hepatic lipidosis may develop spontaneous bleeding following intravenous catheter placement or venepuncture [46]. In cats with extrahepatic biliary duct obstruction (EHBO) requiring surgical intervention, the prevalence of perioperative bleeding is approximately 50% [47,48].

Pathophysiology

Both primary and secondary hemostasis and fibrinolysis are affected by hepatic dysfunction. Despite the fact that the liver produces most hemostatic proteins, spontaneous hemorrhage is rare in the majority of cases. This is because reduced production of coagulation factors is paralleled by decreased anticoagulant proteins. Cholestasis or biliary tract obstruction results in decreased absorption of vitamin K, compromising the carboxylation of coagulation factors II, X VII, IX, PC, and PS.

Although thrombocytopenia is well documented in dogs with advanced HD, the exact causes are unknown [49]. Degree of thrombocytopenia is likely associated with disease severity. Possible causes include decreased hepatic synthesis of thrombopoietin, consumptive coagulopathy from DIC, and splenic-platelet sequestration due to portal hypertension [50]. Thrombocytopenia in cats with diazepam-associated ALF may be secondary to a DIC-like phenotype [51]. Platelet dysfunction has been documented in dogs with HD and congenital portosystemic shunt but little is known regarding the underlying molecular mechanisms [52,53]. Based on human and animal models of cirrhosis, platelet dysfunction is mainly due to compromised intracellular signaling. Decreased activation of phospholipase C, A2, and cyclo-oxygenase/thromboxane synthase results in decreased thromboxane and subsequent transmembrane signaling [54,55]. Platelets from cirrhotic patients also have reduced cytosolic calcium, which is essential for activation [56]. Upregulation of intracellular cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), the main inhibitory mediators, during cirrhosis may be secondary to elevation of circulating factors such as nitric oxide and prostaglandin (PGI₂) [57].

Dysfibrinogenemia occurs due to the failure of enzymatic removal of sialic acid from fibrinogen by the liver. Failure to remove negatively charged sialic acid molecules impairs fibrin polymerization. Fibrinolysis is increased due to reduced hepatic clearance of tPA and decreased levels of PAI-1, alpha-2-antiplasmin, and TAFI. Recently, using TEG, hyperfibrinolysis was documented in dogs with ALF [45]. Elevations of D-dimers and FDPs in dogs and cats with chronic liver disease also suggest primary hyperfibrinolysis.

Diagnosis and Treatment

Approximately 57–93% of dogs with HD are presented with at least one abnormal coagulation parameter [58]. Nearly all dogs with chronic hepatitis and ALF have prolonged clotting times and hence they are not specific at predicting spontaneous bleeding secondary to HD [58]. However, baseline PT/aPTT are still recommended, especially in animals that require invasive procedures such as liver biopsies and surgery. About 50% of cats with hepatic lipidosis have vitamin K-dependent coagulopathy whereas nearly 50% of cats with EHBO had prolonged PT/aPTT [48,59]. Protein invoked by vitamin K (PIVKA) analysis can be used to evaluate vitamin K status, especially in cats with liver disease. However, the diagnostic utility is limited by its availability. TEG provides a more comprehensive assessment of the state of coagulation but its use in dogs and cats with HD requires further evaluation.

Blood products may be given on an individual basis to patients that require invasive procedures (see Chapter 176). A retrospective study showed that hemorrhage following percutaneous ultrasound-guided biopsy of the liver was likely to occur in dogs with $>1.4\times$ prolongation of PT and in cats with $>1.4\times$ prolongation of aPTT. Platelet count of $<86\times 10^9/L$ was also a risk factor for hemorrhage [60] (see Chapter 67). Risk factors for hemorrhage following fine needle aspiration of the liver and hepatobiliary surgeries are unknown. Prophylactic vitamin K1 therapy in cholestatic patients, especially in cats, and those requiring invasive procedures is indicated.

Angiostrongylus vasorum

Bleeding diathesis due to *Angiostrongylus vasorum*, a metastrongyloid nematode, occurs in approximately 33–50% of infected dogs [61,62]. Endemic areas include Western Europe (France, UK, Sweden, Denmark, Germany, Italy) and Atlantic Canada (Newfoundland and Labrador) [61]. The underlying mechanism of *Angiostrongylus*-associated coagulopathy is unknown. Hypofibrinogenemia and hypocoagulable TEG tracings

were reported in one study, suggesting that a consumptive coagulopathy similar to DIC might be taking place during angiostrongylosis [62]. The impact of angiostrongylosis on other components of coagulation such as fibrinolysis and platelet function remains to be determined.

The magnitude of hemorrhage varies greatly between dogs. Conjunctival hemorrhage, hyphema, hematomas, gastrointestinal bleed, postsurgical hemorrhage, hemothorax, hemoabdomen, and intracranial hemorrhage have been reported [63,64]. Episcleral hemorrhage and neurological signs (seizures, ataxia, neck pain, coma) often occur simultaneously [62,65]. Clinical signs can occur with or without respiratory signs.

Diagnosis and Treatment

Dogs with a travel history to endemic areas that present with signs of clinical bleeding should be tested and treated for *Angiostrongylus*. A fresh fecal smear is a highly specific and economical aid to diagnosing angiostrongylosis. A negative fecal smear, however, does not rule out infestation [66]. Regardless of the fecal smear results, a further diagnostic test, such as Baermann sedimentation, should be performed. Prolongation of PT/aPTT in affected dogs is inconsistent and should not be used as a diagnostic criterion for angiostrongylosis-associated coagulopathy [62].

Dogs with or suspicious of angiostrongylosis should be treated with the appropriate antihelmics (fenbendazole, milbemycin oxime, and moxidectin) as soon as possible. Corticosteroids are sometimes used to reduce adverse reactions and inflammation. Blood component therapies may be administered to dogs with severe and life-threatening hemorrhage.

Neoplasia

Clinical manifestations of neoplasia-associated coagulopathy vary greatly from subclinical hypercoagulability, to thrombosis or hemorrhage [35,67–69]. Patients with neoplasia may present with local bleeding diathesis due to tumor invasion or generalized hemorrhage caused by thrombocytopenia, thrombocytopathia, coagulation factor deficiencies, consumptive coagulopathy (DIC), and hyperfibrinolysis. Factor deficiencies may be a consequence of hepatic dysfunction secondary to primary or metastatic hepatic neoplasia or vitamin K deficiency caused by malnutrition and EBTO.

In recent years, activation of coagulation and fibrinolysis has been shown to parallel with the progression of neoplasia. Oncogenic pathways such as oncogene expression and repressor gene-mediated neoplastic

transformation (loss of p53, activation of *MET* or *RAS*) promote TF transcription in cancer cells [70]. Increased TF expression leads to increased fibrin deposition and formation of an impermanent matrix that facilitates angiogenesis, anchorage of neoplastic cells, and protection from immune cells [71,72]. At the same time, microparticles shed by neoplastic cells consist of TF and phosphatidylserine, both of which are potent activators of coagulation [73]. Other prothrombotic mechanisms include platelet activation, production of inflammatory cytokines, and hemodynamic compromise.

For metastasis and invasion to occur, neoplastic cells must break down extracellular matrix by production of various metalloproteases as well as uPA and tPA, which may lead to systemic hyperfibrinolysis. Hyperfibrinolysis was recently documented in dogs with spontaneous hemoperitoneum due to malignancy but its underlying mechanism is unknown [74]. The complex interactions between neoplastic cells and the hemostatic system are

highly dependent on the type and progress of neoplasia, and co-morbidities such as recent surgeries and concurrent diseases.

Hemostatic changes were recently described according to the type and progress of neoplasia in dogs. Compared to lymphoma, dogs with carcinomas (excluding mammary carcinomas) had significantly more hypercoagulable TEG tracings, prolonged aPTT, and increased fibrinogen level. Dogs with clinical evidence of metastasis had elevated D-dimer levels and hypocoagulable TEG, suggesting that progression of neoplasia parallels fibrinolysis and consumptive coagulopathy [75]. The incidence of malignancy-associated DIC is about 10% in dogs and is mostly associated with hemangiosarcoma, mammary gland carcinoma, and pulmonary adenocarcinoma [69]. Hemostatic derangements due to different types of neoplasia are not well characterized in cats although neoplasia is a common cause of DIC and thromboembolism.

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Antithrombotics in the Emergency Room

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Introduction

Hematological emergencies associated with emergency visits most commonly involve bleeding tendencies and blood loss, with the control of bleeding being the focus of emergent care. Increasing appreciation for the coagulation derangements and their potential contribution to morbidity and mortality in animals receiving intensive care has also resulted in greater scrutiny of patients for evidence of hypercoagulability and thrombosis when presenting for emergency care.

Given the lack of readily available tests for hypercoagulable states, our understanding of diseases associated with thrombosis is drawn largely from retrospective necropsy studies in which neoplasia, systemic inflammation (pancreatitis, sepsis), immune-mediated diseases, protein-losing states, use of corticosteroids, and hyperadrenocorticism feature prominently as the most commonly identified underlying conditions in animals with thrombosis [1–7]. The ability of viscoelastic testing to use whole blood for assessment of coagulation status has led to a wave of publications related to altered coagulation in disease states, although their ability to predict thrombosis in any individual patient specifically remains unclear [8–13].

Finally, the question of whether or not to institute anticoagulant therapy represents an analysis of risk that is not often discussed in veterinary medicine, likely due to the small number of animals enrolled in most studies. In the presence of clinically evident thrombosis, the decision is clear. However, in one retrospective study of dogs with pulmonary thromboembolism, documented thrombosis was clinically silent in 41% of dogs and 44% of cats, and thrombosis was clinically suspected in only 38% of dogs and 14% of cats [14,15].

In light of this, clinical awareness of thrombosis and risk of thrombosis is necessary. Cats with cardiomyopathy-induced aortic thromboembolism and dogs with absent femoral pulses secondary to aortic

thromboembolism are easily identified and benefit from immediate anticoagulation. Animals with shortness of breath and other risk factors for hypercoagulability (such as hyperadrenocorticism or heartworm disease) may be treated empirically for pulmonary thromboembolism. The documentation of splenic or renal infarcts, or portal vein thrombosis on abdominal ultrasound in patients presenting with vague signs also warrants anticoagulation and further investigation as to the underlying cause of hypercoagulability.

In the absence of clinically evident thrombosis, the presence of risk factors in dogs with diseases known to have thrombotic complications should trigger institution of prophylactic anticoagulant therapy. Given the likelihood of a thrombotic complication, prophylactic anticoagulation should be strongly considered in dogs with immune-mediated hemolytic anemia, protein-losing nephropathy and enteropathy, pulmonary hypertension, and heartworm disease, and in cats with severe cardiomyopathy.

Anticoagulants may be used for the prevention of clot formation in animals at risk for thrombosis, or following a thrombotic event. In people, selection of anticoagulants has traditionally been considered in light of the system affected (i.e. arterial versus venous) and whether therapy is “therapeutic” or “prophylactic” in nature. In veterinary medicine, cost and route of administration are common drivers of anticoagulant selection due to lack of published guidelines and protocols related to their use. As the newer oral anticoagulants such as factor X inhibitors and direct thrombin inhibitors are studied in animals, options for anticoagulation may be expanded for both short-term and long-term use.

The therapeutic options considered in animals presenting with documented thrombosis include use of thrombolytics to actively lyse existing clots, and the use of anticoagulants to prevent additional clot formation (see Chapter 68). Thrombolytic drugs are meant to

dissolve existing clots, and can be delivered either systemically or locally at the site of a thrombus. Local concentrated delivery of thrombolytics may allow for maximum thrombolysis at lower doses than needed for systemic use, and bleeding complications may be reduced. However, systemic administration can be performed when catheter advancement to the site of the thrombus is considered not feasible.

While thrombolytic drugs seem like the logical choice in animals with clinically evident thrombosis, their potential to cause significant bleeding is such that their use is reserved for very acute and potentially devastating thrombosis. Case reports and a few retrospective studies documenting their use in animals with naturally occurring thrombosis are available but prospective evaluation of their use is lacking.

Streptokinase and tissue plasminogen activator have been most described. Streptokinase consists of a protein derived from beta-hemolytic streptococci that binds and activates plasminogen to plasmin, thus promoting fibrinolysis. A loading dose is commonly employed followed by a continuous infusion to overcome any antistreptococcal antibodies that might be present. One retrospective study of 46 cats with arterial thromboembolism treated with streptokinase documented return of pulses in 54% of cats within 2–24 hours of treatment and return of motor function in 30% of cats within 9 hours to 6 days of start of therapy [16].

Besides bleeding, concerns related to thrombolytic therapy in dogs and cats with arterial thromboembolism in particular include reperfusion injury characterized by life-threatening hyperkalemia. In the Moore study, 24% of cats experienced a bleeding complication following streptokinase infusion and 35% of cats experienced life-threatening hyperkalemia [16]. In another study, three out of four dogs receiving streptokinase experienced minor hemorrhage related to streptokinase infusion [17].

The use of recombinant tissue plasminogen activator, a serine protease that catalyzes the conversion of plasminogen to plasmin, has also been described for rapid dissolution of thrombi [18–20]. In two reports of chylothorax secondary to jugular venous thrombosis, local and systemic administration of tissue plasminogen activator led to reduction in clot size and resolution of pleural effusion [19,20]. In one prospective evaluation of tissue plasminogen activator in 11 cats with aortic thromboembolism, return of pulses and motor function was seen in a similar number of cats as noted with streptokinase (53% and 33% respectively). However, the study was terminated early due to a high incidence of adverse events (11/11 cats), including azotemia, neurological signs, cardiac arrhythmias, hyperkalemia, acidosis, and sudden death [21].

Dosing for streptokinase is based on a feline study of experimentally induced aortic thrombosis, where

90 000 IU of streptokinase administered IV over 20–30 minutes followed by a continuous infusion of 45 000 IU/h was shown to produce systemic fibrinolysis with no detectable adverse events on physical exam, necropsy or histopathology [22]. Thrombolytics are best used for acute thrombotic events, but these few studies suggest that thrombolysis can be seen in clots days after they are noted. Dosing of tPA varies between reports, ranging from 0.4–1 mg/kg IV per hour for up to 10 doses for systemic administration [18,19] and 0.03 mg/kg/h IV when delivered locally to the site of the thrombus [20]. Venipuncture should be limited during administration of thrombolytics, and signs of bleeding should be monitored, including ecchymosis or hemorrhage at IV catheter or feeding tube sites.

In the emergency room setting, acute thrombosis may be strongly suspected but the imaging required for confirmation may not be readily available. The risk–benefit assessment may therefore favor aggressive anticoagulation over thrombolytic therapy.

Endogenous fibrinolysis is triggered shortly after clot formation, so a major priority in treating thrombosis should be preventing additional clot formation through the use of anticoagulant therapy. This is done most commonly using heparin, either unfractionated or low molecular weight heparin (enoxaparin 1 mg/kg BID or dalteparin 150 µ/kg BID).

Unfractionated heparin consists of a mix of variably sized glycosaminoglycans. Formation of a heparin:antithrombin complex occurs with larger monosaccharide units, resulting in inhibition of coagulation factors (thrombin, IXa, Xa, XIa, XIIa), thrombin-induced platelet activation, and factor V and VIII upregulation. Given the short half-life of unfractionated heparin, it must be administered either 3–4 times per day (75–300 U/kg SC) or as a continuous infusion (50 U/kg loading dose then 10 U/kg/h). The recommended dose ranges vary widely, with more aggressive dosing recommended for therapeutic use and in conditions where thrombotic complications are common. Given its low cost, unfractionated heparin is an appealing choice for hospitalized patients but frequent injections of relatively large volumes are not commonly tolerated for long-term therapy. The variable composition of unfractionated heparin and unpredictable clearance require that this drug be monitored, and this is achieved most commonly using the aPTT. Monitoring is performed every 6 hours until the aPTT is consistently 1.5–2.5 times the baseline measurement, then once daily for hospitalized patients. Depending on the disease process it can be difficult to achieve the target aPTT, and in people the anti-Xa measurement is used in selected cases. Though not widely available, anti-Xa measurement is an option for animals, with a target range of 0.3–0.7 U/mL indicating an appropriate degree of anticoagulation. One report of

a dog presenting with acute and severe pain 8 days following humeral fracture repair described a brachial artery thrombus that resolved quickly following a continuous infusion of unfractionated heparin initiated at the time of emergency evaluation [23].

Another option for heparin therapy is the low molecular weight heparin preparation. Low molecular weight heparin is derived through depolymerization of unfractionated heparin to achieve a solution of smaller monosaccharide units with a mean MW of 4000–5000 daltons (one-third that of unfractionated heparins). Molecules of this size exert an anticoagulant effect through factor Xa inhibition rather than through antithrombin upregulation. With a longer half-life, predictable dose response and predictable clearance, fixed dosing at longer intervals make this a more appealing option for long-term use. Though the drug was initially marketed for once-daily dosing, subsequent pharmacokinetic studies suggest more frequent administration is required. In most cases no monitoring is performed, since LMWH results in minimal changes in aPTT. Instead, plasma anti-Xa activity must be measured when monitoring is needed. Plasma anti-Xa activity has been shown to be inversely related to thrombus formation and propagation in experimental canine models but this test is not widely available. Monitoring can be considered with long-term heparin use to prevent over- or under-coagulation, or with short-term use in cases with a high risk of bleeding or high likelihood of thrombotic recurrence. Currently, the low molecular weight heparins are administered a minimum of twice daily in dogs and cats, and limiting factors include cost and the ability or willingness of pet owners to administer injections at home.

Platelet inhibition through the use of non-steroidal anti-inflammatory drugs (NSAIDs) is commonly done either as a standalone approach to thromboprophylaxis or in addition to anticoagulants described above. Due to its availability and low cost, low-dose aspirin is widely used when concern for hypercoagulability is raised. Used at the low dose of 0.5 mg/kg PO SID (81 mg PO q72h in cats), effective platelet inhibition is possible with few adverse effects associated with cyclo-oxygenase inhibition [24]. In a study of 151 dogs treated for immune-mediated hemolytic anemia, those treated with low-dose aspirin in addition to azathioprine had significantly greater rates of survival compared to azathioprine alone. Dogs treated with azathioprine, heparin, and low-dose aspirin also had greater survival compared to dogs receiving azathioprine and heparin alone, suggesting some benefit of aspirin use for control of thromboembolism in this patient population [24].

Clopidogrel, a P2Y₁₂ receptor inhibitor that blocks ADP-mediated platelet aggregation, presents another cost-effective option for platelet inhibition when the

use of NSAIDs is discouraged. A large multicenter prospective blinded study comparing aspirin to clopidogrel in cats with a prior aortic thromboembolic event found that those receiving clopidogrel had a significantly longer time before thrombotic recurrence or cardiac death compared to cats receiving aspirin [25].

Platelet inhibitors may be used alone for prophylaxis or in combination with anticoagulants. Though specific evaluation of standalone versus combination therapy related to NSAIDs or clopidogrel is lacking, studies describing such use in people and in animals suggest that combination therapy is safe. In animals at high risk of thrombosis, controlling coagulation at the factor and the platelet level is logical and should be considered. Though commonly used for prophylaxis, whether or not platelet inhibition alone is sufficient to control a significant thrombotic event is unclear.

The introduction of direct thrombin inhibitors and factor Xa inhibitors in oral form may provide an appealing alternative to the heparins in dogs requiring short- or long-term anticoagulation. Rivaroxaban, a potent inhibitor of free and clot bound factor Xa, has been found to be equivalent to warfarin for prophylactic use (stroke prevention in patients with atrial fibrillation and deep vein thrombosis prevention for patients undergoing orthopedic surgery), and for the treatment of deep vein thrombosis and pulmonary thromboembolism. It is rapidly absorbed, has a predictable anticoagulant response, and requires no monitoring. A case series describing the use of rivaroxaban in four dogs with thrombosis suggested that when administered at 0.6–1 mg/kg PO SID in conjunction with a platelet inhibitor, this drug is well tolerated and effective in dogs [26]. Another study using rivaroxaban for thromboprophylaxis at just under 1 mg/kg in 12 dogs with IMHA also suggests that it can safely be used in dogs [27].

Given the available choices and in the absence of evidence-based protocols, selection of anticoagulant may be based on clinician experience in managing anticoagulation therapy, cost, willingness of the owner to administer injections at home, and the temperament of the patient. Heparin alone or in combination with a platelet inhibitor should be considered in animals with multiple risk factors for thrombosis, and in those that have experienced a thrombotic event. Ultimately, oral therapy is preferable for long-term anticoagulation, especially for animals with documented thrombosis.

A handful of recent studies suggest that rivaroxaban, the new oral factor Xa inhibitor, is safe and effective in dogs for both prophylactic and therapeutic use [26,27] and studies are under way in cats and horses. Continued evaluation of this option in naturally occurring disease states may provide a desirable therapeutic alternative to use of injectable anticoagulants in animals with documented thrombosis.

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Sick Oncology Patients in the Emergency Room

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Introduction

Cancer is the leading cause of death for older dogs and cats and the sick oncology patient now is quite common in an emergency room. The cause of the emergency visit may be a result of the cancer itself (hemoabdomen, thromboembolic disease), a paraneoplastic syndrome (hypercalcemia), or secondary to the treatment of the cancer (neutropenia, gastrointestinal signs, and tumor lysis syndrome). It is important for the emergency clinician to have a good basic understanding of the specific cancer, the pathophysiology leading to the current emergency visit, and treatments. Clearly, there are many potential topics in this area but for the sake of textual economy, several of the more important oncological emergencies are included.

Febrile Neutropenia and Sepsis

Myelosuppression is the dose-limiting toxicity of most chemotherapy agents used in veterinary oncology. Traditional cytotoxic chemotherapy agents are myelosuppressive by nature, since they affect rapidly dividing cells. While certain drugs are considered less myelosuppressive (corticosteroids, L-asparaginase, chlorambucil, bleomycin), others are moderately myelosuppressive (vincristine, vinblastine, cyclophosphamide, melphalan), or highly myelosuppressive (lomustine, carboplatin, doxorubicin, mitoxantrone). Typically, conventional chemotherapy drugs can cause varying degrees of neutropenia, given the short half-life of neutrophils (6–8 h) and the relatively short bone marrow transit times.

Neutropenia generally occurs around 6–8 days following administration of the commonly used cytotoxic drugs, including the vinca alkaloids (vincristine, vinblastine, vinorelbine), doxorubicin, mitoxantrone, and

high-dose pulse alkylators (cyclophosphamide, lomustine in dogs). Carboplatin causes a nadir that may manifest closer to 14 days post treatment in dogs, and around 14 to more than 25 days in cats [1–3]. Lomustine and carboplatin are somewhat unpredictable in cats, with nadirs occurring between 7 to 28 days following administration, depending on the individual patient and the dosage used [2,3]. A more pronounced neutropenia may be observed when vincristine is administered concurrently with L-asparaginase [4].

The signalment is an important consideration such as in dogs with the mutation of the ABCB1-1Δ (MDR-1) gene. The ABCB1 gene codes for P-glycoprotein (P-gp), a drug transport pump that plays a role in the development of multidrug resistance (MDR), important in cancer as well as normal drug metabolism within the liver and kidney. Dogs with a ABCB1-1Δ (MDR-1) gene P-glycoprotein mutation have increased risk of severe adverse effects with certain classes of chemotherapy drugs due to impaired drug clearance resulting in prolonged exposure. Specifically, the chemotherapeutic agents associated include vinca alkaloids (vincristine, vinblastine, vinorelbine), doxorubicin, mitoxantrone, taxanes, and dactinomycin [5–8]. The breeds most commonly harboring the mutation include collie breeds, Australian shepherd, silken windhound, long-haired whippet, Shetland sheepdog, and German shepherd, amongst others [5–8].

Cytotoxic drugs affecting both the gastrointestinal tract and bone marrow may be more likely to result in neutropenic septic events, possibly because of an increased risk of bacterial translocation from the gastrointestinal tract during the neutropenic episode. Two studies demonstrated that risk factors for the development of sepsis in dogs following chemotherapy included lower body weight, the diagnosis of lymphoma, and the administration of doxorubicin or vincristine [9,10].

Many patients present with vague clinical signs such as lethargy, anorexia and a fever. A rectal temperature of $\geq 103^{\circ}\text{F}$ should prompt the owner to seek veterinary attention. An automated complete blood count is warranted and it is a good habit to also perform a manual blood smear examination to confirm the degree of the neutropenia. The severity of cytopenias is graded from 1 to 4, with 1 being lowest and 4 highest [11]. Thoracic radiographs may be considered if there is concern for aspiration or any respiratory signs; however, radiographic signs of infection may be lacking in those animals that are severely neutropenic or those receiving glucocorticoids [9,10,12]. Blood cultures are positive in 11–50% of neutropenic humans and dogs with a fever, making the test of questionable benefit in our veterinary patients [9,10,12].

Treatment is based upon the patient's clinical signs, severity of the neutropenia, and an understanding of the patient's history, specifically the nadir of the most recent drug administered. In stable, afebrile neutropenic patients, oral antibacterial therapy is generally recommended and common choices include trimethoprim-sulfamethoxazole (15–30 mg/kg PO q12h), amoxicillin/clavulanic acid (13–15 mg/kg PO q12h), and cephalexin (22–25 mg/kg PO q12h). In the vast majority of canine patients, the neutropenia will resolve without complication within 2–5 days.

In patients with a neutrophil count $<1000/\mu\text{L}$ with a fever and signs consistent with sepsis/septic shock, hospitalization for aggressive care is indicated (see Chapters 155 and 159). Supportive therapy chiefly involves intravenous fluid therapy along with broad-spectrum antibiotics such as the combination of ampicillin or cefazolin (22 mg/kg IV q8h) and enrofloxacin (5–10 mg/kg IV q24h in dogs; 2.5–5.0 mg/kg IV q24h in cats), ampicillin/sulbactam (30 mg/kg IV q8h), ticarcillin/clavulanate (40–50 mg/kg IV q6h), (consider Zosyn (Piperacillin and Tazobactam) as Timentin is no longer available. Dose for Zosyn: 50–100 mg/kg IV q6 or loading dose 4 mg/kg followed by CRI 3.2 mg/kg/hr) or ampicillin (22 mg/kg IV q8h) and gentamicin (8–12 mg/kg IV q24h in dogs; 5–8 mg/kg IV q24h in cats). If gastrointestinal signs are present, standard gastroprotectants, acid inhibitors, and antiemetics can be utilized (see Chapters 74 and 77). Metronidazole (10–15 mg/kg PO or IV q12h) is recommended if soft stool or diarrhea occurs.

The use of colony stimulating factors (recombinant-human granulocyte colony stimulating factor (rhG-CSF)) is controversial and of questionable benefit since it is thought that high endogenous levels of canine G-CSF are already present during the neutropenic episode. A recent study demonstrated that dogs receiving rhG-CSF for neutropenic septic episodes were at higher risk for longer hospital stays and in-hospital mortality. However, this finding could have been due to a bias in that those dogs receiving the rhG-CSF were inherently in a more

compromised state and thus were considered patients that might benefit from this supplementary therapy [9,10]. In most patients with uncomplicated episodes of neutropenic sepsis, the fever abates rapidly, typically within hours after supportive therapy is begun. More recent studies in humans show that a better prognosis is associated with an increasing neutrophil count within the first week of therapy [9,10,12,13] and a persistent fever (beyond 3 days) may indicate a resistant bacterial infection or secondary infection, either bacterial or non-bacterial cause (fungal, IV catheter site inflammation, thrombosis, etc.) [14].

In humans, cancer has been identified as one of the most common co-morbid medical conditions in septic patients occurring in 2.3% of all hospitalized patients and representing $>10\%$ of those patients with severe sepsis. Additionally, human cancer patients are almost 10 times more likely to become septic and cancer remains an independent predictor of death in septic patients, occurring in 28% of cancer deaths [12,13]. Both human and animal studies agree that those patients with hematological cancers or lymphoma are at a higher risk of sepsis than other cancer patients [12,13,15,16]. In a study of 70 canine cases of chemotherapy-induced neutropenic septic episodes, a reported mortality rate of 8.5% was noted [10]. In that study, the majority of patients (70%) received vincristine or doxorubicin prior to the development of febrile neutropenia. Prognostic factors associated with a prolonged hospital stay included tachycardia at admission, complicating medical issues, G-CSF use, and decreasing neutrophil count after admission. Hypotension and G-CSF use were significantly associated with death in hospital [10].

Hypercalcemia

Hypercalcemia of malignancy (HM) is one of the most common paraneoplastic syndromes in oncology. These syndromes are defined as neoplasm-associated alterations in bodily structure or function, or both, that occur distant to the tumor. Cancer is diagnosed in approximately two-thirds of dogs with hypercalcemia versus approximately one-third of cats.

Lymphoma is the most common cause of HM in dogs and generally is associated with the cranial mediastinal form or other intermediate to high-grade T-cell variants. Other tumors associated with HM in dogs and cats include anal sac apocrine gland adenocarcinoma, multiple myeloma, thymoma, thyroid carcinoma, squamous cell carcinoma, mammary gland carcinoma/adenocarcinoma, melanoma, primary lung tumors, bone tumors (typically metastatic with significant and/or multifocal osteolysis), chronic lymphocytic leukemia, histiocytic sarcoma, and parathyroid gland tumors [16–18].

The pathophysiology of HM is most commonly associated with the production of a parathyroid hormone-related protein (PTH-rP) by tumor cells. This protein binds to the same receptors as PTH and exerts a similar effect, resulting in an elevation in the calcium concentration. PTH-rP causes a negative feedback inhibition of PTH, and the levels of this hormone are often low in these patients. As PTH-rP is produced by the tumor, it is not under any negative feedback control, resulting in a persistent hypercalcemia. Other mechanisms include the production of prostaglandins, osteoclast activating factor (OAF), and receptor activator of nuclear factor kappa-B ligand (RANKL), which is a type II membrane protein which plays a role in the control of bone regeneration and remodeling, activation of vitamin D, and direct tumor osteolysis [17–19].

Patients presenting with HM frequently display clinical signs such as polyuria/polydipsia (hypercalcemia can cause renal tubular insensitivity to antidiuretic hormone (ADH)), and a secondary nephrogenic diabetes insipidus develops, causing polyuria with secondary polydipsia, anorexia, vomiting, and constipation [17–19]. The severity of the clinical signs correlates with the magnitude of the hypercalcemia. Signs are generally mild to moderate when the serum total calcium concentration is less than 14 mg/dL, but become more apparent when the serum total calcium is greater than 15 mg/dL, and can become life-threatening when exceeding 18–20 mg/dL [20]. This prolonged, severe hypercalcemia may result in ischaemic renal damage, tissue calcification, and irreversible renal failure [20].

It is important to note that HM often parallels the underlying malignancy and therefore, successful treatment of the tumor leads to disappearance of the PNS. Alternatively, recurrence of the hypercalcemia may correlate with recurrence of the tumor, often preceding the clinically detectable recurrence of the tumor.

Patients with HM carry a poorer prognosis and associated decreased survival time compared to normocalcemic patients with the same cancer [16–19]. Thus, the history and physical exam will be important in assessing this and determining the underlying cause for an initial hypercalcemic event. When HM is suspected, a thorough physical examination can help determine the location of the primary tumor and whether metastasis has occurred. In dogs, particular attention should be paid to lymph nodes, thoracic auscultation, and rectal palpation to assess the anal glands and sublumbar/medial iliac lymph nodes. A complete blood count and full biochemistry profile are performed to investigate bone marrow status, total organ function, and globulin levels. Thoracic radiographs are performed to assess for pulmonary or mediastinal mass lesions and/or pulmonary metastases. Abdominal ultrasonography is performed to assess for

primary mass lesions, internal lymphadenopathy (sublumbar/medial iliac, gastric and mesenteric), and organ infiltration. Evaluation of PTH, PTH-rp, and ionized calcium may be warranted, but not necessary in an emergent situation [17–19].

Clearly, identifying and treating the underlying condition is paramount, but for the purpose of this chapter, we will focus on emergent treatment of the hypercalcemia, as immediate intervention is necessary to prevent permanent renal damage. Since dehydration accompanies the calcium-induced diuresis, the primary goal of fluid therapy is to correct the dehydration and then to promote calciuresis. The fluid of choice in hypercalcemic patients is 0.9% sodium chloride and the authors commonly use a rate of twice maintenance in attempts to correct the dehydration over 6–12 hours, depending upon the severity [17–19].

Sodium and calcium utilize a similar renal reabsorptive mechanism, so providing additional sodium to renal tubules will diminish calcium reabsorption and increase calciuresis. Furosemide (1–4 mg/kg q6h IV, IM, PO) can enhance calciuresis and is useful for the short-term management of hypercalcemia. However, it should be used only after the patient has been adequately hydrated, as it may actually increase serum calcium concentration in a dehydrated patient. Glucocorticoids (prednisone 0.5–1 mg/kg PO BID) are effective at controlling hypercalcemia via inhibition of osteoclast-activating factor, prostaglandins, and vitamin D, promoting calciuresis. Due to their anticancer effects against lymphoma and multiple myeloma, they should be implemented only after a definitive diagnosis has been obtained [17–19].

Bisphosphonates are potent antihypercalcemic agents that inhibit bone resorption by promoting osteoclast apoptosis. Commonly used bisphosphonates in veterinary medicine include alendronate, clodronate, and pamidronate, with pamidronate (1–2 mg/kg IV over 2 hours q 4 weeks) being the most commonly used, with a long duration of activity (4–6 weeks) [17–22]. Dehydration should be corrected prior to administration, as bisphosphonates can theoretically cause nephrotoxicity. Although reported for use in hypercalcemia, calcitonin (4–8 MRC units/kg SC) and nithramycin (25 µg/kg IV, once or twice weekly) are rarely utilized since the advent of bisphosphonates [21,22]. The change in calcium from bisphosphonates is not rapid and can take several days to show an effect.

Serial monitoring of ionized calcium is indicated during diuresis to ensure it normalizes to allow for the initiation of definitive therapy for the underlying cause of the HM. It is also important to treat with antiemetic and gastrointestinal protectant drugs in patients experiencing gastrointestinal signs [17–20].

Acute Tumor Lysis Syndrome

Acute tumor lysis syndrome (ATLS) is a collection of metabolic complications that can occur after treatment of cancer (chemotherapy, radiation therapy). In human medicine, it is often seen with Burkitt's lymphoma and acute lymphoblastic leukemia. In veterinary medicine, it is uncommon and almost exclusively seen with higher stage lymphomas (stage IV hepatic and splenic involvement and stage V bone marrow involvement) [23]. Although exceedingly rare, spontaneous ATLS has been reported [23].

The syndrome is a result of massive cancer cell death releasing cellular components, leading to hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia [23]. The ensuing hyperkalemia may lead to cardiac or muscular abnormalities and can be life-threatening. This syndrome generally manifests within the 48 hours following therapy. Malignant lymphocytes have four times as much phosphorus as normal lymphocytes and the ensuing hyperphosphatemia results in hypocalcemia due to precipitation of calcium phosphate in the renal tubules and other tissues. Hypocalcemia can cause tetany, muscle cramps, and seizures. A calcium supplement may be required. Large volumes of purines (adenine and guanine) are then released and converted to uric acid via the purine degradation pathway and excreted in the urine. With the high concentrations of uric acid generated by tumor lysis, uric acid may precipitate as monosodium urate crystals and can result in an acute uric acid nephropathy and subsequent acute kidney failure [23].

Clearly, the patient will have a history of recent treatment of a naive lymphoma or leukemia and clinical signs may include lethargy, vomiting, collapse, and death. Treatment involves aggressive IV fluid therapy (0.9% NaCl, with a 2–3 times maintenance rate), aiming to correct electrolyte disturbances, and continuous ECG monitoring to assess resolution of hyperkalemia-induced bradycardia, dampened P-wave, increased P-R interval and QRS, and spiked T-waves [23].

In human and veterinary oncology, treatment is more in the form of prevention via the identification of high-risk patients and hospitalization for fluid diuresis [23]. In human medicine, often sodium bicarbonate may be utilized to alkalinize the urine as well as allopurinol and urate oxidase to decrease uric acid production (see Chapter 174).

Thromboembolism and Hemostatic Abnormalities

Trousseau was the first to describe the relationship between cancer and thrombosis in the 1800s [14]. Since that time, there have been various studies that outline

the association and prevalence of thromboembolism in humans with cancer [14,24]. It is estimated that 10–20% of cancer patients have detectable venous thromboemboli (VTE) [25], although this is a likely underestimation given the potential number of subclinical cases that present. On the veterinary side, the prevalence of thromboembolism, specifically pulmonary thromboembolism (PTE), is suggested to be less than 1% [26] (see Chapter 42). However, this number is again likely to underestimate the affected population as data suggest that within 3 hours of death, 50% of canine thrombi lyse [26]. Multiple small animal studies have identified neoplasia as an underlying condition in animals with both PTE and aortic thromboembolism [27–30], although arterial thromboembolism is much less common than VTE [31].

Tumor cells are known to activate or potentiate the clotting cascade either directly or indirectly by their ability to release procoagulant substances, produce inflammatory cytokines, and/or by their relationship with host cells [14,24,25]. Tissue factor (TF) and cancer procoagulant (CP) are the best characterized procoagulants released by tumor cells and act to promote the formation of fibrin within the vasculature and in the tumor microenvironment [23,24]. TF is produced by multiple different types of tumor cells [14,32] and its presence on tumor cells, coupled with its expression on tumor-associated macrophages and endothelial cells, is upregulated by inflammatory cytokines (IL-1, TNF). TF and CP can also directly activate the clotting cascade via interaction with factors VII and X, respectively [14,24,25]. Both IL-1 and TNF are capable of inducing further expression of TF through activation of macrophages and stimulated T-cells, which can act to significantly promote and amplify thrombosis in cancer patients [14].

Additionally, cancer treatments, including surgery, cytotoxic drugs, and placement of central catheters, are independent risk factors for the development of thrombosis [24]. Drugs such as L-asparaginase, cisplatin, 5-fluorouracil, cyclophosphamide, and methotrexate alone or in combination increase the risk of thrombosis, especially when combined with hormonal therapies and the use of hematopoietic growth factors [14,24].

Clinical signs and physical examination findings attributable to thromboembolic disease can be vague and often overlap with other disease processes, potentially delaying diagnosis (see Chapter 62). The most common clinical sign and physical exam finding in animals with PTE is dyspnea [27–29]. Acute, unexplained dyspnea, especially in animals with predisposing disease processes and hypoxemia, should prompt the clinician to think of PTE as a possible differential diagnosis. Other signs of PTE may include coughing, hemoptysis, cyanosis, syncope, and crackles on thoracic auscultation [29]. The most common findings in pets that present with

aortic thromboembolism (ATE) are hindlimb pain, cool distal extremities, absent hindlimb pulses and decreased neurological sensation and function [30].

Diagnosis may be difficult and clinicians often rely on clinical signs and suspicion of thromboembolic disease based on underlying conditions. Thoracic radiographs, echocardiography, ventilation:perfusion scans, and CT angiography may all be helpful in the diagnosis of PTE [28], although the patient's clinical status may limit testing performed. A retrospective study evaluating the radiographic findings in dogs with spontaneous pulmonary thrombosis or embolism found that the most common radiographic changes were alveolar disease, usually affecting multiple lung lobes, and hyperlucency of a lung or lung lobe, indicative of hypovascularity [33]. Additionally, normal thoracic radiographs were identified in two of 21 patients with confirmed PTE on necropsy. The use of MRI (+/- angiography) may also prove helpful in the future [26].

Abnormalities in hemostatic parameters are common in both veterinary and human cancer patients [19,31,34,35]. Eighty-three percent of veterinary patients in one study [34] were shown to have one or more abnormal coagulation tests and another study showed that the majority of abnormalities were attributable to hypercoagulation [35] (see Chapter 70). Greater than 90% of human cancer patients have abnormalities of coagulation, including elevated fibrinogen levels, thrombocytosis and elevated levels of certain clotting factors [35].

Disseminated intravascular coagulation (DIC) is associated with excessive activation of the clotting cascade and subsequent hypercoagulability [36]; however, consumption of platelets and clotting factors can lead to hemorrhage later in the process [31]. DIC may be difficult to diagnose based on laboratory testing alone, but it is recommended to evaluate platelet count, clotting times (PT and aPTT), red cell morphology (schistocytes), fibrinogen, FDPs and antithrombin levels [36]. D-dimer concentrations >500 mg/mL were 100% sensitive for acute thromboembolism in one study [37]. Cancer is the most common cause of DIC in dogs, with an incidence of approximately 10%, and most commonly seen in dogs with hemangiosarcoma [31,38,39].

Thromboelastography is useful to detect hemostatic dysfunction, showing that 75% of dogs with neoplasia are hypercoagulable versus 25% that are hypocoagulable [40]. Most of the dogs with malignant neoplasia were hypercoagulable, and significantly more so than those with benign neoplasia [32,40]. Although TEG and other coagulation parameters may be altered in cancer patients, there has been no evidence to support these abnormalities as predictors of thromboembolic disease [35].

Treatment of thromboembolic disease remains challenging (see Chapters 42 and 62). Evidence-based

information supporting the use of thrombolytics in PTE (including streptokinase, urokinase, and alteplase (tPA)) is limited in veterinary medicine so there is no specific recommendation for their use [26]. Anticoagulants (unfractionated heparin (UFH) and low molecular weight heparin (LMWH)) have been used in both dogs and cats with thromboembolic disease (see Chapter 71). The variability in dose and frequency as well as unpredictable pharmacokinetics within and among species has somewhat limited their use. To date, no studies evaluating their potential use in PTE exists in small animals [26]. Clopidogrel, an antiplatelet drug, was evaluated in cats with ATE and showed a marked improvement in survival [41].

Supportive care in the form of oxygen and cardiovascular support is indicated and ultimately, treatment of the underlying cause as well as those therapies aimed at limiting clot propagation and preventing recurrence will prove most beneficial in achieving a positive outcome [26].

Hemangiosarcoma

Hemangiosarcoma (HSA) is a highly malignant tumor of vascular endothelial origin. It is more common in dogs, accounting for approximately 45–50% of splenic tumors and 5–7% of all non-cutaneous tumors; the incidence in cats is reportedly 0.5–2% [42,43]. Approximately 60% of those cats that present with hemoperitoneum have HSA, with the spleen also being the most common site [44]. A genetic predisposition is suggested as German shepherds are the most common affected breed and other large-breed dogs are also overrepresented, including Labrador retrievers and golden retrievers. The most common site of occurrence is the spleen in dogs, but the right atrium, liver, and skin are also frequently involved and HSA is the most common primary heart tumor in dogs [42,43]. Metastasis is rapid and has been identified in an estimated two-thirds of those dogs with evidence of HSA on necropsy [45].

Small animals with HSA may present with variable clinical signs, ranging from non-specific signs of lethargy and inappetence to signs of hypovolemic shock secondary to hemorrhage. Patients with splenic tumors may present with physical examination findings of abdominal pain (with or without an associated palpable mass or fluid wave), pale mucous membranes, decreased capillary refill time, poor pulse quality, tachycardia, and tachypnea. Those patients with pericardial effusion secondary to right atrial HSA may also present in shock secondary to decreased circulating blood volume and signs of right heart failure secondary to cardiac tamponade, including ascites, jugular pulses, and dyspnea

(see Chapter 54). Often these patients have decreased or muffled heart sounds and may have pulsus paradoxus, a variation in pulse quality associated with respirations [42]. Pulsus paradoxus results from an exaggerated fall in systolic pressure that occurs during inspiration as the right heart pressures increase secondary to increasing intrapericardial pressures, creating decreased left ventricular stroke volume.

An ECG may show rhythms consistent with pericardial effusion (i.e. electrical alternans or decreased QRS amplitude) [42] or other arrhythmias (sinus or ventricular tachycardia). A retrospective study of dogs found that ventricular arrhythmias are common in dogs with splenic masses and are often associated with anemia, myocardial metastatic disease, and myocardial necrosis. The cause of the myocardial necrosis was not apparent, but may occur secondary to thromboembolic disease, hypoxia with release of vasoactive substances (thromboxane A₂) or sustained tachycardia [46].

Diagnosis of HSA often includes evaluation of lab work (complete blood count, chemistry profile, coagulation profile), thoracic and abdominal radiographs, abdominal ultrasound, and echocardiography. Focused assessment with sonography for trauma (FAST; see Chapter 182) is very useful in the emergency setting to both identify and aid in sampling of abdominal, pleural, and pericardial effusion [47,48]. Both abdominal FAST (aFAST) and thoracic FAST (tFAST) (see Chapter 182) may allow more rapid detection and intervention by facilitating the diagnosis of hemoabdomen and pericardial effusion +/- cardiac tamponade [49]. Confirmation of hemoabdomen may be made via abdominocentesis. The presence of non-clotting blood in the absence of a significant coagulopathy confirms the diagnosis and a PCV/TS that approximates the peripheral blood is consistent with acute hemorrhage.

Anemia, thrombocytopenia, and abnormalities of coagulation are common. Anemia and thrombocytopenia are often the result of internal blood loss and can be accompanied by low total solids (TS). One study identified those dogs with splenic HSA as having significantly lower TS and platelet measurements than dogs with other splenic lesions [49]. In a study evaluating hemostatic abnormalities in dogs with HSA [39], DIC was diagnosed in 50% of the cases and thrombocytopenia was the most common laboratory abnormality, occurring in 75% of patients. Additionally, 25% of the dogs in that

study died as a result of DIC [39]. The overall estimate of coagulopathies is 84% in dogs with acute, non-traumatic hemoabdomens [49].

Treatment is aimed at improving perfusion parameters, including heart rate, capillary refill time, and blood pressure [50]. Lactate is also a useful monitoring tool and has been shown to be elevated in 74% of patients with hemoabdomen before resuscitation [50–52]. Combination fluid therapy with crystalloids, colloids, and blood products is indicated (see Chapters 153, 167, 168, 169, and 176). Surgical exploration for those animals with intra-abdominal hemorrhage is often necessary to control local disease. For patients that present in shock as a result of pericardial effusion and subsequent cardiac tamponade, immediate pericardiocentesis is indicated (see Chapter 54). Surgical resection of a right atrial mass is possible in some cases and a retrospective study [53] found that resectable right atrial tumors in combination with chemotherapy had a significantly longer survival time compared to resection alone. Palliative care consisting of pericardectomy is also possible via either thoracoscopy or thoracotomy and may relieve signs of tamponade, but has not been shown to prolong survival [54], however recent data suggests an improvement in survival when treated with doxorubicin [55].

The prognosis for HSA remains guarded despite surgery, with median survival times reported to be 19–86 days [42,43,54], although recent treatment options may significantly prolong survival times [52,42] in those patients who survive to discharge. Studies have identified anemia, thrombocytopenia, ventricular arrhythmias, the need for massive blood transfusions and the development of respiratory distress as predictors of perioperative mortality [42,43,51,52].

Conclusion

Oncological emergencies represent a growing population of patients within veterinary medicine. These emergencies may occur as a result of the underlying disease, paraneoplastic syndromes or secondary to treatment itself. Clinicians should have a thorough understanding of the underlying pathophysiology, available diagnostics, and current treatment recommendations of the more common emergencies so they are able to recognize, diagnose, and manage these cases more effectively.

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Paraneoplastic Syndromes

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Hypercalcemia of Malignancy

The most common cause of hypercalcemia in dogs is neoplasia, and hypercalcemia of malignancy is the most common paraneoplastic syndromes (PNS) in small animal patients (see Chapter 72) [1]. Hypercalcemia can be a severe and life-threatening emergency requiring rapid treatment. Fast and appropriate treatment requires identification of the underlying cause; work-up includes a thorough history, physical examination, and minimum database. Conditions such as granulomatous disease, hypoadrenocorticism, renal failure, hyperparathyroidism, vitamin D toxicity, or laboratory error need to be excluded (see Chapter 110).

The most common tumors associated with paraneoplastic hypercalcemia in dogs are lymphoma, apocrine gland adenocarcinoma of the anal sac (AGASACA), and multiple myeloma. Hypercalcemia in cats is less frequent than in dogs; the most common underlying causes are idiopathic, neoplasia, and chronic renal failure [2,3]. Of the neoplastic causes, squamous cell carcinoma of the head and neck and lymphoma are the most common [2]. Other tumors that have been reported to cause hypercalcemia in veterinary patients include thymomas, nasal tumors, mammary adenocarcinoma, clitoral adenocarcinoma, thyroid carcinoma, renal neoplasia, and primary lung tumors [4–11]. The etiopathogenesis of the hypercalcemia of malignancy remains unknown in many individual cases. Factors which may be associated include parathyroid hormone (PTH), parathyroid hormone-related peptide (PTHrP), osteoclast activating factor (OAF), prostaglandins in the E series, vitamin D or its analogues, and transforming growth factors.

The most common clinical sign associated with hypercalcemia in dogs is severe polyuria with subsequent polydipsia, and these patients may present for signs associated with dehydration. Cats often only show decreased appetite, and thus will not usually present in an ER setting.

Treatment for hypercalcemia of malignancy requires treatment of the underlying cause as most patients will not achieve normocalcemia until their tumor is treated. Therefore, appropriate identification of the underlying malignancy is crucial.

Supportive treatment may need to be instituted immediately in patients with critically high blood calcium. While glucocorticoids are effective at lowering calcium, it is important not to institute this therapy until a diagnosis is made, as glucocorticoids can both make lymphoma impossible to diagnose and also decrease effectiveness of subsequent chemotherapy. Aggressive saline diuresis possibly with furosemide administration (once the patient is well hydrated) is the most effective way to manage the hypercalcemia while a diagnosis is being obtained.

A thorough physical examination will often identify the underlying cause, as lymphoma and AGASACA are the most common tumors. All peripheral lymph nodes must be carefully palpated, and a thorough rectal examination performed. Anal sacs need to be fully emptied to allow for palpation of what may be a very small, discreet mass associated with the sac. Fine needle aspiration and cytology should be performed on any enlarged lymph nodes or perianal mass.

If physical exam is otherwise unremarkable, additional diagnostics need to be performed. Confirmation of hypercalcemia with an ionized calcium measurement is ideal. A CBC with manual smear examination may reveal lymphoblasts in circulation, which provides a diagnosis of acute leukemia or stage V lymphoma. Aspirates of several peripheral lymph nodes, even if palpably normal, should be submitted for cytology, as this will occasionally reveal lymphoma. Thoracic radiographs are taken to evaluate for lytic bony lesions, particularly in the spinous processes of the vertebral bodies or ribs (associated with multiple myeloma), or mediastinal masses that could be associated with mediastinal lymphoma or a thymoma. An abdominal ultrasound may detect subtle changes in the

spleen, liver or lymph nodes; any abnormalities should be aspirated and submitted for cytology. Aspiration of a normal-appearing spleen should also be considered as lymphoma can have a varied ultrasonographic appearance.

Once a diagnosis has been obtained, appropriate treatments for the underlying cause can be instituted. Normocalcemia is often achieved once the tumor has been treated. Recurrence of hypercalcemia can indicate tumor recurrence; monitoring blood calcium levels is important.

Hypoglycemia

Hypoglycemia (glucose <60 mg/dL) is another PNS in dogs that may lead to emergency evaluation (see Chapter 111). Patients with hypoglycemia can present with a variety of clinical signs, including lethargy and weakness, seizures, tremors, behavioral changes, and even coma. Often, the severity of the clinical signs will depend on the duration of hypoglycemia; a prolonged period of hypoglycemia allows the body time to acclimate and the signs are not as severe as those with an acute hypoglycemic episode. On presentation, a minimum database should be performed and hypoglycemia confirmed to rule out lab error.

Insulinomas (beta-islet cell tumors) [12,13] as well as extrapancreatic tumors may result in paraneoplastic hypoglycemia. Extrapancreatic tumors that have been associated with hypoglycemia include hepatocellular carcinomas, lymphoma/leukemia, gastrointestinal leiomyoma/leiomyosarcoma, plasmacytoid tumors, oral melanoma, mammary carcinoma, hemangiosarcoma, and renal adenocarcinoma [14–18]. With insulinomas, excessive secretion of insulin by the neoplastic islet cells causes hypoglycemia; documentation of normal or high insulin in the presence of hypoglycemia is diagnostic for an islet cell tumor. With extrapancreatic tumors, low glucose is due to production of other factors such as insulin-like growth factors (IGFs), and the serum insulin levels are usually low to low-normal. Other mechanisms by which tumors can cause hypoglycemia include accelerated glucose utilization by the tumor or failure of hepatic gluconeogenesis and/or glycogenolysis.

Paraneoplastic hypoglycemia due to a non-islet cell tumor is a diagnosis of exclusion; all other causes of hypoglycemia need to be ruled out first. In older patients with no indication of sepsis or liver dysfunction, serum insulin levels taken at the same time as documented hypoglycemia should be submitted. In dogs with insulinomas, imaging to identify a pancreatic mass can be challenging. Abdominal ultrasound detects about 40% while CT detects closer to 75% of the tumors; if the insulin results indicate an insulinoma, exploratory with visual examination of the pancreas may be indicated [19].

Patients may present in hypoglycemic crisis, in which case a slow IV bolus of dextrose at 0.5 g/kg diluted in 0.9% saline (1:3 ratio) can be administered followed by a 2.5–5% dextrose drip for maintenance (see Chapter 111) [20]. Caution should be exercised in suspected cases of insulinomas as the tumor response to a bolus of dextrose can be excessive secretion of insulin, leading to refractory severe hypoglycemia.

Long-term treatment of the hypoglycemia is aimed at treating the underlying tumor, which requires surgery. If surgery is not an option, the hypoglycemia can be managed for some time with small, frequent feedings and low doses of prednisone.

Polycythemia

Polycythemia is a pathological increase in red blood cell mass. Patients suffering from polycythemia may present on an emergency basis for clinical signs associated with hyperviscosity, including polyuria and polydipsia; neurological signs including weakness, seizures, ataxia, or blindness; and bleeding abnormalities including epistaxis, hematemesis, hematochezia or hematuria. Polycythemia (>55% for a dog and >50% in a cat) may be relative (dehydration) or absolute. Absolute polycythemia can be either primary or secondary. Primary polycythemia is polycythemia vera, a myeloproliferative disease. Secondary polycythemia may be appropriate, in cases of hypoxia, or inappropriate, which is consistent with a PNS. Paraneoplastic polycythemia may be due to excessive erythropoietin (EPO) production by the tumor, kidney hypoxia with subsequent EPO release, production of an EPO-related hormone, or changes in EPO metabolism. Tumors that have been associated with this PNS include renal carcinoma, renal lymphoma, nasal fibrosarcoma, and renal fibrosarcoma [17,21–25].

Diagnostics needed to rule out a relative polycythemia or an appropriate absolute polycythemia include a minimum database, thoracic radiographs, and blood gas analysis. If determined to be inappropriate absolute polycythemia, abdominal ultrasound or CT scan can be performed for occult tumor assessment. Long-term management of paraneoplastic polycythemia requires treatment of the underlying neoplastic cause. In the acute setting or if the primary tumor cannot be treated, phlebotomy can be performed. Removal of 10–20 mL/kg of blood is performed until clinical signs resolve, or until the target hematocrit is reached (<55% for dogs and <50% for cats) [26]. An infusion of 0.9% saline should be given during the phlebotomy equal to the volume of blood removed, and a PCV rechecked 6–8 hours after; a second phlebotomy may be needed.

Anemia

Anemia is one of the most common PNSs in veterinary patients and can result from almost any tumor type (see Chapters 65 and 66). Causes of anemia in cancer patients are numerous and include chronic disease, blood loss, immune-mediated hemolysis (IMHA), myeloproliferative disease, erythrophagocytosis, and red cell aplasia. Thus, paraneoplastic anemia may be regenerative or non-regenerative. Patients may present on an emergency basis for non-specific signs of lethargy, weakness, or tachypnea. In some cases, there may be apparent hemorrhage.

The severity of clinical signs associated with anemia will vary depending on the chronicity. Acute anemia may lead to a crisis which requires stabilization and supportive care. A CBC with red cell indices will help identify the type of anemia, which can be of benefit in determining the underlying cause. Anemia of chronic disease is characterized by a normocytic/normochromic anemia and is due to disordered iron storage and metabolism, shortened red blood cell lifespan, and decreased bone marrow response.

Blood loss anemia as a PNS is usually due to acute hemorrhage (see Chapter 170). Treatment consists of removing the underlying tumor to stop the bleeding, though patients may need to be stabilized with packed red blood cell transfusions until necessary diagnostics and treatments can be performed. Chronic blood loss anemia is characterized by a microcytic/hypochromic anemia; initially, however, it will be normochromic/normocytic. These patients have very low hematocrits and yet are usually quite stable clinically. Origins of tumors that may lead to this chronic loss include the GI tract, urinary tract, and nasal cavity.

Many tumor types may lead to IMHA (see Chapter 66). Spherocytosis and a regenerative anemia on a CBC are indicative of this PNS. Management requires removal or treatment of the tumor, though patients may have a life-threatening anemia which necessitates supportive care prior to definitive treatment. If a diagnosis has been established, corticosteroids to decrease RBC destruction are indicated (prednisone 2–3 mg/kg/day PO). In patients who have not had a thorough work-up (minimum database blood work, thoracic radiographs, abdominal radiographs/ultrasound, and thorough lymph node palpation), caution should be exercised as steroids may hide a diagnosis of lymphoma or plasma cell tumors. If the patient is clinical from the anemia, transfusion with packed red blood cells may be required.

A less common PNS-related anemia is due to myelophthisis, where infiltration of a cancer, most often lymphoma, into the bone marrow results in an inability of normal hematopoietic cell lines to survive and proliferate. Diagnosis via CBC to identify circulating cancer cells can often be achieved, though a bone marrow aspirate

may be needed. Once a diagnosis is established, steroids (prednisone 2 mg/kg/day PO) are indicated to try and achieve a fast reduction in tumor burden, and continued management with an appropriate chemotherapy protocol should be instituted. Packed red blood transfusions may be needed to stabilize the patient and repeated until red blood cell production resumes (see Chapter 176).

Thrombocytopenia

Thrombocytopenia is another common PNS with several mechanisms for development including immune-mediated destruction, consumption, or decreased platelet production (see Chapter 67). The most common tumors associated with this PNS are splenic tumors and lymphoma. Patients may present on an emergency basis with petechiae, ecchymoses, epistaxis, hematochezia or hematemesis if the platelet count is $<30,000/\mu\text{L}$, or they may present for other causes related to their underlying tumor with subsequent thrombocytopenia noted on a CBC. If thrombocytopenia is suspected, use a peripheral vein for sample collection. Confirm an automated platelet count with a slide review. As for other PNSs, treatment is directed at the underlying cause. If there is bleeding or other coagulopathy secondary to severe thrombocytopenia, patients may need packed red blood cell transfusions and/or plasma transfusions until the platelet count increases (see Chapter 176).

Coagulopathies/Disseminated Intravascular Coagulation

Paraneoplastic coagulopathies are associated with tumors that can cause thrombocytopenia, thrombocytosis, disseminated intravascular coagulation (DIC), and platelet dysfunction. The incidence of DIC in dogs with malignant tumors is roughly 10% [27] and patients may present on an emergency basis with signs of bleeding (petechiae, ecchymoses, intracavitary hemorrhagic effusions). The most common tumor associated with DIC in the dog is hemangiosarcoma, but many tumor types in both dogs and cats may lead to this PNS.

A diagnosis of DIC is made by identifying an inciting cause in conjunction with documenting two or more of the following: thrombocytopenia, prolonged activated partial thromboplastin time (aPTT)/prothrombin time (PT)/or thrombin clot time, hypofibrinogenemia, decreased antithrombin, and elevated fibrinogen degradation products or D-dimers [28]. Patients who present in DIC need immediate supportive care and removal of the underlying inciting cause. These patients

are often deficient in coagulation factors and require fresh frozen plasma (see Chapter 70).

Hypertrophic Osteopathy

Hypertrophic osteopathy (HO) is characterized by periosteal new bone formation along long bones. Non-malignant diseases can result in HO and include heartworm disease, lung atelectasis, abscesses, granulomas, and foreign bodies. HO as a PNS in veterinary patients is most often associated with thoracic neoplasia, either primary pulmonary tumors or pulmonary metastatic disease; however, it can also be seen with intra-abdominal tumors. Proposed mechanisms for HO are release of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), afferent neurological stimulation, and increased circulating vasodilators [29].

Patients typically present with a history of shifting-leg lameness or reluctance to rise or ambulate at all. On physical exam, there is often firm soft tissue swelling of the distal limbs. Thoracic radiographs are performed to evaluate for primary lung lesions or evidence of metastatic disease; if normal, a minimum database and abdominal ultrasound are indicated. Definitive treatment for this condition is removal of the inciting cause, which in many cases is not possible. Non-steroidal anti-inflammatory drugs (NSAIDs) or steroids should be used, if not contraindicated, to help alleviate discomfort. In the authors' experience, steroids at an anti-inflammatory dose (prednisone 1 mg/kg/day PO) have been more effective in controlling swelling and pain than NSAIDs for patients with this condition.

Fever

Fevers in veterinary patients are most often caused by infection, inflammation, or immune-mediated diseases (see Chapter 18). Paraneoplastic fever may be considered for patients who are febrile without a clear underlying cause. The incidence of paraneoplastic fever in veterinary patients has not been established but in humans, cancer is the cause of fever of unknown origin in roughly 10% of

Table 73.1 Additional paraneoplastic syndromes and associated tumors.

Paraneoplastic syndrome	Tumor type(s)
Cancer cachexia	Any tumor type
Gastric ulceration	Mast cell tumor Gastrinoma
Hypergammaglobulinemia	Multiple myeloma Lymphoma Chronic lymphocytic leukemia
Neutrophilic leukocytosis	Hemangiosarcoma Lymphoma Renal carcinoma
Alopecia	Feline pancreatic carcinoma
Flushing (cutaneous)	Mast cell tumor Pheochromocytoma
Nodular dermatofibrosis	Renal cystadenoma/ cystadenocarcinoma (German shepherd dogs)
Superficial necrolytic dermatitis	Glucagonoma
Pemphigus vulgaris	Lymphoma
Glomerulonephritis/ nephrotic syndrome	Multiple myeloma Polycythemia vera Lymphocytic leukemia
Myasthenia gravis	Thymoma
Peripheral neuropathy	Insulinoma

patients [30]. Paraneoplastic fever is predominantly mediated by excessive cytokine production of IL-1, IL-6, and TNF-alpha. Patients that present on an emergency basis with a fever need to be evaluated for all the most common causes of fever prior to a PNS being suspected. Supportive care may be indicated based on the patient's condition.

Miscellaneous

The above-mentioned PNSs are not exhaustive, and the reader should be aware of several other manifestations of cancer in the veterinary patient that may present on an emergency basis. Table 73.1 lists additional PNSs and their associated tumor type(s).

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E. Esophageal and Abdominal Disease

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Vomiting and Regurgitation

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Vomiting

Physiology

Vomiting is the body's mechanism to rid the upper gastrointestinal tract (GIT) of its contents. Vomiting occurs when any part of the upper GIT (pharynx, esophagus, stomach, small intestine) becomes overly distended or inflamed, causing increased neural stimulation to the vomiting center (VC) in the brain. Afferents (both vagal and sympathetic) are stimulated by inflammation and overdistension in the GIT and impulses are transmitted to the VC in the medulla. Additionally, impulses can come from the brain itself to stimulate the VC. These impulses are generated in the vestibular apparatus, cerebrum, and chemoreceptor trigger zone (CRTZ). Impulses from the vestibular apparatus are responsible for vomiting due to conditions such as vestibular disease or motion sickness. Impulses from the cerebrum may be generated due to increased stress or noxious stimuli.

The CRTZ is found on the floor of the fourth ventricle in the area postrema and is very sensitive to drugs and toxins because it does not have a complete blood–brain barrier. Common stimulants of the CRTZ include drugs such as opioids. Impulses are modulated in the vomiting center before efferents travel back to the GIT. The initial response is antiperistalsis which brings food boluses from the lower small intestine all the way to the stomach within minutes. This will further cause distension of the upper small intestine, creating an afferent stimuli to the VC. At this time, efferents cause contraction of the abdominal musculature and diaphragm and a relative relaxation of the lower esophageal sphincter, allowing contents to leave the stomach, move into the esophagus and then out of the body. In concert with the act of vomiting, the glottis is closed to prevent aspiration of contents if there

is normal pharyngeal and laryngeal function as well as normal mentation [1].

Sequelae of Vomiting

Animals with prolonged or profuse vomiting will often show signs of dehydration because of the significant loss of fluid through the GI contents. Additionally, vomiting, associated nausea, and underlying disease will often significantly reduce intake of fluids. Animals may also suffer from aspiration pneumonia from vomiting, but this is less common than in regurgitation because closure of the glottis occurs during the vomiting reflex arc. In cases of chronic vomiting and vomiting with associated malabsorption, significant weight loss may occur.

Diagnostics

Determining the cause of vomiting can be an arduous task because of the many conditions that may contribute to the diagnosis, so clinicians will often divide the cause of vomiting into GI and non-GI causes and differentiation of acute versus chronic vomiting (Table 74.1). These derived differential lists will help guide diagnostics and therapy decisions. Non-GI causes may be associated with other systemic signs or physical exam characteristics of that underlying disease. Additionally, some primary GI causes may initially be found in an animal that still wants to eat but does not keep food down, as opposed to the lack of appetite found in many systemic diseases.

On an emergency basis, some diagnostics may be directed at ruling out conditions that require a specific treatment early on such as a foreign body needing surgery or AKI needing directed hospitalization and therapy. A diagnostic option will be presented as those that should be considered emergently and those that can be performed additionally if initial diagnostics and therapy fail to yield a cause or resolution.

Table 74.1 Gastrointestinal versus non-gastrointestinal causes of vomiting.

Gastrointestinal (primary)	Non-gastrointestinal (secondary)
Intolerance <ul style="list-style-type: none">Dietary indiscretionAllergy	Metabolic <ul style="list-style-type: none">UremiaLiver disease, liver failure
Obstruction <ul style="list-style-type: none">Foreign bodyIntussusceptionVolvulus/torsionMass (granuloma, abscess, neoplasia)	Endocrine <ul style="list-style-type: none">Diabetic ketoacidosisHypoadrenocorticismHyperthyroidism
Infectious <ul style="list-style-type: none">Viral (parvovirus, FIP)ParasiticBacterial (<i>Salmonella</i>, <i>Campylobacter</i>)	Abdominal disorders <ul style="list-style-type: none">PancreatitisPyometraPeritonitisProstatitis
Inflammatory bowel disease	Neurological <ul style="list-style-type: none">Vestibular diseaseMotion sicknessIncreased intracranial pressure
Ulceration	Drugs/toxins
Neoplasia	Inflammatory disease <ul style="list-style-type: none">IMHAITPIMPA

FIP, feline infectious peritonitis; IMHA, immune-mediated hemolytic anemia; IMPA, immune-mediated polyarthritis; ITP, idiopathic thrombocytopenic purpura.

History and Physical Examination

The history and physical examination can give important clues as to the potential cause of vomiting. Directed historical questions should give information on the character, frequency, volume, and chronicity of the vomitus and should help distinguish vomiting from regurgitation or a terminal retch found in respiratory disease. Further questions can identify if there is blood in the vomitus – either frank blood or digested blood (coffee grounds). It is important to ask about any potential indiscretion in the dog’s or cat’s history, including any medications, new foods, or missing toys, etc. that the animal may have been exposed to. Furthermore, since owners do not always know if something is missing from the house, getting an idea of whether the animal has a tendency to eat inappropriate objects can be revealing. Additionally, vaccination, diet, medication, and travel history should be obtained.

The physical examination should be focused to determine the cause of vomiting, the sequelae, or potentially looking for other issues that may point to a non-GI cause of vomiting. In looking for a cause, a good abdominal palpation should identify if there is abdominal pain,

distension, large-volume effusion, or a palpable mass. Based on the animal’s temperament and conformation, abdominal palpation can yield varying degrees of information. In looking for other concurrent issues, examples could include feeling for a thyroid slip in cats, palpating painful kidneys indicative of an acute kidney injury, or a rectal palpation that reveals a distended uterus in pyometra, painful prostate in the case of prostatitis, melena due to ulceration, or fresh blood due to colitis. Finally, the PE should include evaluating for potential sequela such as aspiration, dehydration, or hemodynamic changes from hypovolemic shock (see Chapter 153).

Bloodwork and Urinalysis Analysis

Simple initial bloodwork such as a CBC (or even a PCV/TS and blood smear) and a chemistry with electrolytes can be very useful in ruling many conditions in or out. A chemistry panel can help rule out kidney or liver disease as a cause of vomiting. Because gastric fluid contains high concentrations of hydrogen ions and chloride, common disturbances include a severe hypochloremic metabolic alkalosis especially seen with foreign body obstruction or severe vomiting due to other causes. Hypokalemia is also a common finding with vomiting (see Chapter 109). With some chronicity or with severe fluid loss, a metabolic acidosis may be identified due to lactic acidosis (see Chapter 107) [2]. Electrolyte abnormalities such as hyponatremia and hyperkalemia along with potential hypoglycemia, hypercalcemia, and hypocholesterolemia may increase index of suspicion for Addison’s disease (see Chapters 107–109). Alternatively, severe hyperglycemia should direct further investigation for a diabetic crisis (see Chapter 112). Emergently, urine should be collected as well, when available, as it will help differentiate prerenal azotemia from renal azotemia and also be available for diagnostics should uremia be detected as the cause of vomiting.

Additional diagnostics based on the results of an initial database include a baseline cortisol or ACTH stimulation test for hypoadrenocorticism (see Chapter 115), thyroid hormone concentration (see Chapter 116), evaluation of serum or urine ketones (see Chapter 113), quantitative PLI or a gastrointestinal panel to look at TLI, cobalamin, and folate. Diagnosis of pancreatitis can be difficult with available modalities (see Chapter 86). Unfortunately, serum lipase and amylase which have been classically analyzed for pancreatitis can increase for extrapancreatic causes such as glucocorticoid administration or from decreased kidney function. The TLI test can also be increased in cases with other gastrointestinal disease or decreased kidney function.

Commercial species-specific ELISAs for pancreatitis have been developed (fPLI and cPLI). These measure pancreatic lipase in the serum. The commercial

canine-specific lipase (cPSL) has been found to have a specificity of almost 98% and sensitivity of almost 64% when compared to dogs with macroscopic evidence of pancreatitis at necropsy [3,4]. A cPLI cut-off of $>200\text{ }\mu\text{g/L}$ has been found to have a sensitivity of 43% or 71% with a specificity of 86% for mild or moderate pancreatitis respectively while a cut-off of $>400\text{ }\mu\text{g/L}$ had a sensitivity of 21% and 71% and a specificity of 100% for mild or moderate pancreatitis respectively [4]. In cats, the fPLI was also found to be sensitive and specific, with fPLI on admission $>20\text{ }\mu\text{g/L}$ associated with adverse outcome during hospitalization [5]. The sensitivity and specificity of the fPLI and cPLI have made it the most reliable serum marker in spontaneous pancreatitis cases [6,7].

Imaging

In identifying emergent causes of vomiting, simple imaging techniques such as abdominal radiographs can be invaluable. Radiographic changes may include but are not limited to regional intestinal dilation consistent with a mechanical obstruction, gastric distension, foreign material, loss of serosal detail from effusion, free gas, dilated fluid-filled uterine loops, or mass effects. Though plain film x-rays are not good for determining intestinal wall thickness, they can be used to determine dilation of loops of intestine. Common comparisons used include the the width of a rib or to the height of L5 at its most narrow point in dogs. A loop of intestine should be less than twice the width of the rib or less than 1.6 times the height of L5. In cats, a better measure is not greater than 12mm in diameter or less than twice the height of L4 [8]. Normal abdominal radiographs certainly do not rule out a foreign body but may make an emergent surgical foreign body a less likely diagnosis.

Additional techniques such as a pneumocolonogram to help differentiate colonic loops of intestine from small intestinal loops, barium studies, or repeated x-rays after passage of time can also be very helpful in diagnosing a foreign body. Additional imaging techniques may include an abdominal FAST scan to help identify and collect any free fluid and can be done by the emergency clinician (see Chapter 182). If there is suspicion of aspiration pneumonia or concurrent regurgitation with vomiting, chest radiographs should also be performed (see Chapter 37).

Based on results of those radiographs and clinical response, another diagnostic tool is an abdominal ultrasound. Ultrasound may help to identify a foreign body, especially one that did not cause a full obstruction or has a linear component. Additionally, ultrasound can be used to look at layering changes to the small intestine which cannot be identified on radiographs. Ultrasound can also detect non-GI causes such as renal changes, pancreatitis, liver abnormalities, pyometra, etc.

From these results and other testing, if primary GI disease is suspected or if a gastric foreign body is identified, endoscopy may be considered. Except in the case of a gastric foreign body, endoscopy is rarely an emergently needed procedure for a vomiting patient.

Therapy

Many causes of acute vomiting are self-limiting in the dog and cat. An important exception is identification of a foreign body which necessitates surgery or endoscopy, depending on the location. In general, treatment of non-specific acute vomiting should be based on the animal's clinical presentation. If an animal is not overtly dehydrated and still has an otherwise normal physical examination, it may respond well to outpatient care, including a short period of withholding food and then reintroduction of a bland diet. If an animal continues to vomit despite withholding food, begins to vomit on reintroduction of food, or refuses food when offered, the owner should be instructed to bring the animal back in for further diagnostics and potential hospitalization.

It is generally *not* recommended to give an animal with acute vomiting of unknown etiology antiemetics or prokinetics for multiple reasons. Prokinetics such as metoclopramide or erythromycin may cause increased luminal pressure in the case of an obstruction and increased risk of perforation. Antiemetics may mask vomiting even in the case of a foreign body, thereby reducing the chance of timely diagnosis of a surgical cause of vomiting. If a foreign body has been ruled out or a definitive cause of vomiting has been identified, antiemetics may be warranted.

Remember that vomiting can be caused by stimulation to many areas of the body, including directly to the organs of the GIT (stomach, small intestine), the afferent nerves (vagal, sympathetic, areas of the brain including the vestibular system, cerebrum, or CRTZ), or finally the vomiting center in the medulla. Therefore, antiemetics may target one or multiple sources and combination therapy may be useful.

Maropitant is a neurokinin-1 receptor antagonist blocking the effect of substance P on NK-1. By blocking the effect of substance P, maropitant works on the final pathway of emesis in the brain so it is a central antiemetic but it also works to block NK-1 in the GIT (peripheral effects). Maropitant has been found to be effective for parvovirus, emesis secondary to dietary indiscretion, and pancreatitis. Much higher doses have been used for vomiting from motion sickness [9]. The drug was originally labeled for use as subcutaneous or oral dosing but anecdotally has been used IV for years. Recent studies have shown bioequivalence of IV dosing as compared to subcutaneous (Zoetis label). The benefit of IV dosing is

in patients with poor perfusion but also because the drug has been found to be painful when given SC. The primary clearance route for maropitant is hepatic and so it is recommended to use caution in dosing in patients with liver disease. Maropitant is a very effective antiemetic but anecdotally may have limited effects on decreasing actual nausea and is often paired with other antiemetics for this reason. The author commonly uses doses of 1 mg/kg IV or uncommonly SC, or 2 mg/kg orally every 24 hours for both dogs and cats. It is generally recommended to treat up to 5 days before taking a day off from dosage.

A second group of drugs are the serotonin receptor ($5HT_3$) antagonists such as ondansetron and dolasetron which act as both antiemetics and antinausea medications. The serotonin antagonist competitively binds the serotonin receptor both centrally and peripherally, affecting the vagal afferents peripherally and the CRTZ and vomiting center centrally. These drugs are metabolized by the liver and excreted in the urine and bile and are fairly safe for all disease states in dogs and cats. This class of drug is the author's choice of antiemetic. Ondansetron is dosed at 0.2–0.5 mg/kg q8–12h IV, SC or PO. Dolasetron is given q12–24h at 0.6 mg/kg, again IV, SC or PO.

The use of “gastroprotectants” such as histamine-2-receptor antagonists and proton pump inhibitors is indicated in diseases that cause increased gastric acidity, such as uremia and liver disease, but not warranted in every case of vomiting [10]. H₂ receptor antagonists are competitive inhibitors of the H₂ receptors on the parietal cells of the stomach. This is one of the earlier steps to the production of gastric acid. The general dose for famotidine, which is the most commonly used H₂ antagonist, is 0.5–1 mg/kg IV, SC or PO q12–24h. Proton pump inhibitors block the hydrogen/potassium pump of the parietal cell which is the final common pathway of gastric acid production. The dose for these is 1 mg/kg q12–24h. The injectable form, pantoprazole, can be given IV or SC while the oral medication, omeprazole, can be bought over the counter in 10, 20, and 40 mg capsules.

Prokinetics are the most useful if there is a decreased motility component to the vomiting or regurgitation. Metoclopramide inhibits dopamine receptor and the $5HT_3$ receptor while stimulating the $5HT_4$ receptor. The effects on dopamine and $5HT_3$ make metoclopramide an antiemetic working in the CRTZ. That being said, clinically we see that metoclopramide does not work well as a single-drug antiemetic. Its effects on $5HT_4$ cause an increase in gastric emptying or increased tone of the lower esophageal sphincter which may be more helpful in cases of regurgitation, gastroparesis, or ileus. The effects are stronger when given as a CRI with doses generally 1–2 mg/kg/day. A rare side-effect is extrapyramidal signs

which are generally manifested as abnormal CNS stimulatory signs (excitation, tremors, aggression). A second prokinetic commonly used is erythromycin, a macrolide antibiotic which at lower doses works as a motilin receptor agonist by stimulating peristalsis of the small intestine, increasing lower esophageal sphincter tone, and increasing gastric emptying. The author uses a dosage of 0.5 mg/kg IV every 8 hours.

Other in-hospital treatments include IV fluid therapy for improvement of intravascular volume in the case of hypovolemia, replacement of losses and dehydration, provision of maintenance fluid needs, and accounting for ongoing losses. Treatments for specific causes such as pancreatitis, uremia, liver disease, parvovirus, etc. will be covered in other chapters.

Regurgitation

Physiology

As opposed to the active expulsion of food seen in vomiting, regurgitation is the passive ejection of material from the upper gastrointestinal tract. Regurgitation is more associated with esophageal disease. It can be due to decreased tone or dilation of the esophagus from megaesophagus, an obstruction to the esophagus from a mass or foreign body, decreased tone to the lower esophageal sphincter which commonly occurs secondary to esophagitis, or increased gastric residual volume from decreased gastric emptying [11] (Box 74.1).

Sequelae

Since regurgitation involves the expulsion of food or fluid without the normal vomiting arc, fewer airway protective measures may exist, increasing the risk for aspiration pneumonia. There may be less fluid loss in regurgitation but severe regurgitation, especially when associated with high gastric residual volumes due to decreased gastric emptying, can cause significant fluid and electrolyte loss similar to that seen in vomiting. Recurrent regurgitation can cause significant esophagitis and pain on swallowing as well as serious long-term sequela such as esophageal strictures.

Diagnostics

Historical questions should be aimed at determining whether the animal could have gotten into a caustic or toxic substance or had a recent anesthetic episode which may predispose to reflux. Physical examination may reveal pain in the neck from esophagitis, gas dilation of the cervical esophagus, or other abnormalities of the neck such as masses that could be causing a secondary

Box 74.1 Differential diagnoses for causes of regurgitation.**Pharyngeal diseases**

- Neuromuscular diseases
- Foreign body
- Mass (neoplasia, granuloma, abscess)
- Cricopharyngeal achalasia

Megaesophagus

- Congenital megaesophagus
- Idiopathic megaesophagus
- Secondary megaesophagus
 - Myasthenia gravis
 - Neuromuscular disease
 - Hypoadrenocorticism
 - Hypothyroidism
 - Lead toxicity
 - Extremely debilitated or critically ill patients

Esophagitis

- Drug or toxin
- Reflux (general anesthesia, idiopathic)
- Neoplastic

Obstruction

- Mass (intra- or extraluminal)
- Vascular ring anomaly (persistent right aortic arch)
- Foreign body
- Hiatal hernia
- Gastroesophageal intussusception
- Stricture

obstruction. Additionally, it is important to auscultate for pulmonary changes that indicate aspiration pneumonia, such as increased lung sounds or crackles.

Thoracic radiographs are imperative in the work-up of a regurgitating animal to help determine the cause. Segmental dilation of the esophagus may be indicative of conditions such as a vascular ring anomaly, mass, foreign body, stricture, or obstruction whereas generalized megaesophagus would lead to further diagnostics for an underlying systemic cause such as neuromuscular diseases. Radiographs are generally sufficient in diagnosing esophageal foreign bodies, with the most common

location between the heart base and diaphragm [12]. Thoracic radiographs should also be scrutinized for aspiration pneumonia. The identification of concurrent aspiration pneumonia with megaesophagus has been associated with an increased occurrence of death before discharge and a shorter survival time [13].

Additional imaging such as a barium swallow study can help determine if there is an anatomical abnormality of the esophagus such as a diverticula or whether there are changes such as achalasia or a hiatal hernia which cannot be seen on static films. The diagnostic advantages of a barium swallow must be weighed against the risks of barium aspiration. Additionally, endoscopy can be performed to look at the luminal surface of the esophagus for esophagitis, masses, or other abnormalities as well as to diagnose and treat a foreign body obstruction.

If a generalized megaesophagus is found on radiographs, further testing should be performed to look for a cause. This may include an ACTH stimulation test to rule out hypoadrenocorticism disease, thyroid hormone levels for hypothyroidism, and anti-acetylcholine antibody levels to test for myasthenia gravis as well as consideration of tick paralysis or botulism. Negative results for these tests would be supportive of idiopathic megaesophagus [14].

Treatment

The general treatment of regurgitation is often focused on preventing further esophagitis. Medication to decrease gastric acidity such as H₂ receptor antagonists or proton pump inhibitors are most commonly used and can be given orally, IV or SC, depending on the animal's clinical condition [8]. Sucralfate has been used to decrease ulceration but has not been found to be of greater benefit than the previously mentioned drug classes and must be given orally, which may not be tolerated [15].

Additionally, medications such as metoclopramide or cisapride are controversial but can be used to increase lower esophageal tone to decrease reflux of gastric contents. They may decrease the ability of material to pass into the stomach for the same reason. These medications may have more of an effect in cats because their distal esophagus is smooth muscle and not skeletal muscle as seen in dogs [10].

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Esophageal Foreign Bodies

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Introduction

Esophageal foreign bodies represent a fairly common reason for emergency presentation in small animals. Lodging of foreign bodies within the esophagus can cause complete or partial obstruction to the flow of ingesta, leading to the typical clinical signs. The vast majority of esophageal foreign bodies are bones, accounting for approximately 50–90% of cases [1–7]. Other objects have been described, including chew treats, organic material, plastic, fish hooks [8], sewing needles [9], and rarely trichobezoars [10]. A specific type of dental chew treat has been reported to cause particularly severe esophageal foreign body obstruction [11], though anecdotally the number of cases has declined since the formulation was changed in 2006 to make the treat less soluble and less likely to swell within the esophagus.

Esophageal foreign body obstruction should be treated as a medical emergency, as prompt removal is key to a successful outcome.

Presentation

Esophageal foreign bodies are generally more common in dogs than in cats, likely as a result of their indiscriminate eating habits, their typical chewing behavior and the tendency of dog owners to provide them with objects to chew, such as bones. The exception is sewing needles, which are more common in cats [9]. Most animals are young, with a median age of 4–5 years, though animals of any age can be affected [1,2,7,11]. Small and medium-breed dogs are predisposed [3,5,6,11].

In many cases, animals are presented following owner observation of foreign body ingestion, prior to the onset of clinical signs. This is especially true of foreign objects that are not typically offered to pets such as sewing needles and fish hooks [8,9]. When clinical signs occur, they

can vary. The most common clinical sign is retching or gagging, which is described in approximately 50% of cases [2,7,11]. Owners may also report coughing or hypersalivation. Regurgitation is inconsistently described, occurring in 17–55% of cases [2,7,11]. Non-specific signs such as lethargy and anorexia are common. The reported duration of clinical signs varies widely, from as little as 1 hour following observed ingestion to as much as 40 days [2,6,7].

Diagnosis

Survey cervical and thoracic radiographs are the initial diagnostic test of choice. These will identify virtually all esophageal foreign bodies [2,4–9,11]. Radiographic findings may include identification of the foreign object (as many are bone or metallic radiodensity) or dilation of the esophagus with fluid or gas proximal to the site of foreign body obstruction (Figure 75.1). Thoracic radiographs should be thoroughly evaluated for evidence of complications from the foreign body, including aspiration pneumonia and esophageal perforation. Radiographic signs of esophageal perforation may include mediastinal effusion, pneumomediastinum, pleural effusion or pneumothorax, though these changes are often absent until after endoscopy is performed [4,7]. In some cases, positive contrast radiography may be required to visualize the foreign body [11]. Ultimately, endoscopic examination provides definitive diagnosis in most cases.

The location of esophageal foreign body lodging tends to correlate to areas of anatomical narrowing. There are four areas where the esophagus narrows: upper esophageal sphincter, thoracic inlet due to surrounding soft tissue, base of the heart due to the aorta moving the esophagus to the right, and esophageal hiatus [1]. The most common site of entrapment is the caudal esophagus near the hiatus (50–75% of cases), followed by the heart base



Figure 75.1 Right lateral cervical and thoracic radiograph of a dog with an esophageal foreign body obstruction at the level of the heart base. The foreign body (a rawhide chew treat in this case) is represented by the soft tissue density containing irregular gas opacities (*black arrows*). The esophagus is dilated with gas cranial to the foreign body (*white arrowheads*). Source: Courtesy of Dr Jennifer Reetz, Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

[2,3,5,6,11]. However, fish hooks and sewing needles are more likely to lodge in the cervical esophagus if they pass the upper esophageal sphincter [8,9].

Treatment

Prompt recognition and removal of esophageal foreign bodies optimize the chances of a successful outcome. Treatment should be instituted on an emergency basis.

Endoscopy-assisted removal is the treatment of choice and is effective in approximately 90% of cases

[1,2,5–7,11]. Flexible endoscopes may be used for most foreign bodies. However, a rigid endoscope may be preferred for foreign bodies that are large or have sharp edges (especially if lodged in more cranial portions of the esophagus) as they may be pulled into the rigid endoscope to protect the esophageal mucosa during removal. If possible, the foreign body should be removed via the oral cavity. This is successful in 25–85% of cases. If unable to remove orally, the foreign body may be pushed into the stomach where it can be left to dissolve (in the case of bones, chews, and organic matter) or removed via gastrotomy.

Endoscopy enables visualization of the esophageal mucosa during and after removal to assess for complications such as esophagitis, necrosis, and perforation (Figure 75.2). Endoscopic removal can be challenging and should be performed by an experienced endoscopist. An alternative method for non-invasive removal utilizing hand-held forceps with fluoroscopic guidance has also been described [3].

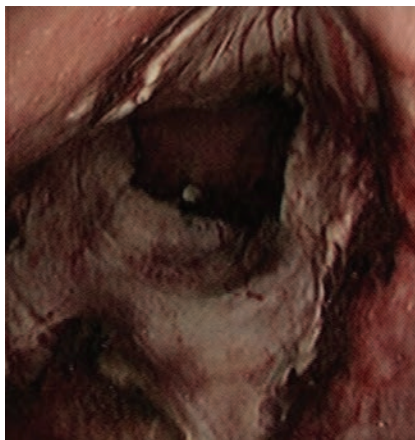
Following foreign body removal, most patients will require treatment for esophagitis. However, the optimal protocol for treatment of esophagitis is unknown and is often chosen empirically based on the degree of esophagitis visualized by the endoscopist.

For cases in which endoscopic removal is not possible, surgical intervention is necessary. In some cases, foreign bodies of the caudal-most esophagus may be removed through a gastrotomy incision. However, in most cases, thoracotomy and esophagotomy are necessary [1–6,11].

Removal of esophageal fish hooks represents a unique situation with more potential for variation in approach. Fish hooks embedded in the esophageal mucosa are more difficult to remove endoscopically than those that are not embedded [8]. Treble-barb hooks (three hooks in one) are more difficult to remove than single-barb hooks [8]. Because of the risk of esophageal laceration upon endoscopic removal, the esophageal mucosa should be



(a)



(b)

Figure 75.2 Endoscopic view of the cervical esophagus of a dog before (a) and after (b) removal of a bone esophageal foreign body. Extensive circumferential necrosis of the esophageal mucosa is present following removal. This dog went on to develop an esophageal stricture at the site of foreign body removal.

protected during removal. This can be accomplished by using a rigid endoscope, as described above, or by passing the flexible endoscope through a large-bore tube (such as a gastric decompression tube or a large endotracheal tube) and passing the large-bore tube into the esophagus. Using endoscopic instruments, the fish hook can be pulled into the large-bore tube and both can be removed from the esophagus simultaneously.

Despite the fact that esophageal lacerations up to 12 mm in diameter have been reported to heal without surgical intervention [8], the author recommends taking care to avoid laceration. Endoscopic removal should not be attempted when the fish hook has penetrated the esophageal wall. In one case with a penetrating fish hook near the heart base, such an attempt resulted in laceration of a pulmonary vein and death of the patient [8]. For penetrating fish hooks, the recommendation is to perform a thoracotomy. If possible, the surgeon can cut the hook and remove the end from the serosal surface of the esophagus, then the remainder can be removed endoscopically. Otherwise, esophagotomy must be performed. It is interesting to note that the time between fish hook ingestion and removal is not associated with whether complications develop or with the location of the hook [8]. Therefore, immediate removal may not be necessary if there are contraindications such as a full stomach which may increase the risk of aspiration during anesthesia.

Outcome

Most patients diagnosed with an esophageal foreign body will have a good outcome. Long-term survival is achieved in greater than 85% of cases in most reports [2,4,5,7]. Risk factors for death include body weight <10 kg [7] and presence of the foreign body for more than 2 days [5]. Cases requiring surgical removal of the foreign body have a worse outcome, with most reports suggesting a mortality rate of 20–100% [3,11], though in one report 13 of 14 dogs survived and were eating by 3 days postoperatively [4].

Non-fatal complications from the foreign body or its attempted removal are common. Complications are more common in dogs <10 kg [7], those with a foreign body present for >3 days [7], those with bone foreign bodies [7], and those with moderate or severe esophagitis following foreign body removal [6]. Commonly reported complications include esophagitis, esophageal perforation, and esophageal stricture formation, all of which are described in further detail below. Rare complications of endoscopic removal include pneumonia [1,5], esophageal diverticulum [6], periesophageal abscess [7], tracheal compression [5,6], bronchoesophageal fistula [2], iliac thromboembolism [5], and hemothorax [12].

Esophagitis

Esophagitis may occur as a result of foreign body ingestion, with injury induced either by mechanical trauma or by pressure at the site of lodging. The incidence of esophagitis secondary to esophageal foreign body is high, ranging from 15% to 100% of cases based on endoscopic appearance [1,2,6,7,11]. In most reports, >70% of cases develop esophagitis. The severity of esophagitis increases with longer duration of esophageal impaction, underscoring the importance of prompt removal. Dogs with mild esophagitis following foreign body removal had a shorter duration of clinical signs and a shorter time to return to oral feeding than did dogs with moderate or severe esophagitis [6].

Esophageal Perforation

Esophageal perforation is an uncommon but significant complication of esophageal foreign bodies. Incidence of perforation ranges from 3% to 36% [1,2,4–7,11]. Perforation has been associated with increased severity of esophagitis [6]. Immature neutrophils in peripheral blood have been suggested as a marker of perforation, though these are commonly seen in dogs with moderate-to-severe esophagitis without perforation [6]. Radiographic findings may include mediastinal effusion, pneumomediastinum, pleural effusion or pneumothorax. However, these findings may be absent in up to 80% of cases with perforation [4]. Perforations may also be missed at the time of endoscopy in up to 80% of cases [7]. There is potential for the insufflation used during esophageal endoscopy to cause severe pneumomediastinum and/or pneumothorax in animals with esophageal perforation, so attempts should be made to identify perforation as early as possible.

Esophageal Stricture

Esophageal injury caused by the presence of a foreign body may lead to esophageal stricture formation as a late complication. Esophageal stricture occurs when inflammation extends into the submucosal and muscular layers of the esophagus, stimulating production of fibrous connective tissue. As it matures, this fibrous connective tissue may contract, narrowing the esophageal lumen [11]. Stricture formation is more likely when circumferential esophageal injury occurs. Despite the apparent risk, the incidence of esophageal stricture following foreign body removal is low, ranging from 0% to 10% in most reports [2,5–7]. A higher incidence of 24% was reported following removal of a specific dental chew treat, likely attributable to unique characteristics of this particular foreign body [11]. Stricture formation is typically identified 9–25 days

following foreign body removal. Owners should be cautioned about the potential for stricture formation, which can lead to a need for extensive follow-up management, including multiple balloon dilation procedures.

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Diarrhea

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Introduction

Diarrhea is a common emergent medical condition in dogs and cats and is defined as abnormally frequent discharge of semi-solid or fluid fecal matter from the bowel. Decreased intestinal absorption and/or increased intestinal secretion is usually blamed for excess fecal water content [1], although an increase in fecal solid substance can be found in patients with diarrhea as well [2]. For clinical purposes, it is practical to categorize diarrhea as being acute or chronic, to localize it to small or large bowel, and to specify whether it is caused by a primary gastrointestinal (GI) disorder or an extraintestinal disease.

Considering the various causes of diarrhea and its potential self-limiting nature, the diagnostic approach will vary between patients, depending on history, severity and duration of diarrhea, concurrent clinical signs, initial clinicopathological findings, availability of diagnostic tests, owner's expectations, economic factors, and the risk of zoonotic transmission. Although the exact cause of acute diarrhea often remains obscure, a systematic diagnostic approach to chronic diarrhea will usually lead to the diagnosis.

Diagnostic Approach

Acute diarrhea (i.e. non-episodic diarrhea of less than 14 days' duration [1]) in properly vaccinated animal is usually mild and self-limiting when caused by a primary GI disease. Infectious diarrhea, dietary indiscretion, food allergy, and toxicities represent the most common etiologies in these patients. Clinical history (i.e. recent kenneling, traveling or show attendance, feeding raw or undercooked meat, known food allergy or food

intolerance, contact with sick animals) and physical examination findings are important in these patients. Fecal mucus, hematochezia, tenesmus, frequent soiling of small amounts, and urgency to defecate indicate large bowel disease, whereas melena and weight loss suggest small bowel involvement [3].

For animals with mild diarrhea and normal demeanor, still eating and drinking, and no vomiting or detectable dehydration, only supportive treatment with minimal diagnostics is often sufficient. Progression of clinical signs (i.e. moderate diarrhea, mild dehydration, decreased appetite and water consumption) and/or anticipated worsening of the disease state dictate the need for at least basic diagnostic tests (i.e. fecal flotation test, direct fecal smear, infectious disease testing if suspected, minimum database). Patients with signs of systemic involvement (i.e. depression, fever, severe dehydration, hypovolemia, inflammatory leukogram, left shift or toxic changes), severe GI disease (i.e. rapid worsening of clinical picture, vomiting, acute hemorrhagic diarrhea, melena, hypoalbuminemia, weight loss), abnormal abdominal palpation (i.e. abdominal pain, palpable masses, intestinal plication, ascites), and those with chronic diarrhea or suspected extraintestinal disease should have a more thorough diagnostic approach. Additional diagnostic tests and procedures (e.g. CBC, serum biochemistry, electrolytes, acid-base analysis, lactate, serum cobalamin and folate, TLI, PLI, infectious disease testing, abdominal radiography and/or ultrasound, intestinal biopsy) should be pursued in these animals.

Fecal cultures, toxin analysis, and genotyping are undertaken in animals with acute onset of bloody diarrhea with evidence of sepsis, with diarrhea outbreaks affecting a group of animals, and with increased risk of zoonotic transmission (i.e. working dogs, immunocompromised owner, contact with small children) [4].

Causes of Diarrhea (Table 76.1)

Primary Gastrointestinal Disease

Bacterial Infections

Clostridium perfringens, *Clostridium difficile*, *Campylobacter* spp, *Salmonella* spp, and *E. coli* have been associated with acute diarrhea in small animals [4]. However, many healthy animals harbor these bacteria and fecal isolation or detection of these organisms does not necessarily imply causation of clinical signs. For *C. perfringens*, it has been suggested that finding three or more clostridial spores on a stained fecal smear per high-power field may be used to diagnose enterotoxigenic-associated disease (Figure 76.1) [5]. Contrary to this, no association between fecal endospore counts and the presence of diarrhea or detection of *C. perfringens* enterotoxin (CPE) has been reported [6]. Despite the apparent relation between *C. perfringens* and acute hemorrhagic diarrhea syndrome (AHDS) [7], no differences in severity of clinical signs, hospitalization time or relevant laboratory parameters were detected between CPE-positive and -negative or between enterotoxin gene-positive and -negative dogs with AHDS [8]. In conclusion, the role of CPE in

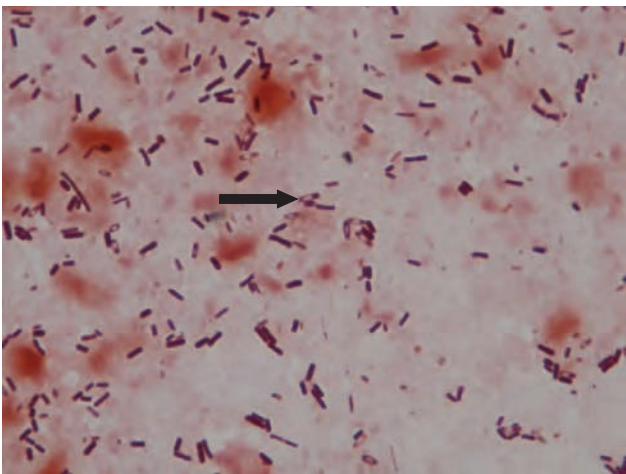


Figure 76.1 A fecal smear at 1000× magnification showing many clostridial spores (black arrow).

Table 76.1 Causes of diarrhea in dogs and cats.

Gastrointestinal	Extraintestinal
Infectious	Pancreatitis
Viral	Exocrine pancreatic insufficiency
Bacterial	Hepatobiliary disease
Parasitic	Hypoadrenocorticism
Fungal	Hyperthyroidism
Protozoal	Renal failure
Algal	Sepsis
Rickettsial	Cardiovascular shock
Adverse reactions to food	
Dietary indiscretion	
Gluttony	
True food allergy	
Other	
Neoplasia	
Inflammatory bowel disease	
Lymphangiectasia	
Drug induced	
Toxin ingestion	
Antibiotic responsive	

the development of diarrhea in dogs and cats remains unclear and *C. perfringens*-associated diarrhea (CPAD) appears more likely to be secondary to disruption of the intestinal microenvironment, enabling sporulation of commensal enterotoxigenic *C. perfringens* [9]. For the diagnosis of CPAD, combining CPE detection by ELISA with PCR detection of enterotoxigenic strains is recommended [9].

Clostridium difficile has been implicated in canine and feline enteric disease but it is not always clear whether this organism is a cause of community-associated disease, an opportunist causing disease concurrently with other enteropathogens, or an incidental finding [9]. Positive toxin A and B detection by ELISA and concurrent fecal detection of organism (i.e. culture, antigen ELISA, or real-time PCR) are needed for a presumptive diagnosis [9]. In a recent study, it appeared unlikely that *C. difficile* toxins A and B play an important role in the pathogenesis of AHDS [8].

Clinical disease caused by *Campylobacter jejuni* and *Campylobacter upsaliensis* is more likely in young animals, and additional factors like stress, crowding, kenneling, or concurrent diseases may contribute to campylobacteriosis [9]. The presence of slender, curved rods with an S shape or seagull-shaped bacteria on direct stained fecal smear suggests the presence of *Campylobacter*-like organisms, but *Campylobacter* enteritis should be confirmed with a positive fecal culture and molecular methods [4].

Salmonella is a pathogen for dogs and cats but not all strains are equally capable of causing enteritis [9]. Isolation of the organism combined with appropriate clinical signs and potential risk factors (i.e. hospitalization, environmental exposure, age, antibiotic treatment) are required for the diagnosis [9].

Certain virulent *E. coli* pathotypes can cause intestinal infection in dogs in the presence of impaired local or systemic immunity [9]. Granulomatous colitis of boxers has been associated with pathogenic *E. coli* strains and similar colonic lesions have been described in the French Bulldog and border collie [9]. PCR is one of the most common methods for detecting and differentiating pathogenic strains of *E. coli* [4].

Viral Infections

When a canine parvovirus (CPV) infection is suspected in AHDS, a rapid in-clinic test for fecal CPV antigen should be done. These tests perform with high specificity but poor sensitivity compared to PCR or immune-electron microscopy [10]. With a negative rapid test, a diagnosis of parvovirus is thus not completely ruled out. Hemorrhagic diarrhea, depression, dehydration, vomiting, fever, abdominal pain, and severe leukopenia are common with this highly contagious and potentially fatal disease and could help with the diagnosis. A similar clinical picture is seen in cats with feline panleukopenia virus infection.

Paramyxovirus (e.g. canine distemper virus) has also been strongly associated with acute hemorrhagic diarrhea [11]. Other viruses like canine and feline coronavirus, feline leukemia virus, feline immunodeficiency virus, rotavirus, and norovirus can cause diarrhea, although severe acute enteritis is not a common clinical presentation.

Gastrointestinal Parasites

Toxocara spp, *Toxascaris* spp, *Strongyloides* spp, *Trichuris* spp, and *Ancylostoma* spp can be important infectious agents causing acute diarrhea in puppies, kittens, and young animals and should be excluded by fecal examination. *Giardia* spp is a common enteric organism in young dogs and cats with diarrhea, especially animals younger than 6 months [12]. Direct fecal saline smear and fecal flotation should be used for initial screening, whereas examining at least three stool samples using fecal flotation with zinc sulfate will enhance detection of *Giardia* spp cysts [13]. In-clinic fecal ELISA antigen assays can be used to detect *Giardia*. Fecal immunofluorescence assay (IFA) and PCR testing are also available. Coccidial parasites (i.e. *Isospora* spp, *Cryptosporidium* spp) can be the causative agent of diarrhea in puppies, kittens, and immunosuppressed animals when infestation is severe. *Isospora* spp oocysts are found on direct examination of a fecal smear or by flotation. *Cryptosporidium* spp oocysts are usually not detected on fecal flotation and an IFA assay is needed [13].

Other Infections

Various fungal, algal, and rickettsial organisms have been associated with diarrhea in small animals, depending on geographical location, and should be excluded with appropriate tests if deemed necessary.

Adverse Reactions to Food, Toxins, and Drugs

While food intolerance (i.e. dietary indiscretion, glut-tony, toxicities) encompasses non-immunological reactions to food, true food allergy (FA) represents an immune-mediated reaction [2]. Consumption of table scraps, garbage, spoiled moldy foodstuffs, and indigestible materials may result in GI irritation and inflammation, and possibly acute pancreatitis. Ingestion of variable foreign bodies should be excluded. While signs of GI upset predominate with food intolerance, pruritic skin disease is usually the primary symptom in true FA [2]. Response to a dietary elimination trial and recurrence of signs during dietary provocation remain the centerpiece of FA diagnosis [14]. Enteral tube feeding with commercially prepared liquid diets can lead to diarrhea as well.

Poisons and toxins such as irritant or corrosive intoxicants, detergents, insecticides, heavy metals like zinc or lead, mushrooms, chocolate, organophosphates, and carbamates are associated with GI upset [15]. Medications (e.g. antimicrobial agents, NSAIDs, chemotherapeutics, antiarrhythmics, lactulose, proton pump inhibitors, immunomodulatory drugs [3]) can also cause acute diarrhea and should be excluded.

Other Intestinal Diseases

Neoplastic intestinal disease (i.e. alimentary lymphosarcoma, GI adenocarcinoma, GI stromal tumors, mast cell tumor), inflammatory bowel disease (IBD), lymphangiectasia and antibiotic-responsive diarrhea can result in resilient diarrhea. Abdominal ultrasound has become indispensable in the diagnostic process of chronic diarrhea because of its ability to detect intestinal masses and foreign bodies, intestinal wall thickening and/or loss of layering, and lymphadenopathy. Fine needle biopsies can sometimes be diagnostic but an intestinal biopsy, either endoscopic or surgical, is usually needed for a definitive diagnosis.

Extraintestinal Diseases

Extraintestinal disease causing secondary diarrhea should be considered in every diarrheic patient. Acute and chronic pancreatitis, exocrine pancreatic insufficiency, hepatobiliary disease, renal failure, hyperthyroidism, hypoadrenocorticism, sepsis, and cardiovascular shock are conditions that should be explored. Historical findings (i.e. garbage eating, increased fecal solid matter) and/or clinical signs (e.g. polyuria, polydipsia, icterus, enlarged thyroid glands, abdominal pain, heart gallop or murmur, cardiovascular shock) may be noted and thus indicate the need for further testing, such as urinalysis, pancreatic lipase immunoreactivity, total T4 and resting cortisol or ACTH stimulation.

Treatment

Based on severity and etiology of diarrhea, the clinical picture, and clinicopathological findings, one needs to decide what, if any, treatment should be implemented. Owner expectations, economic factors, risk for zoonotic transmission, and hospital hours will also influence the course of treatment.

Supportive Treatment

When mild diarrhea is caused by dietary indiscretion, the animal is clinically stable and there is room for a supportive treatment trial only, dietary modification, oral rehydration, and probiotics are often adequate. Food should be withheld for 24 hours and feeding with small amounts of a bland diet several times a day restarted thereafter. Even moderate dehydration in the absence of frequent vomiting can be effectively corrected with oral electrolyte solutions [16], while use of probiotics may reduce the convalescence time in acute, uncomplicated gastrointestinal disease [17]. When significant diarrhea is caused by a patient's current medications, the treatment plan should be modified and incriminated drugs discontinued. Activated charcoal can be used in patients with acute diarrhea to remove ingested toxins, bacteria, and bacterial toxins. Medications affecting intestinal motility (e.g. loperamide, diphenoxylate, opium tincture) are rarely used to control diarrhea because treatment of primary disease provides the best means for cure [3].

Fluid Therapy

Parenteral fluid therapy is needed when diarrhea results in significant dehydration. Fluid deficits, whether intravascular, interstitial or intracellular, should be corrected, as well as electrolyte and acid–base abnormalities. Subcutaneous fluids can be used in animals with mild dehydration. However, when diarrhea results in significant dehydration, electrolyte and acid–base imbalances, or the animal is in hypovolemic shock, intravenous or intraosseous administration of a balanced crystalloid is indicated (see Chapter 153). The volume of fluids given should be adequate to correct for hypovolemia, dehydration, maintenance needs, and ongoing losses. The type of crystalloid solution used will depend on the patient's acid–base and electrolyte balance (see Chapter 167).

Antiparasitic and Antimicrobial Therapy

Intestinal parasitism is treated with appropriate antiparasitic drugs. Proper hygiene must also be implemented

to stop reinfection and spread. In patients that are symptomatic from *Giardia* infections, treatment with metronidazole and/or fenbendazole is indicated [13].

Commonly, prophylactic antimicrobials are used in the treatment of hemorrhagic diarrhea to control bacterial translocation, bacteremia, and sepsis. However, in a study of patients with idiopathic AHDS, the incidence of bacteremia did not differ from healthy dogs and its presence had no effect on clinical course or survival [18]. In addition, use of amoxicillin/clavulanic acid in non-septic patients with AHDS did not affect severity of clinical signs, duration of hospital stay or mortality rate compared to placebo in another study [19]. Thus, while supportive therapy and appropriate hygiene control should be considered in all animals with suspected or confirmed bacterial-associated diarrhea, antimicrobials should only be used in animals manifesting systemic signs of illness [9].

Most isolates of *C. perfringens* are susceptible to ampicillin, metronidazole, and macrolide antibiotics [20]. For treatment of *C. difficile* infection, metronidazole (10 mg/kg PO or IV q12h for 5 days) is commonly administered, and increasing soluble fiber in the diet has been recommended [9]. Macrolides (i.e. erythromycin 10–15 mg/kg PO q8h; azithromycin 5–10 mg/kg PO q24h, for 5–21 days) or fluoroquinolones are most commonly used for treatment of campylobacteriosis [9]. In patients with salmonellosis, a combination of ampicillin and enrofloxacin is recommended as empirical therapy, although antimicrobial susceptibility testing should also be performed [9]. Granulomatous colitis associated with *E. coli* responds well to enrofloxacin (10–15 mg/kg PO q24h for 8 weeks) or other fluoroquinolones [9]. Antibiotic-responsive diarrhea is commonly treated with tylosin, metronidazole or oxytetracycline [2].

All small animals with idiopathic or infectious diarrhea caused by any of the bacteria described above should be considered potentially contagious to other animals and people [9].

Dietary Therapy

The essence of long-term management of FA and food intolerance is feeding a food with novel sources of protein and carbohydrates, and avoidance of offending food ingredients. Similarly, animals with IBD should be given a novel protein diet or a diet with hydrolyzed protein source, whereas those with lymphangiectasia may benefit from a low-fat diet [3].

Other Therapies

Most animals with moderate-to-severe IBD will need some degree of immunomodulation (e.g. glucocorticoids, azathioprine, chlorambucil, cyclosporine)

to obtain clinical remission [3]. Surgery is indicated for patients with obstructive intestinal foreign body or intussusception, and surgically treatable neoplastic disease. Chemotherapy might be beneficial

either as a sole line of treatment or in combination with surgery for animals with intestinal neoplasia. Extraintestinal disease causing diarrhea must be addressed accordingly.

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Hematemesis and Gastrointestinal Hemorrhage

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Introduction

Gastrointestinal (GI) hemorrhage is an important cause of blood loss. The exact prevalence of GI bleeding in veterinary patients is unknown, but it is reported frequently in dogs and less commonly in cats [1,2]. Blood in the vomit (hematemesis) can come from ingested food containing blood, swallowed blood originating from the oral, nasal, or pharyngeal region, the esophagus, or the stomach or proximal duodenum (Figure 77.1). Hematochezia (frank red blood in the stool) occurs with hemorrhage originating in the small or large intestines (Figure 77.2). Melena (digested black blood in the stool) occurs with hemorrhage originating in the stomach or proximal small intestine. Occult, low-grade bleeding may not visibly change stool color. Blood loss can be minor and short-lived, or acute and

large volume requiring intensive therapy. Targeted therapy requires localizing the source of hemorrhage, and understanding the etiology and pathophysiology of GI injury.



Figure 77.1 Hematemesis.



Figure 77.2 Hematochezia.

Etiology and Pathophysiology

Trauma, infection, and inflammatory lesions, as well as coagulation disorders affecting the oral or nasal cavity or esophagus, can result in injury to the epithelial lining and bleeding. Blood can be expelled from the oral and nasal cavity or swallowed and subsequently recognized as hematemesis or melena. Hemorrhage of the GI tract may involve more complex factors.

There is only one cell layer that maintains a barrier protecting the gastric wall from gastric acid and digestive enzymes. On the mucosal surface, a layer of mucus containing bicarbonate-rich fluid neutralizes the gastric acid. The bicarbonate is delivered by the mucosal blood supply. Mucosal blood flow is regulated through prostaglandin-mediated mechanisms. Similarly, the small intestinal mucosal lining is a single cell layer of epithelial cells, but it has a more specialized architecture and

function. A complex protein-to-protein network links adjacent cells and selectively seals the intercellular space. The small intestinal interstitium has a higher concentration of albumin compared to other organs, so that when there is disruption of the epithelial barrier, a large amount of protein can be lost in the stool [3].

Box 77.1 outlines the various categories and causes of GI hemorrhage. Conditions leading to erosive or ulcerative gastroenteritis are the most common cause of GI hemorrhage [4]. Pathological processes that reduce gastric mucosal blood supply and/or result in a severe metabolic acidosis change the gastric mucosal surface layer and make it susceptible to the caustic effects of bile acids. The protective intestinal lining is also highly susceptible to the effects of a reduced blood supply. In cats, neoplasia, including systemic mast cell disease, intestinal lymphoma and gastrinoma, has been reported to be the most common cause of gastric ulceration. In canine patients,

Box 77.1 Causes of gastrointestinal hemorrhage.

Erosive/ulcerative gastroenteritis

Infectious

Bacterial

Campylobacter
Clostridium spp
Salmonella
Pythium

Parasitic

Coccidia
Hookworms
Roundworms
Whipworms

Inflammatory

Neoplasia

Systemic neoplasia (e.g. mastocytosis)
Adenocarcinoma
Leiomyoma
Lymphoma

Systemic disease

Uremia
Heatstroke
Hepatic disease
Hypoadrenocorticism
Pancreatitis
Neurological disease (head trauma, intervertebral disk disease)

Tissue hypoxia/ischemia

Gastric dilation volvulus
Mesenteric volvulus
Intussusception

Systemic inflammatory response syndrome/sepsis
Stress-related mucosal disease

Viral

Coronavirus
Distemper
Parvovirus
Rotavirus

Fungal

Histoplasma
Acute hemorrhagic diarrhea syndrome

Toxicities

Chemotherapeutic agents
Glucocorticoids
Non-steroidal anti-inflammatory agents
Ricin (castor bean)
Others

Coagulopathy

Anticoagulant toxicity
Thrombocytopenia
Congenital factor deficiencies
Prekallikrein deficiency
Hepatic failure

Vascular anomalies

Esophageal varices
Colonic vascular ectasia
Arteriovenous fistulae

Trauma

Foreign objects
Forceful emesis

hepatic disease and NSAID use have been described as the most common risk factors for ulceration [5,6].

The mechanism of NSAID- and corticosteroid-induced ulceration involves prostaglandin inhibition via non-selective inhibition of cyclo-oxygenase 1 and 2, which leads to decreased epithelial mucous production, decreased bicarbonate secretion, and decreased mucosal blood flow [7]. Ingested NSAIDs also have a direct irritant effect on the gastric mucosa. The detrimental effects of NSAIDs are compounded by use of multiple NSAIDs, high doses, and concurrent corticosteroid or anticoagulant therapy [8]. All commonly used NSAIDs have been found to cause gastric lesions of varying severity and in some cases, full-thickness ulceration leading to perforation has been documented [7,9].

Hepatic failure is associated with increased gastrin secretion and mucosal blood flow alterations [5]. The mechanism of uremic gastritis also involves increased gastrin concentrations secondary to decreased renal clearance. Gastrin stimulates the release of hydrochloric acid from parietal cells which may lead to hyperacidity and potential chemical damage to the gastric mucosa [10]. Decreased blood flow due to hypotension, shock or sepsis can lead to mucosal ischemia and subsequent erosion and ulceration. These conditions are discussed further in specific chapters in this text (see Chapters 152–155). Coagulopathies may also result in gastrointestinal hemorrhage [1,4] (see Chapter 70). Although the mechanism is not well elucidated, thrombocytopenia is the most commonly reported coagulopathy leading to GI hemorrhage in dogs [1] (see Chapter 67). Trauma caused by foreign objects or violent and persistent emesis can also result in hemorrhage.

Vascular anomalies, such as gastroesophageal varices in patients with cirrhosis, are a common cause of GI hemorrhage in humans [11]. Vascular anomalies are rarely documented in veterinary patients, with jejunal arteriovenous fistula and colonic vascular ectasia having been reported [12,13]. These should be investigated for only after the more common causes of GI hemorrhage have been ruled out.

Clinical Signs and Physical Examination

The presence of GI tract hemorrhage can be identified with gross evidence of blood in vomitus or stool, or suspected when clinical signs of hemorrhage exist without evidence of thoracic, peritoneal or retroperitoneal bleeding. Historical information may include the visible presence of blood in the vomitus or stool, hyporexia, and/or exposure to medication or toxins associated with GI ulceration.

Acute GI hemorrhage with or without GI perforation will manifest with clinical signs associated with

hypovolemia, including tachycardia (dog), bradycardia (cat), mucous membrane pallor, poor pulse quality, cool extremities, and hypothermia (see Chapter 153). Chronic GI hemorrhage may cause more insidious signs of general malaise related to anemia without hypovolemia, including weakness, pallor, tachycardia, and bounding pulses (see Chapter 10). Examination of the patient may reveal visible signs of blood in the stool and painful reaction to abdominal palpation. Immediate therapeutic intervention may require oxygen supplementation, analgesia administration, rapid, low-volume fluid resuscitation to desired hemodynamic endpoints, and transfusion administration (see Chapter 170).

Once stabilization efforts have been initiated, a comprehensive secondary survey is obtained. It should include an oropharyngeal examination, careful abdominal palpation before and after analgesia administration localizing intra-abdominal mass lesions and/or the presence of fluid, and a digital rectal examination documenting the presence and character of blood in the stool.

Localizing the site of GI bleeding is necessary to determine which diagnostic and definitive treatment options are indicated. Hematemesis can occur not only with bleeding from the stomach and/or upper duodenum, but also with bleeding from the oral, nasal, or pharyngeal region and/or esophagus. Melena occurs when blood originating in the stomach and/or upper small intestinal tract has been partially digested. Hematochezia is most indicative of large intestinal, rectal, or anal hemorrhage. However, if a decreased GI transit time is present, frank blood from the upper GI tract may also appear in the stool [4]. Diagnostic evaluation may include laboratory testing, diagnostic imaging, endoscopy, and surgical intervention.

Laboratory Evaluation

Laboratory analysis includes a comprehensive serum biochemistry panel, a complete blood count, and coagulation testing (prothrombin time, activated partial thromboplastin time, and possibly viscoelastic testing). Gastric and small intestinal hemorrhage can cause an increase in the blood urea nitrogen in the absence of other indicators of renal failure (e.g. creatinine elevation, loss of urine-concentrating ability) due to intestinal absorption of digested blood proteins [1,14]. Electrolyte disturbances may result from profound fluid shifts or hypoadrenocorticism [15]. Anemia may be characterized by a normocytic, normochromic non-regenerative anemia with acute GI hemorrhage, and a microcytic hypochromic anemia (with or without a regenerative response) from loss of iron with chronic GI hemorrhage [1]. Thrombocytopenia must be profound (e.g. due to

an immune-mediated process) to be considered a cause of GI hemorrhage [1]. Hepatic failure, anticoagulant toxicosis, and hereditary factor deficiencies are considered with significant prolongation of coagulation times (see Chapters 69, 90, and 130).

Hypocortisolism has been reported as a cause of severe GI hemorrhage in canine patients and ACTH stimulation testing should be considered if other causes have been ruled out [15,16] (see Chapter 115).

Fecal evaluation for GI parasites should routinely be performed, and fecal occult blood testing considered in cases where GI hemorrhage has not yet been confirmed. Several test kits for fecal occult blood testing are available, most of which rely on hemoglobin's peroxidase activity. False-positive results are possible with patients fed a red meat-based diet or food rich in peroxidase. Feeding a meat-free diet for at least 3 days is recommended prior to testing [17].

Diagnostic Imaging

Survey two-view abdominal radiographs may detect the presence of masses, foreign material or intraperitoneal gas, but are not helpful in identification of mucosal lesions [5,18]. Thoracic and cervical radiographs looking for esophageal dilation or intraluminal objects are indicated when esophageal bleeding is suspected. Radiographic GI contrast studies (e.g. barium swallow) may outline ulcerative lesions, but this modality has been largely replaced by ultrasound and endoscopy [4].

Abdominal ultrasonography may identify GI luminal foreign material, obstructions and/or masses [18]. Ultrasonography also allows evaluation of GI wall thickness and can identify ulcerative lesions, which are characterized by increases in wall thickening with focal mucosal disruption and accumulation of microbubbles at the site of the ulcer crater [19]. Abdominal computed tomography (CT) angiography may be useful for identification of masses, full-thickness disease such as perforations, and vascular anomalies. Ultrasonography and CT also allow evaluation of other intra-abdominal structures and associated pathology, such as changes associated with pancreatitis, malignancy, and GI blood flow [20].

Endoscopy

Endoscopy is a sensitive method for identifying esophageal, gastric, and upper (duodenal) and lower (colonic) intestinal tract lesions that can cause hemorrhage [21]. It allows for direct visualization of the mucosal surface and biopsy sample collection [21]. When traditional management of gastric ulceration has failed, endoscopic-directed

injection of epinephrine, thrombin, and fibrinogen into an ulcer may allow for control of hemorrhage [22,23]. Application of endoclips to a visible bleeding vessel and use of endoscopic cautery have also been described [22]. Iatrogenic ulcer perforation and exacerbation of GI bleeding are potential risks associated with endoscopy.

Exploratory Laparotomy

Exploratory laparotomy may be necessary to obtain full-thickness samples for histopathological evaluation and culture, and with cases of intractable hemorrhage to identify and attain acute hemorrhage control.

Treatment

The mainstay of therapy for all patients with GI hemorrhage includes restoring and maintaining tissue perfusion and hemorrhage control. Gastroprotectant agents including acid-reducing drugs, prostaglandin E1 analogues, and coating agents are prescribed when gastric hemorrhage is suspected. Acid reducers increase the gastric pH, making the gastric environment more conducive to healing, and reduce hemorrhage and rebleeding risk [21,22].

Proton pump inhibitors, such as omeprazole and pantoprazole, inhibit gastric proton pump transport of hydrogen. Histamine-2 (H₂) receptor antagonists such as famotidine, cimetidine, and ranitidine inhibit the action of histamine at the gastric H₂ receptors, leading to a reduction in gastric acid secretion. Proton pump inhibitors are largely considered to be superior to H₂ antagonists, particularly in cases of NSAID-induced GI bleeding or stress-related mucosal disease [24–29].

Misoprostol, a prostaglandin E1 analogue, can be administered prophylactically to prevent the development of gastric mucosal lesions during NSAID administration or overdose [30] (see Chapter 133).

Sucralfate coats ulcerated gastric mucosa. It dissociates to form sucrose octasulfate and aluminum hydroxide, binding to ulcerated mucosa, preventing back diffusion of hydrogen ions, and inactivating pepsin. Administration of sucralfate concurrently with other medications may reduce their absorption due to chelation with aluminum. Sucralfate, therefore, should be given at least 30–120 minutes apart from other medications. Sucralfate is more effective when administered as a suspension as opposed to tablet formulation [31].

Antinausea therapy including maropitant, dolasetron, and metoclopramide can be administered in cases of persistent vomiting. There is a theoretical risk of increasing gastric bleeding with the use of prokinetic medication

(e.g. metoclopramide), but this has not been determined to be a clinically relevant problem.

Placement of a nasogastric tube (NGT) should be considered. Nasogastric tubes provide a means to initiate early enteral nutrition, administer oral medication, decompress a fluid- or gas-dilated stomach, characterize gastric fluid, and identify presence/persistence of hemorrhage. They also allow quantification of residual gastric fluid volume/blood. Benefits of enteral feeding include maintenance of the intestinal mucosa health, prevention of villous atrophy, preservation of immunological function and increased safety and ease of nutrition supplementation compared to parenteral nutrition [32,33]. Initiation of early enteral nutrition may also decrease the requirement for gastroprotectant administration, particularly in cases of stress-related mucosal disease [34]. Once recommended for the management of GI hemorrhage, iced saline lavage via a NGT has not been shown to prevent or decrease upper GI bleeding [35].

The use of broad-spectrum antibiotic therapy in cases of GI hemorrhage is controversial. Use should be restricted to treatment of known or suspected primary GI bacterial overgrowth/infection as a causative agent for GI hemorrhage. Patients with acute hemorrhagic diarrhea syndrome without signs of sepsis treated with a placebo or broad-spectrum antibiotic therapy had no significant difference in morbidity or mortality [36,37]. In patients with signs of severe sepsis or septic shock, antimicrobial treatment may be indicated and blood culture samples considered. Broad-spectrum coverage to consist of a beta-lactam and a fluoroquinolone or aminoglycoside, or a combination of a cephalosporin,

metronidazole, and a fluoroquinolone or aminoglycoside, is most appropriate in septic patients with GI barrier dysfunction [4].

Transfusion of red blood cell products is indicated when clinical signs associated with anemia are present (see Chapter 176). Several retrospective analyses report that 6–11.7% of administered packed red blood cell transfusions were for dogs with GI hemorrhage [1,38]. Plasma product and vitamin K administration are indicated with significant hemorrhage related to coagulation factor deficiency. Guidelines for administration of blood products to cardiovascularly stable, yet anemic patients are not established in veterinary medicine. A recent study in people documented improved outcomes with a restrictive strategy for transfusion (a transfusion is administered once the hemoglobin concentration falls below 7 g/dL), compared with a liberal strategy (transfusion administered once the hemoglobin concentration falls below 9 g/dL) in people with severe acute upper GI bleeding [39].

Prognosis

The majority of cases of mild hematemesis and GI hemorrhage are self-limiting and respond well to medical management, but prognosis varies with the underlying cause. In cases of GI hemorrhage severe enough to require blood transfusion in dogs, prognosis has been shown to be fair to poor, with mortality rates of 29–45% reported [1,38]. Mortality rates in people are similar, with a reported 3-year mortality rate of 36.7% following upper gastrointestinal bleeding [40].

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Parvovirus Enteritis

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Pathogenesis

Canine parvovirus (CPV), type 1 and type 2, is a small non-enveloped DNA virus that replicates in rapidly dividing cells. The more virulent strain (type 2) has undergone genetic alterations over the past four decades. Categorization of type 2 CPV currently involves three strains: CPV-2a, CPV-2b and CPV-2c. An epidemiological study within the United States indicated that CPV-2b and CPV-2c predominate with naturally occurring disease. Clinical research suggests that disease severity and outcome do not differ between CPV-2b and CPV-2c infection [1].

Canine parvovirus often infects unvaccinated puppies between 6 weeks and 6 months of age. Breed, genetic background, and the innate immune system all factor into individual response to infection. Tumor necrosis factor alpha production by peripheral blood monocytes has been shown to be greatest in dogs with breed-related risk for CPV, specifically Dobermans and rottweilers [2–4]. It is likely that both genetic and environmental factors affect the risk of CPV infection for a given individual. Lack of vaccination poses the greatest threat to puppies exposed to CPV.

An incubation period of 7–14 days follows oronasal exposure to CPV-contaminated feces. Virus replication occurs in lymphoid tissue of the oropharynx, thymus, and regional lymph nodes. Viremia occurs within 1–5 days of infection, facilitating CPV movement into the germinal epithelium of enterocytes [5]. Small intestinal crypt cells undergo necrosis, causing villous collapse, leading to altered gastrointestinal tract function. The compromised blood–gut barrier encourages movement of gram-negative and anaerobic bacteria from the intestinal lumen into the bloodstream. Secondary bacteremia may result in life-threatening complications, including sepsis and coagulation disorders.

Although the gastrointestinal tract is the organ primarily involved with CPV infection and transmission, other tissues may be affected. Myocardial disease has been reported with neonatal infection; myocarditis may precede intestinal signs and result in peracute death in such cases [6]. Other organs affected by CPV may include the bone marrow, respiratory system, liver, and kidneys.

Clinical Signs

Non-specific signs of illness such as lethargy and anorexia may be noted in the peracute phase of infection. Following this brief period, symptoms of enteritis predominate. Classic symptoms of CPV include anorexia, vomiting, and diarrhea. Diarrhea can range from mucoid to hemorrhagic and is often large in volume, frequent, and liquefied. Activation of peripheral small intestinal receptors signals afferent vagal pathways and stimulates the emetic center within the central nervous system.

Severe vomiting and diarrhea lead to dehydration, hypovolemia, and cardiovascular collapse. Dogs often present with abnormal perfusion parameters, including tachycardia, abnormal mucous membrane color, prolonged capillary refill time, weak or absent pulses, and altered mentation (see Chapter 153). Mentation changes and generalized weakness may be due to hypoperfusion, hypoglycemia, hypokalemia or any combination thereof.

Most CPV patients display moderate-to-severe abdominal pain. This visceral pain is most likely associated with diffuse enteritis, although intestinal intussusception should remain a differential diagnosis for severe pain. Rarely, respiratory signs may occur in dogs infected with CPV. This may be due to concurrent aspiration pneumonia, pulmonary involvement of CPV, systemic or metabolic disturbances (i.e. metabolic acidosis), or acute respiratory distress syndrome.

Diagnostic Tests

Given the highly infectious nature of CPV, animals suspected of having it should be kept isolated and caregivers should wear barrier precautions until the diagnosis is determined. All animals confirmed to have CPV will need to be cared for in an isolation facility.

The most common diagnostic test used for detection of CPV is an enzyme-linked immunosorbent assay (ELISA). The ELISA is a rapid, inexpensive, and clinically useful test to detect antigen. The CPV ELISA detects viral antigen in feces or rectal swabs for all CPV type-2 variants, although false-negative results can occur [7]. Low viral shedding load in the feces, binding of CPV-neutralizing antibodies with antigen in diarrhea, performing the ELISA ≥ 10 days after initial infection, or dilution of the virus in liquid feces may all contribute to false-negative results [7,8]. False-positive CPV ELISA results following modified live virus vaccination were not demonstrated in dogs from a recent study [9].

Polymerase chain reaction (PCR) assays detect DNA in whole blood or feces. Proposed benefits of PCR include increased test sensitivity and characterization of the viral strain. PCR may be considered in cases when ELISA is suspected to be falsely negative or further epidemiological information is desired. Disadvantages associated with PCR assays include accessibility, expense, and laboratory turnaround time. Other methods used to diagnose CPV include hemagglutination, virus isolation, and electron microscopy.

Ancillary diagnostic tests for CPV dogs include complete blood count (CBC), venous blood gas and electrolyte panel, biochemical profile, coagulation panel, fecal flotation, and cavitory imaging. Although these diagnostics are considered ideal, treatment is prioritized in cases of financial constraint. Minimum diagnostics should include a packed cell volume and total protein, blood glucose, as well as a blood smear and electrolytes to screen for leukopenia, thrombocytopenia, hypokalemia, azotemia, and hypoglycemia. A fecal flotation is ideal, although empirical deworming is often pursued with treatment.

Destruction of hematopoietic progenitor cells often leads to leukopenia. Neutropenia is due to myeloblast destruction within the bone marrow and consumption of peripheral neutrophils. A degenerative left shift may be associated with improved survival, as it indicates some degree of bone marrow response [10]. Lymphopenia is a common finding that has been demonstrated to be more severe in CPV non-survivors at 24 and 48 hours post hospital admission, whereas a rebound in lymphocyte count was positively associated with survival [10]. Other CBC abnormalities can include a non-regenerative anemia, secondary to

gastrointestinal hemorrhage and acute blood loss. Age of the puppy, hemodilution with intravenous fluids and iatrogenic blood loss from frequent blood sampling may also contribute to anemia. Thrombocytopenia may occur following systemic inflammation, development of a hypercoagulable state, and subsequent platelet consumption.

Venous blood gas often reveals a metabolic acidosis from hyperlactatemia, prerenal azotemia, hyponatremia (dilutional acidosis), and/or gastrointestinal bicarbonate loss. Metabolic alkalosis may be appreciated from hypochloremia and vomiting of upper gastrointestinal contents. Hypokalemia, secondary to gastrointestinal loss and decreased intake, often requires aggressive supplementation throughout hospitalization. Hyponatremia and hypochloremia also occur secondary to diarrhea and vomiting, but correct quickly with appropriate electrolyte replacement fluid therapy. Hypoglycemia may develop as a result of excessive glucose utilization, decreased intake, and decreased gluconeogenesis. Hypoglycemia may require ongoing supplementation to normalize and maintain serum values.

Treatment and Monitoring

Early goal-directed therapy may help improve outcome in septic people and has been evaluated in septic dogs [11]. Aggressive interventions to optimize hemodynamic endpoints should also be performed in CPV patients. Cardiovascular stabilization is best achieved with (IV) fluid administration, and rapid IV resuscitation should be pursued in all CPV cases, regardless of the ultimate treatment protocol. The ideal fluid type is an isotonic balanced electrolyte solution with no additives (see Chapter 153).

Once perfusion parameters have normalized, a maintenance fluid plan should commence to include correction of dehydration, ongoing maintenance and ongoing insensible losses (see Chapters 171 and 172). The volume of ongoing losses in CPV can easily be underestimated and the volume status of these patients needs frequent re-evaluation. Electrolytes should be checked a minimum of q24h, as ongoing losses and fluid shifts can be dynamic and rapidly affect serum sodium concentrations.

Colloidal support can be considered in cases of refractory hypovolemia, progressive hypoalbuminemia, and/or developing signs of interstitial edema. Most CPV dogs tolerate fairly low albumin concentrations without significant adverse effects. Either synthetic or natural colloids may be considered in selected cases of CPV. Synthetic colloids are typically administered as a constant-rate infusion (CRI). If indicated, it is recommended to use

Table 78.1 Injectable antiemetics available for use in CPV.

Drug	Mechanism of action	Site of action	Dose
Maropitant citrate	Neurokinin antagonist	CRTZ and emetic center	1 mg/kg SC or IV q24h
Ondansetron	Serotonin antagonist	CRTZ	0.3–0.5 mg/kg SC or IV q8h
Dolasetron	Serotonin antagonist	CRTZ	0.5–1.0 mg/kg SC or IV q24h
Metoclopramide	Dopamine antagonist	CRTZ, GI smooth muscle	CRI of 1–2 mg/kg/day
Chlorpromazine	Alpha-2 antagonist	CRTZ and emetic center	0.1–0.5 mg SC or IV q6–8h

CRTZ, chemoreceptor trigger zone; GI, gastrointestinal; IV, intravenous; SC, subcutaneous.

the lowest possible dosage to minimize potential adverse effects on coagulation (see Chapter 168).

Canine plasma products have been previously advocated in the treatment of CPV, citing provision of antibodies and coagulation factors, in addition to oncotic support. Infusion of canine plasma with confirmed high titer of neutralizing anti-parvovirus antibodies to CPV-infected puppies did not confer a survival advantage in one study [12]. Considering the risks and cost associated with plasma transfusion, routine use of plasma in CPV puppies is not recommended [13]. In cases of disseminated intravascular coagulation with overt hemorrhage, fresh frozen plasma may be administered at a dose of 10–20 mL/kg.

Hypoglycemia and hypokalemia can be severe and life-threatening complications. Altered mentation, weakness, ataxia, decreased or absent vision, or seizures may be observed when serum glucose drops below 50 mg/dL. If the blood glucose of a symptomatic CPV puppy is found to be ≤ 60 mg/dL, an IV dextrose bolus should be administered immediately. The recommended dose of 50% dextrose is 0.5–1 mL/kg (0.25–0.5 g/kg) diluted 1:2 with isotonic saline. Additional dextrose boluses can be administered if needed, and dextrose may be placed in the base fluids as a CRI during the maintenance fluid stage (see Chapter 111).

Severe hypokalemia (see Chapter 109) can have adverse effects on multiple organ systems. Severe hypokalemia (≤ 2.5 mEq/L) results in neuromuscular weakness, ataxia, diaphragmatic and respiratory muscle fatigue, gastrointestinal stasis, and cardiac arrhythmias [14,15]. Potassium supplementation of fluids, guided by regular monitoring of serum potassium concentration, as part of the daily fluid plan is an important part of management of the CPV patient. Severe hypokalemia may need a continuous infusion of KCl (see Chapter 109). Magnesium is an important co-factor in potassium homeostasis, and supplementation may help restore normal serum potassium levels rapidly (see Chapter 110).

Vomiting and nausea should be promptly addressed to improve patient comfort and limit ongoing losses. A

multimodal approach may be required to control vomiting. Table 78.1 summarizes commonly used injectable antiemetics in CPV.

Metoclopramide and phenothiazines have been reported to be the antiemetics most commonly used with CPV [16]. Since then, newer antiemetics have become first-line agents for control of emesis. Maropitant is an effective antiemetic in dogs for a wide range of etiologies, including CPV. In a 2012 randomized blinded study, maropitant and ondansetron appeared to be equally effective in controlling vomiting and nausea in dogs with CPV [17]. In this study, maropitant was used at a dose of 1 mg/kg IV q24h.

Dogs with CPV demonstrate moderate-to-severe visceral pain. Several classes of analgesics may be considered; given the debilitated nature of most CPV cases, reversible opioids are preferred and titratable CRIs may allow optimal dosing. For cases of mild visceral pain, the partial opioid agonist buprenorphine may be considered. Other analgesics such as lidocaine and ketamine can be sequentially added to improve abdominal comfort. Non-steroidal anti-inflammatory drugs should be avoided and alpha-adrenergic agonists should be used with caution in these patients (see Chapter 193).

Intravenous, bactericidal antibiotics are indicated in CPV puppies with leukopenia. It is recommended to use the narrowest antimicrobial spectrum and shortest treatment duration possible. Single-agent antibiotic options include penicillins with beta-lactamase inhibitor activity (e.g. ampicillin-sulbactam, piperacillin-tazobactam) and second-generation cephalosporins. In the authors' hospitals, single-agent ampicillin-sulbactam (Unasyn™) is frequently used at a dose of 50 mg/kg IV q6–8 h. Alternatively, cefoxitin or ceftriaxone may be administered at 22 mg/kg IV q6–8 h. If using ampicillin (22 mg/kg IV q6–8 h), it should be paired with another antibiotic to increase the gram-negative spectrum. Enrofloxacin (5–10 mg/kg IV q24h) may be considered in addition to a first-line beta-lactam, remembering that fluoroquinolones have been associated with cartilaginous damage in juvenile animals.

Early enteral nutrition has been associated with improved clinical outcome and weight gain in CPV dogs [17]. A randomized, controlled clinical trial found that dogs receiving early enteral nutrition had more rapid normalization of attitude and appetite, in addition to faster resolution of vomiting and diarrhea [18]. The most practical method to ensure enteral nutrition is by placement of a nasal feeding tube, either nasoesophageal (NE) or nasogastric (NG). An added benefit of NG tubes is the ability to intermittently suction gastric contents. Removal of stagnant gastric fluid appears to reduce nausea and quantification of these ongoing losses can assist in tailoring fluid therapy.

Immunotherapy has been advocated to lessen the severity of CPV-related disease; most immunotherapies have not been found to significantly influence clinical recovery or survival. No definitive benefit has been identified following the administration of antiviral drugs (neuraminidase inhibitors) or recombinant granulocyte colony-stimulating factor [19,20].

One treatment shown to reduce CPV-related illness is recombinant feline interferon-omega [21]. This therapy is not USDA approved and therefore not available for administration in the United States without a special permit.

Prognosis

Prognosis is variable and likely dependent on age, breed, vaccination history, concurrent illness, timing

of medical intervention, and level of medical care provided. Survival rates are reported to be as high as 90% for puppies that receive timely admission for intensive in-hospital treatment [3,4,22]. Without treatment, survival rate may be as low as 10% [3,4,22]. As such, intensive inpatient supportive care enhances likelihood of survival.

Hospitalization may become cost prohibitive for some owners or shelter programs. In these circumstances, a modified outpatient treatment protocol may be considered. At one of the author's institutions, a CPV outpatient treatment protocol was developed and studied in a controlled setting [23]. Results suggest that intensive outpatient therapy results in a good prognosis in certain settings.

Husbandry Considerations

Canine parvovirus is resistant and survives in the environment for weeks to months. Most disinfectants do not sufficiently inactivate CPV. Dilute bleach (1 part sodium hypochlorite to 30 parts water) is effective against CPV when the surface is exposed to the solution for a minimum of 10 minutes. Bleach works best if organic material has been first removed from the surface. CPV patients should be isolated from other patients in the hospital, with barrier precautions and dedicated materials. Consider bathing these patients prior to discharge to minimize environmental contamination.

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Hemorrhagic Gastroenteritis

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Introduction

Canine hemorrhagic gastroenteritis (HGE) is a clinical syndrome characterized by acute onset of vomiting and hemorrhagic diarrhea with concurrent hemoconcentration. The clinical presentation of dogs with HGE varies from mild clinical signs of vomiting and diarrhea to severe hypovolemic shock and possible sepsis from bacterial translocation. Therefore, prompt recognition and therapy of dogs with severe clinical signs is essential to ensure a successful outcome. Fortunately, with appropriate and timely treatment, the prognosis for dogs with this condition is excellent.

Investigation into the Underlying Etiology

The first reports of canine hemorrhagic gastroenteritis appeared in the veterinary literature over 40 years ago [1–3]. However, despite widespread clinical recognition of this syndrome, the inciting cause has proven to be elusive to veterinary investigators. A number of infectious etiologies, including *Salmonella*, *Escherichia coli*, *Campylobacter*, and *Clostridium*, have been investigated in dogs with HGE. However, definitively confirming that a particular organism is responsible for the syndrome of HGE is difficult as many of these organisms are found naturally in the gastrointestinal tract in dogs and therefore isolation rates are often similar for dogs both with and without diarrhea [4–7].

Of the bacterial causes investigated, *Clostridium perfringens* is the organism most frequently implicated in dogs with HGE. *Clostridium perfringens* is an anaerobic, gram-positive bacillus that has been identified as a cause of necrotic enteritis. This condition identified in domestic animals results from the production of enterotoxins

by *C. perfringens* and is the leading cause of food-borne illness in people [8,9].

There are several case reports implicating *Clostridium* species as the cause of death in previously healthy small-breed dogs that died of peracute hemorrhagic enteritis. In these case reports, large numbers of clostridial organisms (*C. welchii* in two dogs and *C. perfringens* in two dogs) were found adhered to the necrotic epithelial surfaces of the intestinal tract [3,10,11]. In the most recent case report, the authors proposed that opportunistic bacterial overgrowth of *C. perfringens* occurred in dogs following physical stress, decreased immunoreactivity, or hypermotility of the gastrointestinal tract [11]. In addition to these case reports, several veterinary studies have found that there is an increase in the number of *C. perfringens* bacteria and *C. perfringens* enterotoxin (CPE) in dogs with acute diarrhea compared to normal dogs [12,13]. In a recent study evaluating bacterial cultures of endoscopic gastrointestinal biopsies in dogs with acute hemorrhagic diarrhea, there was a significant difference in detection of clostridial-type bacteria and positive cultures for *C. perfringens* compared to control dogs [14]. As *C. perfringens* is rarely cultured from duodenal contents, this study provides compelling evidence for a role of *Clostridium* species in the pathogenesis of the syndrome of HGE. Additionally, similar to the necropsy reports of dogs dying acutely with clinical signs of acute hemorrhagic diarrhea, the histology of the small intestinal biopsies revealed adherence of large rod-shaped bacteria to the necrotic epithelial surfaces of the small intestine [14].

However, questions remain whether the clostridial overgrowth identified in these dogs with HGE is a consequence rather than the underlying inciting cause of illness.

Clinical Recognition and Diagnosis

Hemorrhagic gastroenteritis should be suspected in a previously healthy dog that is presented on an emergency basis for acute onset of vomiting and diarrhea with hematochezia (<48 h in duration). Dogs may also have a history of anorexia and lethargy. This disease syndrome has been reported to occur at any age and in any breed of dog but is reported to be more common in dogs 2–4 years of age and in small-breed dogs such as the miniature schnauzer, miniature and toy poodles, and Yorkshire terriers [1,7]. The median weight of dogs with HGE in one study was 12 kg, with a range of 2.2 to 33 kg [7]. There is also no reported seasonal component and dogs with HGE are likely to present throughout the year [1].

On initial physical examination, dogs may be stable hemodynamically with normal tissue perfusion parameters or in hypovolemic shock due to severe fluid and electrolyte losses from the gastrointestinal tract. The physical examination findings of dogs presenting with hypovolemic shock includes depressed mentation, pale mucous membranes, prolonged capillary refill time (>2 sec), tachycardia, tachypnea, weak or absent peripheral pulses, cold extremities, and hypothermia (see Chapter 153). Abdominal pain is an uncommon finding and is reported to occur in approximately 20% of dogs [1]. On rectal examination, bloody feces are present and the perineum may be stained with fecal material. A variable amount of vomiting may have occurred and could be blood-tinged but generally does not contain blood clots. Dogs may have signs of nausea such as ptyalism or exaggerated swallowing efforts (Figure 79.1).

In addition to the above clinical signs and history, initial biochemical testing prior to therapy should reveal hemoconcentration with an elevated packed cell volume



Figure 79.1 A dog with hemorrhagic gastroenteritis.

of at least 50–60% but it may be as high as 86% [1,7]. The markedly elevated packed cell volume is thought to occur due to a combination of fluid losses into the gastrointestinal tract and splenic contraction [15]. Prior to therapy, the serum total protein (TP) measured via refractometry is usually in the reference range but generally decreases during therapy due to continued losses of protein-rich fluid into the gastrointestinal tract in addition to dilution from intravenous crystalloid therapy. In an unpublished review of 106 HGE cases at the author's institution, the median TP at hospital admission was 7.0 g/dL with a range of 4.2–11.3 g/dL. Blood electrolytes are generally normal, but blood lactate may be elevated, reflecting abnormal tissue perfusion.

A diagnosis of HGE is one of exclusion and therefore other causes of vomiting and hematochezia should be sought such as pancreatitis, foreign body, Addison's disease, and other infectious etiologies such as ancylostomiasis (hookworms) and parvovirus. Therefore, a complete diagnostic evaluation of a dog suspected to have HGE may include a complete blood count, biochemistry screen, blood coagulation profile, abdominal imaging either abdominal radiography and/or abdominal ultrasonography, resting cortisol and/or ACTH stimulation, and fecal testing to evaluate for parasites, parvovirus, and protozoa. Results of fecal testing for bacterial organisms should be interpreted cautiously as many of these organisms can be found in both diarrheic and non-diarrheic dogs. Currently, the recommended diagnostic approach for evaluation of *Clostridium perfringens* is the use of a CPE ELISA in conjunction with PCR for detection of enterotoxigenic strains [8].

Thoracic radiography may be indicated in animals with thoracic auscultation abnormalities to evaluate for the presence of aspiration pneumonia or in older dogs to evaluate for neoplasia. However, clinical discretion should be used when recommending these tests as a full diagnostic work-up may not be indicated in dogs with only mild self-limiting clinical signs and acknowledging the difficult inherent in interpreting fecal testing results.

In one study, the complete blood count findings were reported in 37 dogs with HGE, a stress leukogram was common and the median white blood cell count was 12 300 with a range of 3200–35 800 [1]. A degenerative left shift may be seen in some critically ill dogs with HGE which may indicate sepsis from bacterial translocation.

To date, there is no published information on the blood biochemistry values that may be seen in dogs with HGE. In this author's experience, some dogs may have mild elevations in blood urea nitrogen (BUN) and creatinine secondary to dehydration but these values should improve with intravenous fluid therapy. In addition, a few dogs may have mild elevations in alanine aminotransferase

(ALT) and aspartate aminotransferase (AST) which may be secondary to hypoperfusion. Finally, critically ill dogs may have signs consistent with disseminated intravascular coagulation including thrombocytopenia, increased prothrombin time, increased partial thromboplastin time, D-dimers, and fibrin degradation products [1].

The gross necropsy findings that have been reported in eight dogs included frank hemorrhage into the gastrointestinal tract lumen with lesions that were isolated to a single or multiple segments of the small intestine in a few dogs, with the entire small intestine and colon being affected in other dogs. Due to rapid autolysis, histopathological changes were not described. In a recent premortem study of dogs with acute hemorrhagic diarrhea that underwent gastroduodenoscopy with biopsies, lesions were found in the small intestine and large intestine and included severe epithelial mucosal necrosis and neutrophilic inflammation [14].

Emergency Stabilization and Treatment

The treatment of dogs with HGE will vary depending on the severity of their clinical signs. In dogs with only mild clinical signs, outpatient therapy may be offered whereas dogs with severe clinical signs and hypovolemic shock should be hospitalized and treated aggressively with intravenous fluids.

In dogs with abnormalities in tissue perfusion parameters, an intravenous catheter should be placed and blood drawn for evaluation of PCV, TP, venous blood gas analysis, electrolytes, glucose, BUN, creatinine, and lactate. Additional blood for a complete blood count and chemistry screen should also be drawn at this time. A coagulation profile may be indicated in dogs with suspected sepsis to evaluate for disseminated intravascular coagulation. A blood pressure measurement should be done to help guide initial fluid resuscitation measures and assess response to treatment. However, it is prudent to be aware that in the early stages of shock, the blood pressure may be normal or even elevated due to compensatory physiological responses.

For initial intravascular volume resuscitation, it is reasonable to start with aliquots of a balanced isotonic crystalloid (10–30 mL/kg IV over 10–30 min) and/or a colloid (hetastarch 5–10 mL/kg or tetrastarch 10–20 mL/kg IV over 20–30 min) (see Chapter 169). To date, there is no evidence to support the use of a colloid over a crystalloid as a superior choice for intravascular fluid resuscitation. Once clinical endpoints of fluid resuscitation (see Chapter 152) have been reached, the patient may be started on a constant rate infusion of crystalloids and/or colloids to maintain intravascular volume and replace

any ongoing gastrointestinal losses. Intravenous fluid therapy should be continued until the dog is able to eat and drink on its own and the diarrhea has resolved. During hospitalization, PCV, TP, electrolytes (Na⁺ and K⁺), glucose, BUN, and creatinine should be checked daily or more frequently depending on the severity of clinical signs and response to therapy.

There is currently no consensus regarding the use of antimicrobials in dogs with HGE. Proponents for the use of antimicrobial therapy suggest that in addition to a suspected underlying infectious etiology, antimicrobials should be administered due to the risk for bacterial translocation from the gastrointestinal tract. This is supported by evidence in the veterinary literature that dogs with suspected hemorrhagic gastroenteritis were found to have high circulating levels of endotoxin [16]. Therefore, it is clinical practice for many veterinarians to prescribe metronidazole (10 mg/kg IV or PO q12h) [17], which has activity against obligate anaerobes such as *Clostridium*. In a study evaluating the *in vitro* antimicrobial susceptibility profiles of 131 isolates of *C. perfringens*, most isolates were also susceptible to ampicillin and macrolide antibiotics in addition to metronidazole, with a variable percentage of isolates showing resistance to tetracycline [18]. Dogs with HGE and suspected sepsis (i.e. complete blood count indicates a degenerative left shift with toxic changes +/- hypoglycemia) may benefit from additional antimicrobial coverage (e.g. ampicillin 22 mg/kg IV q8h [17] and enrofloxacin 10–15 mg/kg IV q24h [17]) in addition to metronidazole.

In a placebo-controlled study in 60 dogs with acute hemorrhagic diarrhea evaluating the use of clavulanic acid/amoxicillin (Clavamox at 7 mg/kg SC for 24h, followed by 12.5 mg/kg PO for 7 days), a broad-spectrum antimicrobial with activity against gram-negative aerobes and anaerobes including clostridial organisms, compared to placebo, the administration of Clavamox did not shorten the duration of clinical signs or improve outcome even in dogs with positive blood cultures [19]. However, dogs that were positive for *C. perfringens* enterotoxin and treated with Clavamox did have an improvement in their diarrhea score on day 5 compared to dogs treated with placebo [19]. An important cautionary note from this study is that dogs with suspected sepsis were excluded as the current standard of care is to provide broad-spectrum antimicrobial therapy to these animals. More prospective clinical studies are needed to evaluate whether antimicrobial use is justified in dogs with HGE before definitive recommendations can be made.

Antiemetics (maropitant 1–2 mg/kg IV q24h [17] or ondansetron 0.2 mg/kg q8h [17]) are generally prescribed to control nausea and vomiting until clinical signs have resolved. Gastric acid suppressants such as a proton pump inhibitor (pantoprazole 1 mg/kg IV q24h

[17]) or histamine type 2 receptor antagonist (famotidine 0.5–1 mg/kg q12–24h [17]) may be used either in dogs with ultrasonographic evidence of gastritis or when there is concern for gastric ulceration (hematemesis or blood-tinged vomiting). These medications are considered safe to use but there is currently no evidence suggesting whether or not they are beneficial to dogs with HGE. An opioid analgesic, such as methadone or hydromorphone (0.1–0.2 mg/kg IV q4–6h) [17], is indicated for dogs with abdominal pain. However, in this author's experience, if significant abdominal pain is present or develops during the course of hospitalization, investigation into other underlying etiologies such as pancreatitis or an intestinal intussusception should be pursued.

In dehydrated patients with only mild clinical signs (limited vomiting and small-volume diarrhea) and normal tissue perfusion parameters, outpatient therapy may be offered. Ideally, a minimum database (PCV, TP, BUN, and glucose) and blood electrolytes should still be evaluated to help guide the decision on whether to treat the dog on an outpatient basis or to admit to the hospital for supportive care. For outpatient treatment of dehydration, options for fluid therapy include subcutaneous fluids (10–30 mL/kg of an isotonic crystalloid) or oral fluids. Oral rehydration therapy with an oral electrolyte solution is a reasonable option and may be considered more physiological than subcutaneous or intravenous fluids. Oral electrolyte solutions are designed to take advantage of sodium-coupled water reabsorption in the small intestine, maximizing water uptake and thereby rehydration [20]. In human pediatric patients, oral rehydration therapy is considered the gold standard for treatment of dehydration associated with gastroenteritis [21] and it has been shown to be a cost-effective treatment in dogs with mild-to-moderate dehydration associated with hemorrhagic diarrhea [22].

Some newer oral rehydration solutions in the veterinary market contain amino acids, such as glutamine, in addition to electrolytes. Glutamine might help gut function, the immune system and other essential processes in the body during times of stress and therefore these products are appealing. Additional studies will be needed to determine if these new oral electrolyte solutions provide any additional benefit to our patients.

Patients treated on an outpatient basis will also benefit from the administration of an antiemetic (see above) to ensure adequate oral intake of fluids at home to prevent dehydration. Owners of pets that are being treated on an outpatient basis should be cautioned to monitor their pet closely at home for worsening diarrhea and inadequate water intake or urination which may indicate progressive clinical disease and need for hospitalization.

Accumulating evidence suggests that the microbiome of the gastrointestinal tract is altered in dogs with acute hemorrhagic diarrhea, allowing for pathogenic bacteria to increase in numbers [13]. Probiotics, which are living microbes such as *Bifidobacterium*, *Lactobacillus* species, *Enterococcus faecium* or non-bacterial organisms such as the non-pathogenic *Saccharomyces boulardii*, may be a beneficial part of the treatment plan by re-establishing the natural bacterial balance in the digestive system after stress from infection, stress or antibiotic therapy [23].

There is some limited information on the utility of probiotics in dogs with acute diarrhea. In one industry-sponsored study, the use of a canine-derived *Bifidobacterium animalis* strain AHC7 probiotic significantly reduced the time to resolution of diarrhea (4 days versus 6 days) and reduced the percentage of dogs that were given metronidazole compared with dogs given placebo [23]. To date, there are no studies on the utility of probiotics in the treatment of HGE and therefore definitive recommendations cannot be made at this time.

Prognosis

With appropriate supportive care, the prognosis of dogs with HGE is excellent, with reported mortality rates ranging from 0% to 6.4% in hospitalized dogs [1,14]. Despite its excellent prognosis, euthanasia may be elected for critically ill hypotensive dogs where financial limitations preclude hospitalization. In one recent study, the average hospitalization time was 3 days (range 2–6 days), with the majority of dogs showing rapid clinical improvement in the first 48 hours of treatment [14]. Some dogs may require longer hospital stays due to prolonged diarrhea and regurgitation or the development of complications such as sepsis or aspiration pneumonia.

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Protein-Losing Enteropathy

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Introduction

Protein-losing enteropathy (PLE) is a clinical syndrome characterized by loss of protein from the gastrointestinal tract, and moderate-to-severe loss of body condition. Some patients also have concurrent disruption of cholesterol and calcium metabolism. Not all PLE patients present with classic gastrointestinal clinical signs, so PLE is often a diagnosis of exclusion following evaluation of liver and kidney function (e.g. proteinuria). Presentations of animals with PLE are often acute in nature and mostly due to the effects of severe hypoalbuminemia. At the time of the acute presentation, owners should be prepared for long-term management of this chronic disease. Treatment is often multimodal, with nutritional management, anti-inflammatory medications, and therapy targeted at an underlying cause, if one is determined.

Pathophysiology

The pathophysiologic hallmark of PLE is intestinal loss of serum albumin and globulin. Three mechanisms of loss are possible, including lymphatic obstruction, increased mucosal permeability, and structural or mechanical injuries to the intestinal wall. One mechanism usually prevails, but all three mechanisms may be operative in one patient, leading to a continuum of clinical signs.

Intestinal lymphangiectasia (IL), defined as the dilation of the individual lacteals within the intestinal mucosa, occurs in dogs secondary to compressive or obstructive lesions within the lacteal. This occurs at a microscopic level where there is inflammation and edema within the mucosal layer causing loss of protein, lipid, and lymph back into the intestinal lumen via the mucosal surface [1]. Idiopathic and congenital forms of

this disease have been identified in the Norwegian lundehund [2–4], rottweiler [5], and Yorkshire terrier [6]. Lymphatic leakage may be inflammatory and perpetuate ongoing compression of the lacteal. Granulomas, occasionally referred to as lipogranulomas, can be focal [7] or diffuse [8]. Neoplastic causes, including gastrointestinal lymphoma or discrete intestinal masses (which may ulcerate and worsen protein loss), are a common cause of PLE in middle-aged to older animals [9]. Rarely, younger animals have been affected.

Changes in mucosal permeability are commonly associated with underlying inflammatory bowel disease [10]. The local infiltrate of inflammatory cells changes both the structure and function of the intestinal wall. Breed associations have been reported in the basenji [11] and soft coated wheaten terrier, the latter of which may be complicated by protein-losing nephropathy (PLN) [12].

Mechanical disruption of the intestinal mucosal layer and beyond causes massive intestinal loss of proteins, which is frequently accompanied by blood loss as well. Gastrointestinal ulceration, which is covered in Chapters 77 and 84, is the most common mechanism by which this may occur. Acute intestinal intussusception causes pressure changes within adjoining lacteals and subsequent focal protein loss [13]. Infectious causes, such as parvovirus [14] in young, unvaccinated dogs, should also not be overlooked (see Chapter 78). Histoplasmosis [15,16] and pythiosis [17,18] have been identified as infectious causes of PLE in dogs. This stresses the importance of obtaining a thorough travel history for all PLE suspects. Parasitic infections, such as hookworms and *Giardia*, can also be associated with PLE but no causal relationship has been reported. Bacterial populations within the intestinal tract are unlikely to be the primary cause of PLE, but there is potential for dysbiosis and the need for appropriate therapy in some patients.

Clinical Presentations and Laboratory Data

Chronic diarrhea is usually not the domain of emergency services, but the hypoalbuminemia that results from PLE can lead to a number of emergent clinical presentations. Peritoneal effusion is considered first, as the low albumin reduces the oncotic pressure within abdominal vessels, giving way to transudation. This mechanism can also lead to pleural effusion, which can result in changes in respiratory patterns and, if left unmanaged, dyspnea (see Chapter 45). Peripheral edema can also result. Diarrhea can be associated with PLE, and typically is mixed bowel in origin. Depending on the underlying mechanism, melena or hematochezia may also be present.

Laboratory data testing should include, at minimum, a complete blood count (CBC), serum chemistry, and urinalysis. White blood cell counts may reflect a lymphopenia secondary to intestinal loss of lymph, although this is uncommon. Serum chemistry panel will confirm the decrease in albumin. Serum globulin concentrations in a classic case will be decreased as well, but in the presence of inflammation-induced globulin production, the serum globulin may be within the normal range. Documentation of protein loss within the intestinal tract is generally presumed, but measurement of fecal or serum alpha-1-proteinase inhibitor may be correlated with the presence of lesions within the intestinal tract [19].

Calcium levels are predictably low, due to the depletion of albumin and the bound calcium fraction. Follow-up with ionized calcium concentrations is therefore recommended, particularly if clinical signs of hypocalcemia are present. Ionized calcium can be truly diminished due to the decreased absorptive capacity of intestinal epithelial cells for fat-soluble vitamin D [20]. The presence of pancreatitis may also contribute to hypocalcemia. Cholesterol concentrations are often decreased as well, thus differentiating the condition from a classic protein-losing nephropathy case where cholesterol levels are often increased.

Interpretation of liver function is challenging in these cases, as many PLE dogs are anorexic, leading to decreased blood glucose and hypocholesterolemia.

Fasting and postprandial serum bile acids or ammonia levels should be considered to more definitively rule out liver dysfunction (see Chapter 90). Analysis of a urine sample to evaluate for the presence of urine protein (and a urine protein to creatinine ratio, if indicated) should be performed. A summary of the differences in laboratory parameters is found in Table 80.1.

In an emergency setting, where full laboratory data testing may not be readily available, evaluation of a PCV/TS, blood smear, and a urine test screening for protein in a typical breed may be sufficient to tentatively diagnose PLE and to initiate an appropriate treatment plan for the next 12–24 hours. Definitive diagnosis ultimately requires intestinal biopsy to confirm typical histopathological changes to the intestinal wall. Infectious disease testing and abdominal imaging should be considered, when appropriate, prior to taking intestinal biopsies with the animal under general anesthesia since these patients are higher risk anesthetic candidates.

Treatment

On initial presentation, the decision must first be made whether these patients require hospitalization or if they can be managed on an outpatient basis. Considerations for inpatient management should be given to those with severe cavitory effusions and intractable gastrointestinal signs leading to clinically significant dehydration. Patients may be stable enough for submission of laboratory data and referral to an internal medicine specialty practice for evaluation within the next few days, although best clinical judgment is always warranted. Overnight stabilization of those patients that warrant in hospital care is outlined in the sections below.

Hypoalbuminemia

Albumin transfusions are not routinely performed in veterinary medicine for multiple reasons. Canine albumin concentrate is intermittently available and quite

Table 80.1 Comparison of expected clinicopathologic data in diseases commonly associated with hypoalbuminemia.

Disease	Protein disturbances	Cholesterol	Other abnormal laboratory parameters
Protein-losing enteropathy	Panhypoproteinemia	Low	Hypocalcemia
Protein-losing nephropathy	Hypoalbuminemia	High	Azotemia possible
Hepatic failure	Hypoalbuminemia	Low	Liver enzyme elevations Low BUN, glucose, cholesterol

BUN, blood urea nitrogen.

expensive. Human albumin carries a risk of anaphylaxis and delayed hypersensitivity reactions in canine patients, although severe reactions are hard to distinguish from severe underlying disease in the canine population [21]. Human albumin is typically considered in animals with acute, marked decreases in albumin, such as critically ill septic patients, in whom the short-term benefit may outweigh the possibility of long-term risk [22]. Use of human albumin for chronic disease processes, such as PLE, has not yet been validated or explored in veterinary patients. Additionally, human albumin should not be given repeatedly due to sensitization after the first dose, thus preventing its use in patients with a relapse of their PLE. Plasma transfusions could be considered in smaller patients, as this is the patient population in which the therapy is most cost-effective (see Chapter 176). However, the hypercoagulability associated with PLE and loss of antithrombin should be considered when transfusing plasma with active clotting factors. Treatment of the underlying condition is the most specific therapy for patients with chronically low serum albumin levels, although even when treated appropriately they may be refractory to therapy.

Stabilization for general anesthesia can include cautious supplementation of colloid support and judicious use of crystalloid solutions. Long-term supplementation of synthetic colloids is not practical, and potential complications from these fluids should be considered (e.g. coagulopathy, increased intravascular hydrostatic pressure, kidney injury; see Chapter 168).

Hypercoagulability

Loss of serum proteins within the gastrointestinal tract includes the loss of antithrombin, thus leading to a hypercoagulable state (see Chapter 70). Hypercoagulability has been documented in PLE patients using thromboelastography (TEG) [23], and there is likely a multifactorial pathogenesis of thrombosis. Anticoagulant therapy is commonly used in these patients, but the most effective drug is currently unknown (see Chapter 71).

Nutritional and Fluid Support

With inflammation of the GI tract, many patients are dehydrated and anorexic. Addressing dehydration and hypovolemia in a hypoalbuminemic patient is a balancing act between meeting the patient's needs and worsening of the low blood oncotic pressure and subsequent effusive disease. The use of nasoesophageal and nasogastric tubes may enable increased water and caloric intake for these patients. Isotonic crystalloids should be used

judiciously to correct hypovolemia and dehydration, in conjunction with colloidal support to help prevent further loss of fluid from the vascular space during rehydration of the patient (see Chapters 153, 167, and 168). Low-fat diets are also indicated in patients diagnosed with lymphangiectasia [24]. The use of hypoallergenic diets could be considered to treat empirically for underlying inflammatory bowel disease. Supplementation of cobalamin is warranted, especially if ileal disease is suspected in canine patients [25].

Calcium Homeostasis

Patients displaying clinical signs of hypocalcemia should have an evaluation of serum ionized calcium (see Chapter 110). Parenteral calcium supplementation may be necessary and should be closely monitored. If parenteral supplementation is initiated, then patients are transitioned to oral supplementation of calcium and, in severe cases, calcitriol prior to discharge from the hospital. Calcium supplementation can typically be discontinued once albumin levels approach normal concentrations. Calcium abnormalities have been reported in Yorkshire terriers, and may be further exacerbated by co-existing disturbances in magnesium [26].

Immunosuppressive Therapy

Glucocorticoids are the first-line choice for treatment of inflammatory bowel disease. Care should be taken to rule out infectious causes or severe intestinal ulcerations. Secondary immunosuppressive agents, such as cyclosporine, mycophenolate, and azathioprine, may become necessary (Table 80.2). Typically, a single agent is started in smaller dogs, depending on the severity of the disease. In larger dogs, that is, those larger than 30 kg, a second agent is usually started in addition to glucocorticoids in order to allow for faster tapering of glucocorticoid medications and reduced risk of side-effects.

Prognosis and Follow-Up Care

Long-term prognosis for patients definitively diagnosed with PLE is guarded and can be quite variable given the high rate of relapse for these patients. Severity of hypoalbuminemia has been reported to be prognostic, with lower serum albumin concentrations carrying a more guarded prognosis [27]. Median survival times of dogs diagnosed with PLE were reported as 67 days in one study, although the range of survival time was reported as 2–2551 days [28]. Both clinical response and a rise in serum albumin following appropriate

Table 80.2 Drug dosages for treatment of PLE in the dog [32,33].

Drug	Drug dosages
Prednisone	Body weight (BW) <30 kg: 1–2 mg/kg/day PO BW >30 kg: 30 mg/m ² /day PO
Dexamethasone-SP	0.1–0.2 mg/kg q12–24h IV
Cyclosporine	5 mg/kg q12–24h PO
Azathioprine	2.2 mg/kg q24h for 2 weeks, then decrease to q48h PO DO NOT USE IN CATS
Mycophenolate	10–15 mg/kg PO, IV q12h
Chlorambucil	0.1–0.2 mg/kg every 24 to 48 hours PO No parenteral form available
Budesonide	0.125 mg/kg q8–12h PO [32] BW <7 kg: 1 mg q24h PO [33] BW 7–15 kg: 2 mg q24h PO BW 15–30 kg: 3 mg q24h PO BW >30 kg: 5 mg q24h PO
Clopidogrel	1 mg/kg q24h PO May consider loading dose of 10 mg/ kg once
Aspirin	1 mg/kg q24h PO (dog) and q72h (cat)

therapy were associated with a better prognosis in a retrospective study [29]. In that same study, prognosis for dogs with an underlying diagnosis of gastrointestinal lymphoma was poor. Identification and treatment of an underlying cause can therefore change the prognosis dramatically.

Follow-up care at an internal medicine specialty practice is vital for patients tentatively diagnosed on an emergent basis. Frequent rechecks of laboratory data are required during the onset of therapy and while tapering medications. Client education regarding the dynamic course of PLE is important, and communication of progress at home to monitor response allows for appropriate medication management.

Protein-Losing Enteropathy in Feline Patients

The majority of this chapter has been devoted to PLE in the dog, as PLE in feline patients has not been reported [30]. Additionally, cats are less prone to developing clinically significant consequences, such as ascites or edema, from hypoalbuminemia. Feline pancreatic disease has been implicated as a cause of hypoalbuminemia, and may play a role in chronic gastrointestinal disease [31].

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Gastrointestinal Obstruction

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Introduction

Gastrointestinal (GI) obstruction can be a potentially life-threatening and devastating disease process requiring preoperative stabilization, rapid diagnosis, close anesthetic monitoring, prompt surgical intervention, and attentive postoperative care. Diagnosis can often be challenging and difficult to distinguish between disease processes resulting in focal or generalized ileus, a process better treated with medical management. Unnecessary delays in intervention could place the patient at risk of intestinal devitalization and development of septic peritonitis, prolonging recovery and increasing both morbidity and mortality. Despite these common challenges, with appropriate perioperative and intraoperative care, discharge rates are documented as high as 96% [1].

While other references have detailed surgical techniques, this chapter will focus on the etiology and pathophysiology of GI obstruction as well as the clinical signs, diagnosis, and perioperative care.

Etiology

Ingested foreign bodies are the most common cause of GI obstruction in dogs and cats, with intussusception being second. Other less frequent causes of intestinal obstruction include entrapment (i.e. hernia or adhesion), stricture/abnormal angulation of the bowel (i.e. post plication), neoplasia, granuloma, hematoma, and abscess formation [2–4]. Dogs tend to ingest latex treats, plastic/rubber objects (balls, toys, garbage bags, etc.), stones, corn cobs, coins, sewing needles and, less frequently, fabric (carpet, socks, scarves, etc.) [2,3,5]. Cats tend to prefer linear foreign material such as string or thread often anchored to a needle, but obstruction with almonds, plastic, rubber, and trichobezoars have been

documented as well [3,5–8]. Any of the above causes can result in a partial or complete GI obstruction and risk for perforation potentially resulting in septic peritonitis (see Chapter 87).

Pathophysiology

Obstructive gastrointestinal foreign bodies induce both local and systemic abnormalities affecting the patient. Once fixed, the obstructive foreign body serves as a barrier to further ingesta from passing. Oral to the foreign body, fluid accumulates, resulting in an atropine-mediated increase in contractile activity [9]. Myenteric stretch stimulates cyclo-oxygenase-2 (COX-2) expression soon after obstruction, resulting in increased prostaglandin production. Specific prostaglandin receptor (EP2, EP3) density increase and stimulation of these receptors by prostaglandin E2 result in ileus [10] with periodic increased myoelectric spike activity [11]. Aboral to the obstruction, the lack of ingesta and inhibition of motor activity can result in the appearance of a generalized ileus.

With intestinal function diminished by the obstruction, accumulation of ingesta, gas, and intestinal secretions from GI tract, pancreas, and biliary system results in further intestinal dilation. Intestinal dilation is a time-dependent phenomenon and was found to be worse with upper GI obstruction when compared to lower obstruction [12]. Progressive ileus induces serosal stretch receptors passing through the sympathetic neurons to the CNS, which activates the vagus and splanchnic nerves, inducing pain, retching, decreased heart rate, decreased cardiac contractility and relaxation, as well as decreased respiratory rate. This serosal stretch activates the emetic center, resulting in profound nausea, inappetence, and vomiting [13].

A combination of fluid losses from vomiting, diarrhea, decreased intake/absorption, and persistent intestinal fluid secretion can result in profound electrolyte, fluid, and acid–base derangements in 40–50% of dogs with GI obstruction [14]. The voluminous GI losses can result in a hypochloremic metabolic alkalosis. The acidic environment of the stomach (gastric pH 1.0=1 million times the hydrogen concentration of blood), high gastric chloride (~150 meq/L), and potassium (~10 meq/L) concentrations result in a dramatic loss with profound vomiting. For every hydrogen ion produced by the parietal cells, a bicarbonate is released into the blood. Normally, the duodenum senses the low pH of the gastric fluid and bicarbonate is secreted by the pancreas to neutralize the gastric acid, but when the acidic gastric contents are vomited, this stimulus is blunted. This alkalotic state is exacerbated by low chloride, which is normally reabsorbed with sodium in the distal tubule maintaining electroneutrality. In the absence of chloride, a positive charge is created and the intercalated cells secrete a hydrogen ion to re-establish electroneutrality [15].

Volume contraction and severe hypokalemia play a contributory role in the development of mixed acid–base derangements and metabolic alkalosis. The renin-angiotensin-aldosterone system is activated when the juxtaglomerular cells of the kidneys sense a drop in renal blood flow. Prorenin is converted to renin, which once within the plasma converts angiotensinogen into angiotensin I. In the pulmonary capillary, angiotensin I is converted to angiotensin II by angiotensin converting enzyme. While angiotensin II is a potent arteriole constrictor, it also stimulates the release of aldosterone from the adrenal's zona glomerulosa. Aldosterone acts directly on the distal nephron and collecting duct, causing sodium reabsorption by activating the Na-K-ATPase pumps of the principal cells and by increasing the number of sodium channels in the luminal membrane. Aldosterone's effect is so strong that it can decrease urine sodium concentrations to as low as 1 mEq/L, effectively increasing circulating volume.

Contrary to previous descriptions, in the pure hypovolemic state, kaliuresis is not induced, which is in contrast to when aldosterone release is stimulated by hyperkalemia. This process is referred to as the “aldosterone paradox,” which seems to be influenced by the presence or absence of angiotensin II, and is further influenced by the reduced tubular flow as the result of decreased glomerular filtration rate, and both proximal/distal tubular sodium reabsorption. Correction of the hypovolemic state, hypochloremia, and hypokalemia by administration of fluids rich in chloride (i.e. 0.9% NaCl), supplemented with potassium chloride, will stop renal excretion of hydrogen ions and help expedite resolution of the metabolic alkalosis [15].

Decreased regional perfusion to the intestines is multifactorial, with both local and systemic effects. Locally, the intestinal intraluminal pressure exerted on the outer wall, for example 18 cmH₂O or greater for 15 minutes, dramatically decreases blood flow [12,16]. With time, this pressure is translated orad, with the accumulation of intraluminal contents affecting larger areas of the intestine [12]. With focal obstruction, perfusion may be maintained initially by the increased blood flow orad to the obstruction. At the site of obstruction, blood flow is initially maintained as well. The normal basal intestinal tone relaxes, commonly referred to as “delayed compliance,” dropping the intestinal intraluminal pressure and allowing local perfusion to be maintained [16,17]. Increasing intraluminal pressure will eventually overwhelm the protective delayed compliance, and venous collapse will occur. Loss of the protective delayed compliance increases capillary hydrostatic pressure, resulting in edema and eventually compromised arteriolar blood flow [16]. While metabolic oxygen demand is lower at the aboral segment of intestines, perfusion is decreased to this region as well [17].

Bowel obstruction can lead to hypovolemic shock and is a known risk factor for intra-abdominal hypertension in people [18] and, if present, these systemic effects can further exacerbate local hypoxemia secondary to global hypoperfusion. With the present local and systemic risk factors, the intestine is at risk of irreversible damage if not treated in a timely manner (see Chapters 152, 153, and 155).

The developing regional damage, intestinal bacterial overgrowth, bacterial translocation, concurrent acid–base and fluid balance disorders in dogs and cats suffering from intestinal obstruction increase the risk of loss in homeostasis between proinflammatory and anti-inflammatory mediators. The escalating inflammation, activation of the cytokine cascade and release of other inflammatory mediators, including histamine, serotonin and arachidonic acid metabolites, lead to SIRS and potentially even sepsis. The overall effect of this systemic illness can progress to multiple organ dysfunction syndrome, resulting in cardiovascular collapse, acute kidney injury, acute respiratory distress syndrome, and disseminated intravascular coagulation, leading to prolonged hospitalization with required intensive care and a worse prognosis [1,19,20] (see Chapter 159).

Clinical Signs and Physical Exam

Younger pets tend to be more adventurous, with a seemingly higher frequency of ingestion of foreign materials, but dogs of all ages (mean $\pm$ SD 1.5–7.5 years) [1] are at risk due to behavioral disorders, endocrine diseases,

and illnesses requiring medications causing polyphagia (e.g. phenobarbital and prednisone). Cats that ingest foreign bodies are most commonly younger (1.8–2.7 years) [3,21] though ingestions in older cats have been documented (range 0.2–19 years) [5].

The most common historical and clinical signs for dogs are non-specific and include vomiting, anorexia, and lethargy [1,3]. Dogs with linear foreign bodies more commonly exhibit these clinical signs [1]. In one study, owner-witnessed ingestion occurred in 78.4% of cats with sewing needle foreign bodies [5] while others report owner-witnessed ingestion 24% of the time for dogs and cats combined [3]. Ingested foreign bodies may not have associated clinical signs for the first hours to weeks after ingestion [3,22,23]; owners who witness ingestion are more likely to present their pet 2 days earlier than unwitnessed ingestions [3].

Physical exam findings include dehydration, abdominal pain, palpation of an abdominal mass lesion or visualization of a sublingual or rectal string [1,3]. Abdominal palpation of a mass has been documented in 13.3–53% of patients [1,24]. Abdominal pain was more commonly noted in patients with linear foreign bodies (54.5%) compared to non-linear foreign bodies (37.8%) [1]. Patients with abnormal mentation, injected (bright red) mucous membranes, prolonged or brisk capillary refill time, tachycardia or bradycardia, tachypnea, poor-quality pulses, and abdominal effusion should be further evaluated for altered oxygen delivery and SIRS or sepsis [20,25] (see Chapter 155).

Diagnostics

An extended database, including packed cell volume, total solids, electrolytes, acid–base status, lactate, blood urea nitrogen, creatinine, and glucose, should be considered on presentation. The most common electrolyte and acid-base disturbances regardless of location of obstruction included hypochloremia (51.2%), hypokalemia (25%), hyponatremia (20.5%), metabolic alkalosis (45.2%), and hyperlactatemia (40.5%) [14]. Despite the proposed pathophysiology, hypochloremic metabolic alkalosis did not correlate with location of obstruction in one study [14]. Interestingly, hyponatremic patients were more likely to have a linear foreign body than a discrete foreign body, but clinically, hyponatremia alone will not definitively distinguish a linear from discrete foreign body [1,14].

Complete blood cell count (CBC) abnormalities commonly include a leukocytosis due to neutrophilia with or without a left shift. While the CBC changes are not prognostic for survival following small intestinal surgery, nor predictive of perforation [26], the change in leukogram

may help guide the clinician in the postoperative period. Thrombocytopenia, rare in this clinical population, should be confirmed cytologically and if persistent, may indicate the presence of a consumptive coagulopathy and risk of hemorrhage (see Chapter 70). Blood chemistry abnormalities are often non-specific, with the most common abnormality reported being azotemia [2,21], but this was not repeated in another study [1]. CBC and blood chemistry will provide baseline values for assessment of trends in the white blood cell and band count, leukocyte morphology and biochemical profiles (including but not limited to albumin, creatinine, total bilirubin, and electrolytes) that will affect further care.

An abdominal focused assessment with sonography for trauma (aFAST), used to evaluate for free peritoneal fluid in patients with abdominal discomfort, can increase diagnostic sensitivity and guide sampling [27] (see Chapter 182). Preoperative bedside fluid analysis and cytology can provide critical information and drive more urgent interventions (see Chapters 6 and 87). A peritoneal fluid lactate concentration greater than blood by 2.5 mmol/L was 100% sensitive and 91% specific for septic peritonitis in the dog [28]. The same study found that a fluid lactate above 2.5 mmol/L in cats was only 67% sensitive and specific. A blood-peritoneal fluid lactate difference of greater than 2.0 mmol/L is 63–100% sensitive and 100% specific for septic effusion in dogs. Comparing blood with peritoneal fluid glucose, a difference of 20 mg/dL is 100% sensitive and specific for septic peritonitis in the dog and 86% sensitive and 100% specific in the cat [29]. A septic effusion is suspected if degenerative neutrophils are present. Total nucleated cell count greater than $13 \times 10^9/L$ is 86% sensitive and 100% specific for septic effusion in the dog and 100% sensitive and specific in the cat [29].

Intracellular bacteria on cytological evaluation confirms the diagnosis of septic effusion with 57–100% accuracy, and gram stain can increase sensitivity [28–30]. Culture and sensitivity should always be performed on the fluid. The most commonly isolated organisms associated with foreign body obstruction in dogs include *Escherichia coli*, *Enterococcus* spp, *Enterobacter* spp, *Klebsiella* spp, and *Pseudomonas* spp [2]. Septic peritonitis in cats is typically associated with *Escherichia coli*, *Enterococcus* spp, *Clostridium* spp, and *Pseudomonas* spp [31].

Radiography

Abdominal radiography is currently the diagnostic tool most commonly used in the diagnosis of GI obstruction. Definitive results were provided in 70–94% of clinical patients [32,33], but rates of diagnosis are as low as 56% for radiolucent foreign bodies [34]. Intestinal obstruction

diagnosed on screening abdominal radiographs may include segmental intestinal dilation by fluid and/or gas, detection of foreign material within the intestinal tract, abnormal position of the bowel, and/or focal granular material in the intestine [32,34,35]. Comparing the maximum small intestinal diameter to the height of the fifth lumbar vertebrae at its narrowest point on a lateral radiograph has been evaluated as a diagnostic tool for determining the presence of an intestinal foreign body obstruction in dogs [35,36]. A ratio greater than or equal to 2.4 is likely to be obstructive, less than 1.4 was normal, and falling between 2.4 and 1.4 indicated further evaluation [36]. Despite this objectivity, one study did not show any increased accuracy of diagnosis regardless of trainee experience, remaining at 66% [37], a finding contradicted by yet another study [36]. Linear foreign body cases may have plication and intestines may gather in the right side of the abdomen. One report found that luminal gas bubbles tapering at one or both ends was suggestive and the presence of three or more bubbles was always associated with a linear foreign body [21].

Other radiographic changes to note include decreased serosal detail (though non-specific and can be caused by decreased intra-abdominal fat or peritoneal effusion) [34], pneumoperitoneum, and non-specific mass-like structures [24,38].

Contrast radiography can be considered a second line in abdominal imaging. Negative contrast pneumocolograms or left lateral abdominal radiographs can help to differentiate the colon and pyloric outflow tract, respectively [39]. Barium, used as a positive contrast for upper gastrointestinal series, can be considered in cases where intestinal obstruction is suspected but perforation is thought unlikely [40]. Should there be a concern for perforation and no alternative imaging is available, non-ionic iodinated contrast agents with low osmolality such as iohexol can be used [41].

More recently, ultrasonography has gained availability and attention, and been compared to radiography in the diagnosis of mechanical obstruction (Figure 81.1), with the yield of a definitive diagnosis ranging from 94% to 97% in dogs depending on user experience [32,33].

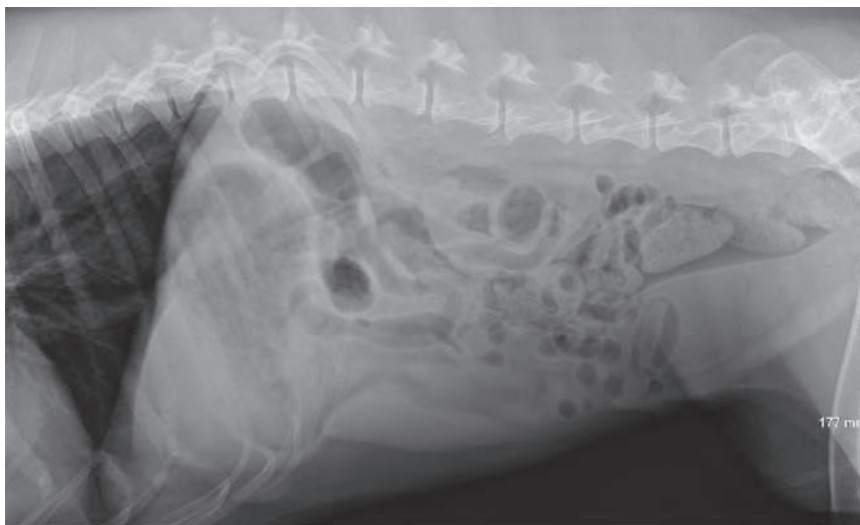


Figure 81.1 A right lateral radiographic projection of an obstructive duodenal foreign body with confirmatory sagittal ultrasound image of a thickened duodenum extending aboral into a hard shadowing partially obstructive duodenal foreign body.

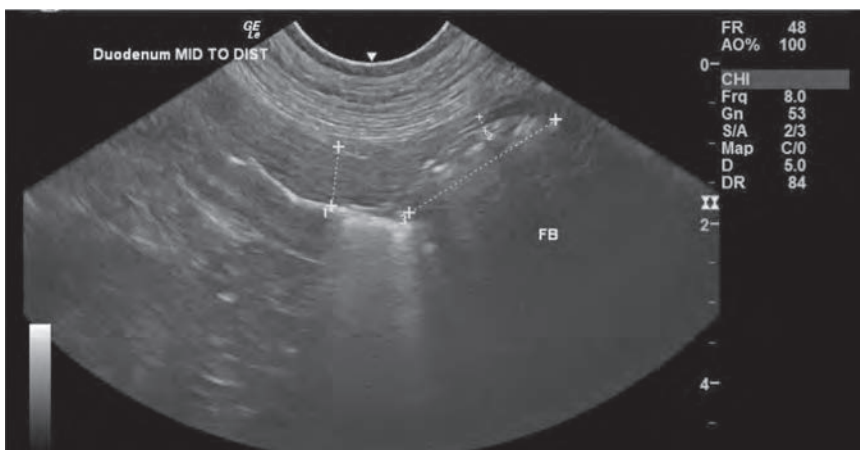


Figure 81.2 A transverse image of a jejunal intussusception with central string foreign body. The central hard shadowing string has joined the intussusceptum (inner intestine), becoming telescoped into the intussusciens (outer intestine), resulting in intestinal obstruction. Source: Courtesy of Steve Ting DVM.



Findings include gastrointestinal distension (canine jejunal dilation >1.5 cm), fluid-filled intestinal loops, intestinal hypermotility and hypomotility, hard-shadowing foreign body, and hyperechoic mesentery [34,42]. GI perforation secondary to intestinal FB obstruction or intussusception can result in hyperechoic mesentery, effusion, pneumoperitoneum, loss of normal gastrointestinal wall layer, and lymphadenopathy [43]. Contrast-enhanced ultrasound increases the sensitivity for the diagnosis of pneumoperitoneum and decreased focal intestinal blood flow, though availability is not widespread [33].

Ultrasound diagnosis of intussusception in dogs and cats is based on the presence of a target-like mass with multiple hyperechoic and hypoechoic rings around a hyperechoic center when the intestine is imaged from the transverse plane, as seen in Figure 81.2. The hyperechoic center represents mesenteric fat associated with the intussusceptum. One study found that Doppler ultrasonography was helpful in identifying mesenteric blood flow, and of those with blood flow, 75% could be reduced at the time of surgery [44]. Caution should be exercised with ultrasonography, as success rates are highly user dependent and images can be captured that are suggestive of obstruction or intussusception when not present.

With the growing availability of computed tomography (CT) in veterinary medicine, availability of multi-detector helical CT and sedated protocols, abdominal imaging in acute abdomens is being routinely performed

in some practices. While ultrasound may offer the ability to capture small volume fluids in real time, the time for imaging is dramatically decreased and patient care can be prioritized [33]. CT offers greater sensitivity in the diagnosis of localized pneumoperitoneum, with commonly identified infiltrative fat near a thickened intestinal loop and evidence of obstruction [45]. While MRI is an option for further evaluation of the acute abdomen, excessive motion artifact, required general anesthesia, long acquisition time, lack of suitable oral contrast agents, and cost limit the utility of this modality. As technology improves and further imaging techniques such as high-speed MRI (HASTE) provide optimal images in a short period of time, this amongst other imaging modalities will be evaluated [46].

Specific Conditions

Non-Obstructive Foreign Body

While witnessed foreign body ingestions can be prevented from causing intestinal obstruction or perforation, strict guidelines for which intervention is most appropriate for a particular foreign body ingestion do not exist in veterinary medicine. The American Society of Gastrointestinal Endoscopy practice guidelines recommend endoscopic removal of all amendable ingested sharp objects in people. If retrieval is not possible by

minimally invasive routes (e.g. foreign body has passed into the jejunum) and the patient is subclinical, monitoring via examination of serial radiographs is recommended until passage of the foreign body. Surgical intervention is recommended in patients who become clinical or those in which the foreign body fails to advance after 3 days [47]. The NASPGHAN Endoscopy Committee created guidelines for the management of ingested foreign bodies in children which may serve as a good guide for veterinary medicine though further evaluation is recommended [48].

Clinically, in small animal patients, the induction of emesis has been considered, when the risk of allowing the foreign body to remain outweighs the risk of acute esophageal obstruction or damage, oropharyngeal obstruction, aspiration or vagally mediated collapse. If all minimally invasive techniques have failed, surgical exploratory may also be considered.

Linear Foreign Bodies

Aborally directed peristaltic movement of the intestines over a fixed (commonly under the tongue or pylorus), linear structure leads to bunching of the intestine with subsequent partial to complete obstruction. This secondarily results in direct mucosal injury and perforation of the mesenteric bowel [3,8,49]. Historically, linear foreign bodies have required more aggressive surgical intervention, longer intraoperative times, longer postoperative care (about 1 day), and a higher incidence of postoperative complications. All these variables in some studies have been associated with a worse prognosis and higher cost (about 10%) when compared to discrete foreign bodies [1–3], although a more recent comparison of linear versus discrete foreign bodies found comparable survival rates (96%) between the two groups [1].

Intussusception

Typically, intussusception is an illness affecting young dogs and cats but has been diagnosed in older animals. Causes include viral enteritis, intestinal parasitism, gastrointestinal foreign bodies, recent gastrointestinal surgery, renal transplant, intestinal neoplasia, and gastroenteritis, but most are considered idiopathic [24,38,50,51]. Development of intussusception is thought to occur when a normal intestinal contraction intersects with a focal abnormal intestinal segment that has a sudden change in diameter or motility [24,38,51]. The intussusceptum becomes telescoped into the intussusciptum, causing an obstruction. The arterial and venous flow becomes occluded and intestinal ischemia results in focal edema, ulceration, necrosis, and eventual perforation.

The most commonly reported locations include enterocolic and enteroenteric while gastroesophageal, pylorogastric, and colorectal intussusceptions have been reported as well [24,38,52,53]. Transient intussusception has been described in the dog [53,54], though it is a rare condition.

Manual reduction of the intussusception is recommended; if unable to reduce or the bowel is overtly devitalized, resection and anastomosis are recommended [55]. The recurrence rate ranges from 3% [52] to 18.5% [24]. The reduction in recurrence has been proposed to be secondary to the routine use of perioperative opioids [50]. Surgical enteroplication remains a controversial topic due to an increased risk of related complications, as high as 20% in one publication [52]. These risks include but are not limited to intestinal obstruction and strangulation.

Postoperative Complications and Care

Postoperative care of the intestinal obstruction patient should include ensuring the patient remains euvolemic and euhydrated (see Section 5), with appropriate pain control (see Chapter 193) and nutritional support, and is closely monitored for postoperative complications (see Chapter 88). Appropriate initial antibiotic therapy is a key factor for survival in both veterinary and human patients suffering from sepsis in general (see Chapter 200). Common isolates in dogs with septic peritonitis include *Escherichia coli*, *Enterococcus* spp, *Klebsiella* spp, *Pseudomonas* spp, *Clostridium* spp, and *Streptococcus* [2,56] while in cats *Escherichia coli*, *Enterococcus* spp, *Clostridium* spp, *Pseudomonas* spp, and *Acinetobacter* spp predominate [31]. Commonly prescribed antibiotics include ampicillin, amoxicillin/clavulanic acid, fluoroquinolone, cefazolin, cefoxitin, and cefuroxime providing broad antibacterial coverage [31,56].

The determination between an escalation and de-escalation antibiotic approach should be directed by individual patient variations including source of infection, previous antibiotic therapy, immune competence, and severity of illness. Appropriate initial antibiotic therapy should be targeted at this time, although when comparing surgically treatable sepsis (i.e. septic peritonitis) to non-surgically treatable sepsis (i.e. pneumonia), the benefit seems to not be as profound in both veterinary and human studies [56,57]. The mechanical function of debridement, source control, and lavage significantly decreases bacterial load and eliminates continued contamination, decreasing the need to rely on initial antibiotic selection and appropriate immune physiological response. Despite a lack of survival benefit proven by

appropriate initial antibiotic selection in surgical sepsis, careful attention to perioperative antibiotic selection is still recommended until further studies have evaluated non-survival endpoints, including duration of hospitalization, severity of illness, impact on cost of care, and description of important subgroups [56].

Complications associated with GI obstruction include postoperative ileus, dehiscence of the surgical site, septic peritonitis, aspiration pneumonia, and malabsorption. These affect patient recovery and prognosis and alter the postoperative course of patients undergoing surgery. Extensive resection can cause short bowel syndrome with clinical signs including diarrhea, malabsorption, weight loss, fluid, and electrolyte abnormalities [57]. One study noted that dogs and cats tolerated a resection of 50% or more small intestine, with 8/10 dogs and 4/5 cats having good outcome [57].

Reported dehiscence rates following surgery for gastrointestinal foreign body obstruction range from 3% to 27.7% [14,58–61]. Risk factors for dehiscence in dogs with obstructive foreign bodies include presence of intestinal foreign body and hypoalbuminemia of 2.5 g/dL or less [58,60]. This finding was contrary to Harvey et al.'s finding where hypoalbuminemic dogs undergoing full-thickness biopsy had the same incidence of perforation as those with normal albumin levels, although this patient population did not have intestinal foreign body. While not specifically evaluating dehiscence, a retrospective study in dogs suffering septic peritonitis secondary to dehiscence with recut found that hypoalbuminemia was not predictive of survival [57]. One study found that dogs with intestinal dehiscence had a much higher postoperative band neutrophil count, when compared to those without dehiscence [58]. Dogs with dehiscence of the surgical site have a reported mortality

of 56–80% although financial impact was not fully evaluated in those studies [26,58,62].

Dogs and cats with linear foreign bodies have septic peritonitis rates of 41% and 16% respectively (see Chapter 87). Animals with septic peritonitis have a longer duration of hospitalization, greater cost of care, and worse prognosis [2,21]. Animals with septic peritonitis consistently develop hypoalbuminemia postoperatively but this has not been found to affect survival [63]. Mortality rate of 31% has been reported in animals with peritonitis associated with small and large intestinal surgery [26].

Reported complications following surgical correction of intussusception include recurrence, ileus, intestinal obstruction, intestinal strangulation, and peritonitis [24,38,52]. The overall recurrence rate for dogs with intussusception ranges from 3% to 19% [24,51,52]. The reported short-term survival rate for cats with surgical treatment for intussusception ranges from 74% to 80% [24,38].

Overview

Overall survival rate in one study of dogs and cats with focal GI FB removal was 92% and 88% respectively [3], and a survival rate of 99% was reported for dogs in a separate study [14]. Cats with linear FB obstruction have a reported survival rate of 62–100% [3,6,21] and reported survival rate for dogs with linear FB obstruction is approximately 80–96% [1–3]. Dogs with either a linear or non-linear foreign body had a survival rate of 96% despite a higher frequency of intestinal necrosis, perforation, peritonitis, longer surgical times, longer hospital stay, and increased cost with linear foreign bodies [1].

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Gastric Dilation-Volvulus*Elke Rudloff, DVM, DACVECC**Lakeshore Veterinary Specialists, Glendale, WI, USA***Introduction**

Gastric dilation-volvulus (GDV) occurs when the stomach rotates along its axis and dilates with gas and fluid. Owner presenting complaints typically include non-productive retching, restlessness, excessive salivation and swallowing, and abdominal distension. Although most commonly seen in large-breed dogs, GDV can occur in any breed or species of animal. Decreased incidence has been reported in dogs in which the owners perceived a personality trait of happiness, that received table food or canned food, egg or fish supplements, and undertook moderate exercise [1–3]. Characteristics associated with increased risk for the development of GDV include having a first-degree relative that suffered GDV, lean body condition, increasing age, large drops in environmental temperature over a short period of time, feeding single large meals, overeating, small kibble size, elevated feeding bowls, postprandial exercise, anesthesia, and aerophagia [2,3]. The ability to predict the development of GDV has remained an enigma, and reported findings have contradicted each other.

The mechanism that initiates a GDV event has not been definitively elucidated, be it gastric rotation followed by dilation or dilation followed by rotation. Studies suggest that the initiating event may involve bacterial fermentation from either ingested food or duodenal reflux producing carbon dioxide and hydrogen gases [4–6]. As the stomach dilates, it may stretch its attachments and rotate in either a clockwise or counterclockwise fashion, preventing the expulsion of contents. Gastric motility disorders have also been proposed to be a predisposing mechanism [7].

Gastric distension leads to nausea and attempts to vomit. Non-productive retching will stimulate the production of tenacious saliva that is swallowed and accumulates in the esophagus. This can be regurgitated

and obstruct the airway. The distended stomach causes displacement of the diaphragm cranially and reduced thoracic capacitance, increasing the work of breathing. Severe gastric dilation also increases intra-abdominal pressure, reducing venous return and cardiac output and resulting in tissue hypoxia and maldistribution of blood flow (see Chapter 152). Hypovolemia can be profound, and is a result of translocation of protein and fluid into the stomach as well as hemorrhage from torn short gastric and gastroepiploic vessels (see Chapter 153). Hypoxic and ischemic tissues initiate a systemic inflammatory response syndrome (see Chapter 159). Circulation of cytokines and myocardial hypoxia often result in ventricular dysrhythmias (see Chapter 53).

Diagnosis and Treatment

In most situations, a working diagnosis of GDV can be made when gastric tympany is discovered on initial examination. Occasionally, the caudal thoracic ribs prevent palpation of the distended stomach. Prior to obtaining radiographs, treatment for hypovolemic shock, administration of pain medication, and gastric decompression are indicated (see Chapters 153 and 190).

In the initial resuscitation period, flow-by oxygen should be provided, IV access attained, and continuous ECG monitoring started as soon as possible. Ventricular tachyarrhythmias are common in the GDV patient and continuous ECG monitoring should be maintained throughout the preoperative, perioperative, and postoperative periods. See Chapter 53 for further discussion of management of arrhythmias.

Given the size of most animals with GDV, large-volume fluid resuscitation may be required. This may necessitate the placement of one or two large-bore IV catheters. Hypovolemic shock resuscitation involves infusion of

a balanced, buffered, isotonic crystalloid solution (see Chapter 153). Initial studies have suggested that resuscitation with hydroxyethyl starch, hemoglobin-based oxygen carriers, and/or hypertonic saline may reduce the total amount of initial fluid volume required to achieve resuscitation endpoints, and potentially improve outcome (see Chapter 169) [8,9]. Given the limitations of these studies and the potential adverse effects of hydroxyethyl starch, strong recommendations for the ideal approach to fluid resuscitation of the GDV patient cannot be made. Analgesia using full mu-agonist opioids (e.g. hydromorphone, morphine, oxymorphone, fentanyl) is commonly indicated early in the resuscitation period. Initiation of a lidocaine infusion (2mg/kg bolus IV and 0.05mg/kg/min continuous rate IV infusion) at the time fluid resuscitation is initiated may reduce the risk of cardiac dysrhythmias and acute kidney injury, as well as reducing hospital stay [10]. However, prospective randomized studies are needed to assess the true benefit of lidocaine in the GDV patient.

Gastric decompression can be performed with percutaneous placement of a large-bore over-the-needle catheter into the stomach (trocarization) or orogastric intubation. Trocarization is less stressful and more successful than orotracheal intubation [11], but improper placement can result in puncture of other abdominal organs. The site of trocarization should be chosen as an area of palpable gastric tympany, caudal to the ribs. This is more commonly along the right side but can occur on the left. Ultrasonography can be used to identify the location of the spleen when selecting the site. The area is clipped free of hair and prepared in an aseptic manner, and catheter placement is performed using aseptic technique (Figure 82.1). In most

dogs, a 14G or 16G size catheter is introduced and the stylet removed. Gas and fluid are expelled through the catheter as a result of gastric pressure. Gentle compression of the abdominal wall opposite the side of the catheter may aid in maximizing decompression. Once the stomach has been decompressed, the catheter is removed to minimize the risk of abdominal contamination with gastric contents.

Orogastric intubation will require manual restraint and sedation of the alert patient. A smooth, flexible tube is lubricated and gently passed into the oropharynx and esophagus. Orogastric intubation carries a risk for aspiration, esophageal trauma, and gastric perforation [12]. If there is resistance at any point or regurgitation, this technique should be aborted.

Gastric decompression by these methods is not a definitive treatment as it usually does not result in gastric repositioning.

A complete radiographic series (orthogonal views) of the abdomen is usually not necessary to confirm GDV. A standard right lateral cranial abdominal radiograph is most diagnostic. Classic radiographic evidence of a GDV includes the presence of a gas- or fluid-distended stomach with displacement of the pylorus, giving the stomach a “double-bubble” appearance or “Popeye arm” (Figure 82.2). It is not unusual to see a dilated esophagus, and this usually resolves after the stomach is repositioned [13]. Rarely, a left lateral or dorsal-ventral projection is needed when the right lateral view is equivocal. On a dorsoventral view, the pylorus appears as a gas-filled structure to the left of the midline with GDV. Depending on patient signalment and physical examination findings, thoracic radiographs may be indicated to identify



Figure 82.1 Trocarization for gastric decompression of a dog with gastric dilation-volvulus. An area over the region of tympany has been clipped and prepared in an aseptic manner and a 14G catheter passed into the lumen of the stomach to allow expulsion of gas and fluid.

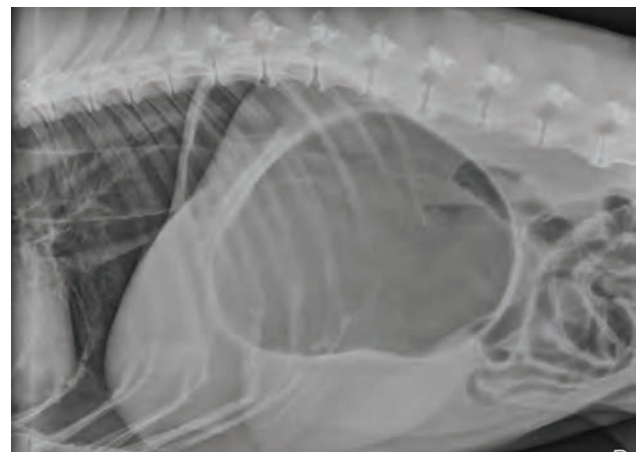


Figure 82.2 A right lateral radiograph of the cranial abdomen of a dog with gastric dilation-volvulus. This radiograph demonstrates the classic “double-bubble” or “Popeye arm” appearance of the gas-distended stomach. The pylorus is evident craniodorsal to the stomach, separated from the stomach by soft tissue. This abnormal positioning of the pylorus confirms the diagnosis of GDV.

aspiration pneumonia, cardiomegaly and survey for neoplasia which could alter prognosis [14].

Blood samples for an emergency laboratory database are collected, and a packed cell volume (PCV), total protein (TP; by refractometer), venous blood gas, electrolyte panel, and glucose and lactate levels are evaluated. Hemorrhage is evidenced by a decreased PCV/TP. A metabolic acidosis characterized by hyperlactatemia is common. A number of retrospective studies have looked at the predictive value of plasma lactate in cases with GDV [15–19]. An initial plasma lactate <4 mmol/L and/or a $>40\%$ reduction in plasma lactate following fluid resuscitation are associated with increased survival and fewer complications. An initial lactate level >6 mmol/L may be associated with gastric wall necrosis and increased cost of care. However, the overlap in values and overall survival rate are great enough that treatment should always be recommended [20]. More comprehensive, preanesthetic laboratory evaluation, including a CBC, serum biochemical profile, urinalysis, and coagulation profile, is indicated following patient stabilization.

Empirical antibiotic administration is not indicated routinely in the GDV patient other than the standard perioperative coverage. Indications for antibiotic therapy include evidence of gastric perforation, aspiration pneumonia or overwhelming inflammation indicated by neutropenia or a degenerative left shift on the CBC (see Chapter 200).

Surgical Management

A 50–80% rate of GDV recurrence is reported in medically managed cases, and therefore GDV is considered a surgical emergency [21,22]. Consideration of anesthesia for a high-risk patient should be undertaken (see

Section 7). Abdominal exploration allows manual guidance of the orogastric tube into the stomach for decompression, repositioning of the stomach and other displaced organs, identification of ischemic tissue and/or areas of perforation that may require removal or repair, and fixation of the pyloric antrum to the peritoneal wall by gastropexy. Gastropexy may not reduce the risk of gastric distension, but will reduce the risk of rotation and associated circulatory shock. Type of gastropexy is the surgeon's preference and includes incisional, circumcostal, beltloop, gastrocolopexy, and ventral midline techniques. The incisional technique is rapidly performed and may be associated with the lowest recurrence rate [23]. History of chronic gastrointestinal signs warrants gastrointestinal biopsy collection for histopathology. Placement of a nasogastric tube at the time of surgery permits postoperative monitoring of residual gastric volume, removal of excessive gas/fluid, and initiation of nutritional support.

Outcome

Mortality rates of 10–43% have been reported [1,15,24–28], with an increase in survival associated with rapid intervention, reduction in lactate levels with treatment, absence of gastric necrosis, and a serum myoglobin level <168 ng/mL [26,29]. Prophylactic gastropexy might reduce the incidence of GDV, and should be recommended to clients with giant and large-breed dogs, dogs undergoing any abdominal surgical procedure (e.g. ovariohysterectomy, splenectomy or gastrointestinal foreign body removal), as well as all first-degree relatives of a dog that has experienced a GDV. Laparoscopic gastropexy may provide a minimally invasive option for at-risk dogs that do not have other indications for abdominal surgery.

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83

Mesenteric Torsion

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Introduction

Mesenteric torsion (MT) is a rotation of the intestines around the mesenteric axis causing luminal obstruction and ischemia to the affected bowel. Mesenteric torsion occurs infrequently because of the shortness of the mesentery [1]. The torsion may be partial or complete and involve the small intestine, large intestine, or both [2]. It is often a fatal condition in dogs, with a mortality rate of 58–100% [3–8]. The disease generally affects young to middle-aged dogs of medium and large breed, with a breed predisposition in German shepherds [2,4,5]. Torsion may be associated with enteritis, exocrine pancreatic insufficiency, intussusception, gastric dilation-volvulus, neoplasia, gastrointestinal foreign body, lymphocytic-plasmacytic enteritis, and ileocecolic carcinoma [2,4,8–11]. Only five cases have been reported in cats; four cats had rotation of the small and large intestine [12,13] and the other had a jejunal herniation through a tear in the mesentery with a 360° clockwise rotation around the mesenteric root [14].

In humans, MT is classified as primary or secondary. Primary MT occurs in patients with no abdominal pathology and is caused by factors such as high-fiber diets or altered gastrointestinal motility. Secondary MT occurs as a result of a pre-existing factor or condition such as abdominal adhesions, congenital abnormalities (including malrotation), hernias, pregnancy, and previous surgery [15].

Pathophysiology

The intestines are not attached to the peritoneum or adjacent bowels and are suspended within the mesentery where they can easily move within the abdominal cavity. During physical activity and normal peristalsis, the

intestines undergo physiological movements, torsions, and rotations.

The great mesentery is in the form of a large fan hanging from the cranial part of the sublumbar region, with the free distal border attached to the jejunum and ileum. The great mesentery is 20 cm wide, 5 mm thick and 1.5 cm long and contains the cranial mesentery artery, the intestinal lymphatics, and a large mesenteric plexus of nerves [16]. The mesentery-intestinal border extends from the duodenojejunal flexure to the ileocecolic junction, and is as long as the jejunoileum (about 250 cm). If the mesenteric root is unable to control excessive bowels torsions, intestinal obstruction and compromised vascular perfusion may occur.

Distension of the intestinal lumen by ingesta or gas causes an increase in peristalsis, thus predisposing the gastrointestinal system to distension and dislocation. Torsion and volvulus of the small intestine can cause mechanical obstruction and strangulation, leading to vascular obstruction of the cranial mesenteric artery and its branches as well as venous congestion and edema to the distal duodenum, jejunum, ileum, cecum, ascending colon, and proximal descending colon [2].

Different degrees and direction of rotation may occur, ranging from 180° to more than 360° and going either clockwise or counterclockwise. When the intestine is twisted, fluid and gas accumulate within the loops. The mucosal villi are rapidly compromised and the tissue hypoxia and ischemia lead to ileus and abdominal pain. The compromised perfusion causes an ischemic intestinal necrosis, abdominal fluid accumulation, and loss of the intestinal barrier integrity, leading to bacterial translocation and sepsis or septic shock (Figure 83.1). The abdominal fluid is initially a transudate from serosal vessel transudation secondary to venous and lymphatic congestion. Due to bacterial translocation, the peritoneal fluid becomes exudative with toxic neutrophils and



Figure 83.1 Intraoperative appearance of small intestines with ischemic necrosis.

intracellular bacteria. Arterial and venous thrombosis may develop and be severe enough to be detected during surgery. Necrosis and ulcers of the intestinal mucosa often cause hematochezia.

The ileus allows the bacterial flora present in the intestinal lumen to rapidly multiply, particularly anaerobic species such as *Clostridium* spp and coliforms, both of which are known to release endotoxins and exotoxins. Bacterial growth in the small intestine can increase from 10^5 cfu/mL to 10^8 – 10^{11} cfu/mL within 6 hours of strangulation [1]. Bacteria easily translocate from the intestinal lumen to the peritoneum and bloodstream, often causing a systemic inflammatory response syndrome (SIRS), sepsis or septic shock, and in severe cases, multiple organ dysfunction syndrome (MODS) and death [17] (see Chapter 159).

Hepatopathy can be associated with MT due to direct bacterial or endotoxic insults to hepatocytes [18]. The release of inflammatory mediators from Kupffer cells can also cause hepatocellular damage [19]. Major tissue damage to viable bowels can occur when perfusion is re-established due to reperfusion injury and the release of oxygen-derived free radicals [20].

Death typically occurs from septic shock secondary to intestinal necrosis, euthanasia or postoperative complications [6,21].

History and Clinical Signs

Generally, male, young dogs (2–4 years), German shepherds and Pointers are more predisposed to MT. History of diarrhea, pancreatic exocrine insufficiency, and gastrointestinal disease are predisposing factors for MT. A history of collapse or cardiovascular shock associated with gastrointestinal disorders and a distended abdomen should

increase the index of suspicion [6]. Predisposing diseases or factors include gastrointestinal obstruction, gastric dilation-volvulus (GDV), gastrointestinal disease causing weight loss, enteritis, inflammatory bowel disease (IBD), intussusception, abdominal mass, trauma, gastrointestinal foreign body, gastrointestinal parasites, recent gastrointestinal surgery, large meal ingestion, and heavy exercise.

Clinical signs can be acute or chronic and include weakness, recumbency, anorexia, vomiting, hematemesis, diarrhea, hematochezia, abdominal distension, abdominal pain, praying position, fever, hypothermia, shock, and signs of SIRS. The septic patient generally has hypotension, injected mucous membranes, rapid capillary refill time, tachycardia, and warm extremities (see Chapter 159). Patients with colonic volvulus may show similar chronic abdominal symptoms [18,22]. Typical clinical signs detected during the physical examination include distended abdomen, free abdominal fluid (can be transudate, exudate, blood or mixed), pain, intestinal wall thickening, fever, palpable abdominal mass (often painful with direct palpation), and abdominal auscultation (for at least 1 minute) may reveal reduced borborygmi.

Diagnostics

Abdominal radiographs generally show distended, gas-filled loops of small intestine (large intestinal dilation is less common) and reduced abdominal detail due to the presence of fluid and peritonitis (Figure 83.2). The bowel loops commonly lie in parallel on abdominal radiographs and gastric distension may be present [6]. Serial abdominal radiographs can reveal progressive gaseous distension of individual portions of the intestinal tract [22].



Figure 83.2 Lateral abdominal radiographs of the patient in Figure 83.1 prior to surgery. Dilated intestinal loops and poor serosal detail are present. Image courtesy of Dr. Kenneth J. Drobatz.

If abdominal effusion is suspected, an abdominal focused assessment with sonography in trauma (aFAST) (see Chapter 182) should be performed. Abdominal ultrasonography (US) can readily detect the presence of free fluid in the abdominal cavity, as well as intraluminal accumulation of air and fluid, intestinal loops surrounded by abdominal fluid, intestine wall thickening with maintained or edematous layering, reduced or absent peristalsis in some intestinal loops, and intraluminal or intramural obstruction.

Abdominocentesis with fluid cytological analysis may reveal the presence of toxic neutrophils with intracellular bacteria, indicative of a septic peritonitis and the need for an emergency celiotomy (see Chapter 87). US can also detect the presence of a “whirl sign,” which appears when bowels rotate around the mesentery, creating a mesh of concentric intestinal loops, blood vessels, and fat.

Contrast-enhanced abdominal computed tomography (CT) was reported as a technique to diagnose mesenteric volvulus in a dog, revealing thrombus formation within the jejunal vein, moderate fluid accumulation, distension of the small intestine, a small volume peritoneal fluid, and left-sided displacement of the cecum and ascending colon [23]. In human patients, contrast-enhanced abdominal CT is the preferred modality to diagnose and evaluate small bowel volvulus [24]. CT can detect a whirl sign that has been shown to occur in people with not only MT but also adhesion formation, external or internal abdominal hernia, neoplasia, and post colectomy. For this reason, the whirl sign on CT is considered an important indicator of an abnormality, but is not specific [25]. In the dog, the whirl sign may be associated with the splenic pedicle and abnormally placed surrounding soft tissues [26].

The serum biochemical profile may be within normal limits or may indicate hypoalbuminemia, hypoproteinemias, and hypokalemia [2,4]. The total protein is generally reduced because of peritonitis and a subsequently low albumin and increased globulins. Mild azotemia and elevations in blood urea nitrogen may be present in animals with intraluminal intestinal hemorrhage, especially when hematochezia is present. Creatinine may be increased because of the systemic hypoperfusion and decreased renal perfusion during shock. Hypoglycemia may be present due to a non-insulin-mediated increased consumption, decreased intake, and decreased hepatic function/gluconeogenesis [27]. In chronic cases, due to hepatic dysfunction, an elevation of alanine aminotransferase, alkaline phosphatase (ALP), gamma-glutamyltransferase, and total bilirubin may be present [18].

Blood gas analysis frequently reveals a metabolic alkalosis if the patient is vomiting, metabolic acidosis if the patient has diarrhea or elevated blood lactate levels, or a mixed metabolic acidosis and respiratory alkalosis (the first due to systemic hypoperfusion and the second to

respiratory alkalosis secondary to pain). Metabolic acidosis with reduced base excess and increased blood lactate levels may be useful for the detection of systemic hypoperfusion.

A complete blood cell count (CBC) may reveal a typical stress leukogram with a neutrophilic leukocytosis with a left shift in acutely affected animals while chronically affected patients may have a normal CBC. Anemia, if present, may be due to intestinal and abdominal hemorrhage and decreased production.

Treatment

Patients in a state of shock require rapid shock fluid therapy (see Section 5) to improve perfusion and tissue oxygenation. When an effective circulation is re-established or at least improved, urgent surgery is indicated.

If the patient is septic, sepsis “bundles” for treatment may prove beneficial; septic human patients managed with the use of bundle therapy had better outcomes [28,29]. The following are the therapeutic bundles suggested by the Surviving Sepsis Campaign:

- blood lactate measurement within the first 6 hours of admission and prompt fluid resuscitation in patients with lactate concentration 4 mmol/L or greater
- blood culture and susceptibility testing for guidance with antimicrobial therapy
- removal of the source of infection and administration of early antimicrobials [30]
- treatment of hypotension with isotonic and/or hypertonic crystalloids and vasopressors if indicated (see Chapter 159).

Artificial and natural colloids are acceptable, but the current recommendation in people is to avoid synthetic colloids in septic patients and use albumin, plasma or crystalloid instead due to the increased requirement for continuous renal replacement therapy following synthetic colloid administration [31] (see Chapter 169).

Central venous pressure monitoring may be useful for monitoring cardiac preload and vascular tone and central venous oxygen saturation (ScvO₂) may be useful for the detection of tissue hypoxia or a reduced oxygen distribution to the tissues. An ScvO₂ < 70% is considered to be a marker of global oxygen debt [28,32].

In patients with acute MT, most of the intestinal loops are ischemic and necrotic. Therefore, euthanasia is commonly requested during or prior to surgery. During and after surgery, derotation of the intestinal loops leads to reperfusion injury, which can cause multiple organ dysfunction due to a rapid increase in circulating oxygen radicals. Chronically affected animals have a better prognosis because the ischemic damage is typically less severe and large intestinal resection is less commonly necessary. In

animals with severe, acute MT, surgery is often successful in removing the affected portion of the small intestine, but the animals frequently experience short bowel syndrome postoperatively. This may persist indefinitely and require

long-term medical care, but early recognition and treatment of MT are of paramount importance to improve patient outcome and reduce the need for an extensive enterectomy and a prolonged hospital stay.

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Hemoperitoneum

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Introduction

Hemoperitoneum, or hemoabdomen, can be defined as the presence of a hemorrhagic effusion within the peritoneal cavity. Hemorrhagic peritoneal effusion may be broadly classified as traumatic or non-traumatic (spontaneous). Hemoperitoneum is more commonly diagnosed in dogs than in cats [1,2]. In cases of traumatic hemoperitoneum, stabilization of the patient is necessary followed by medical or surgical management of the injuries. Prognosis is variable and depends on the severity of the injuries and the degree of systemic compromise but can be favorable with appropriate care [3–5]. In cases of spontaneous hemoperitoneum, patient stabilization is followed by identification of the underlying cause which then determines definitive care and prognosis.

Underlying causes of spontaneous hemoperitoneum include atraumatic rupture of a benign or malignant abdominal mass, coagulopathies, and organ torsion [6]. In the dog, the cause of spontaneous hemoperitoneum is more likely to be a malignant process [1,7–9] while in cats malignant and non-malignant causes are seen equally as often [1,2]. The prognosis for spontaneous hemoperitoneum in dogs is variable and is highly dependent on the underlying cause (benign versus malignant process). In cats, regardless of etiology, the prognosis is often unfavorable [1,2].

History and Signalment

A thorough history is valuable in the evaluation of dogs and cats being investigated for a suspected or confirmed hemoperitoneum. Any history of known or suspected trauma should alert the clinician that a traumatic hemoperitoneum is possible. Trauma from a motor vehicle is the most common cause of traumatic hemoperitoneum

in dogs [4,10]. If there is no history of trauma and a very low likelihood of toxin ingestion, the suspicion for a spontaneous hemoperitoneum secondary to a ruptured abdominal mass increases. Dogs with an intermittently bleeding abdominal mass may have a history of waxing and waning lethargy, weakness, and/or decreased appetite/anorexia [11]. Cats with spontaneous hemoperitoneum most commonly present with a history of anorexia, lethargy, recumbency, and vomiting [1,2].

The signalment of the patient is also important in determining the cause of hemoperitoneum. Young animals are more likely to suffer a traumatic event, ingest a toxin, or have anaphylaxis than to present with a bleeding abdominal mass. Young pure-bred animals may have a heritable coagulopathy. Older dogs without a history of trauma or toxin exposure are more likely to have a bleeding abdominal mass, with some breeds such as golden retrievers, German shepherds, and Labradors being overrepresented [7–9]. Great Danes and German shepherds are overrepresented in cases of splenic torsion [9,12]. Cats with spontaneous hemoperitoneum most commonly have a ruptured abdominal mass, coagulopathy, or hepatic necrosis [1].

Clinical Signs and Physical Examination Findings

Clinical signs and physical exam findings may be variable depending on the species, the underlying cause, the severity and acuteness of the hemorrhage. In cases of traumatic hemoperitoneum, there may or may not be other injuries. Care should be taken to perform a full physical examination in all trauma patients, including a full evaluation of the respiratory, cardiovascular, urinary, musculoskeletal, and neurological systems to evaluate for evidence of other injuries (see Chapter 160).

The suspicion of a traumatic hemoperitoneum will be increased with findings of abdominal pain or distension, or a palpable fluid wave in a patient with hemorrhagic shock and a history of trauma. Patients should be fully evaluated for any other evidence of hemorrhage that could indicate a coagulopathy, including hyphema, bruising, petechiae or ecchymotic hemorrhages. Abdominal pain or an abdominal fluid wave may or may not be appreciated. It has been reported that 40 mL/kg of abdominal fluid must be present in order to detect a fluid wave on examination [11]. In some cases, an abdominal mass may be palpated.

In cases of traumatic and spontaneous hemoperitoneum, animals may present collapsed and in a state of hemorrhagic shock or may present with minimal or no abnormalities. Apparently stable patients should be closely and serially monitored as some may subsequently deteriorate if there is significant ongoing blood loss. Perfusion parameters should be noted and serially monitored, including mucous membrane color, capillary refill time, mentation, pulse rate and character, and body temperature. Dogs with acute severe hemorrhage may present in decompensatory shock with white or pale mucous membranes, an absent or prolonged capillary refill time, hypothermia, bradycardia or tachycardia, absent or weak peripheral pulses, generalized weakness, and an obtunded or depressed mental state [11,13] (see Chapter 153). Cardiac arrhythmias with or without pulse deficits may be noted [14,15]. These cases require immediate stabilization. Sudden death may occur with severe acute peritoneal hemorrhage.

Dogs with a slower or less severe hemorrhage may present in compensatory shock with normal to hyperemic mucous membranes, a rapid capillary refill time, hyperdynamic pulses, and a variable tachycardia [11]. Cases of mild or intermittent hemorrhage may only have subtle findings, such as mild lethargy and weakness, and may have stable cardiovascular parameters [11,13]. Cats with spontaneous hemoperitoneum may have variable findings on exam, but the most common physical exam findings in two retrospective studies were depressed mentation, hypothermia, pale mucous membranes, poor pulse quality, and dehydration [1,2].

Initial Treatment and Stabilization

Animals with traumatic or spontaneous hemoperitoneum presenting in any stage of hemorrhagic shock should be stabilized prior to performing advanced diagnostics, although some initial diagnostics such as packed cell volume (PCV), total protein (TP), a limited/focused ultrasound examination (see Chapter 182) and abdominocentesis (see Chapter 186) may be performed during

the initial stabilization. Initial resuscitation efforts should focus on correcting perfusion parameters by restoring intravascular volume and providing adequate oxygen-carrying capacity. Secondary goals are to arrest any active hemorrhage and avoid rebleeding (see Chapter 163). In cases of traumatic hemoperitoneum, other injuries may also need to be addressed.

Vascular access should be obtained using a short, large-bore catheter capable of higher rates of intravenous fluid administration and blood product administration as necessary [16]. The recommended fluid type (crystalloid versus colloid) (see Chapter 169) and rate of fluid administration are controversial, and further studies are necessary to determine if these choices have a significant effect on outcome. Conventional (“large volume” or “shock dose”) fluid resuscitation strategies have several disadvantages including increased infusion times and the ultimate redistribution of fluids leading to tissue edema. In patients with hemorrhagic shock, large-volume resuscitation can lead to exacerbation of hemorrhage through increasing intravascular hydrostatic pressure and clot disruption and prolonged clotting times due to dilution of clotting factors [11,17] (see Chapters 163 and 170).

Low-volume or limited fluid volume resuscitation (LFVR) has been described for both human and veterinary patients with hemorrhagic shock and may be a better approach in an actively bleeding patient (see Chapter 170). This resuscitation strategy seeks to restore perfusion to vital organs while minimizing the risk of exacerbating hemorrhage. Small volumes of crystalloids (isotonic or hypertonic) alone or with colloid solutions are titrated to reach low-normal resuscitation goals (mean arterial pressure of 60–70 mmHg) until definitive hemostasis takes place (with either medical management or surgical correction). Using LFVR, isotonic crystalloid boluses are given in 20–30 mL/kg increments, hypertonic saline in 2–4 mL/kg increments, and/or colloids in 5 mL/kg increments until resuscitation goals are met. Benefits of LFVR include faster infusion times and a decreased risk of dilutional coagulopathy [11,16,18].

Ultimately, in developing a fluid resuscitation plan, each case must be evaluated individually, taking into account the severity of shock and any pre-existing conditions (i.e. cardiac or metabolic disease) that may complicate or increase the risks of fluid therapy.

Supplemental oxygen (see Chapter 181) may be administered to maximize the oxygen content of arterial blood, but this will not eliminate the need for blood product administration if there has been significant blood loss. The need for a blood transfusion will be based partly on current hemoglobin levels and on the timeframe over which blood loss occurred (see Chapter 176). Compensation mechanisms (i.e. increased cardiac output and increased release of oxygen at the tissue level) can take

place with a more chronic drop in hemoglobin, making the need for a blood transfusion less urgent. Transfusions should be considered for patients with hemorrhagic shock that are not stabilized with fluid therapy alone or patients with continued blood loss. While there is no set packed cell volume for which transfusion is mandated (i.e. a “transfusion trigger”), patients with a PCV < 25% who will require surgery will likely require blood products [11]. Ideally, transfusions would “replace what was lost” using fresh whole blood, but as this is often not readily available, a combination of packed red blood cells (PRBCs) and, if necessary, plasma can be administered. The volume of plasma or blood required to normalize clotting times will vary; standard doses should be used to start and then clotting times monitored until they have normalized.

Blood product administration decisions may also be determined by the availability and costs of blood products, underlying disease process, and owner goals. If blood products are readily available, blood typing (and ideally a cross-match) should be performed early in the evaluation process. In cats, type-specific blood transfusions are imperative to avoid serious transfusion reactions. Polymerized hemoglobin solutions provide a shelf-stable alternative to blood transfusions, but they are currently unavailable.

If blood products are not readily available and a transfusion is necessary, autologous blood transfusion (ABT) or “autotransfusion” may be considered. Autologous blood transfusion involves the sterile acquisition of the shed blood and reinfusion intravenously through a filter. Blood collection from the abdominal (or thoracic) cavity can be performed percutaneously using a catheter or needle, extension set, and syringe, or at surgery with a syringe or suction. The benefits of ABT include lower cost, readily available materials, no need to type or cross-match and no need to warm the blood. Potential complications include inadvertent administration of air or clot emboli or the administration of blood that was contaminated with gastrointestinal contents, bile or urine, or tumor cells. While using blood contaminated with bacteria, urine, or bile should be avoided, it is controversial if transfusion of malignant cells significantly affects outcome, particularly in cases of ruptured hemangiosarcoma [19], which likely has disseminated via the hematogenous route prior to diagnosis [20]. From a practical standpoint, if a patient’s only option to survive an acute crisis is an autologous blood transfusion, it is likely better than the alternative of bleeding to death.

Efforts at stopping or slowing abdominal bleeding can also include abdominal counterpressure which can be applied during the initial stabilization. The goal of abdominal counterpressure with an abdominal bandage (“belly wrap”) is to apply enough pressure to slow

or stop hemorrhage of vessels or organs through direct pressure and a tamponade effect, but not reduce blood flow significantly to vital organs. The wrap can also be extended to incorporate the pelvic limbs to shunt blood from the larger veins of the pelvic limbs to the more vital structures of the heart, lungs, and brain [11]. Abdominal counterpressure should not be applied in every case; animals with lung or chest trauma or a diaphragmatic hernia can have respiratory function further compromised by an abdominal wrap. The time for which an abdominal wrap is left on should be minimized to avoid ischemic complications, and when it is removed, it should be cut back slowly from cranial to caudal at 15-minute intervals to avoid recurrence of hemorrhage or hypotension [11].

Diagnostics

Initial diagnostics can often be performed during the stabilization process. A PCV/TP is readily available and inexpensive, and can provide a baseline for future trends. With acute hemorrhage, there may be a lag in the drop of the PCV and the first indication of significant hemorrhage may be a low TP. A normal PCV and low TP in a patient with signs of hemorrhagic shock should trigger the suspicion of internal hemorrhage and the PCV should be serially monitored during resuscitative efforts. A low PCV in a hemodynamically stable animal likely indicates a more chronic disease process.

A complete blood count (CBC) to evaluate red and white blood cell parameters and platelets should also be performed. Low platelets are frequently seen in dogs with spontaneous hemoperitoneum from a bleeding abdominal mass and could indicate consumption or disseminated intravascular coagulation (DIC) [21,22]. A serum biochemical panel should be performed and may provide information on organ involvement in traumatic or spontaneous hemoperitoneum. Elevated liver enzymes are commonly seen in cases of blunt abdominal trauma from hepatocellular injury and enzyme leakage [3]. In cases of spontaneous hemoperitoneum, elevated liver enzymes may indicate hepatic involvement in the disease process, particularly in cats [1,2].

Evaluation of coagulation status is imperative in all cases of spontaneous hemoperitoneum to evaluate for a possible coagulation defect as the cause of the hemorrhage (see Chapter 70). Significant prolongation of the prothrombin time (PT) and activated partial thromboplastin time (aPTT) should trigger suspicion of a vitamin K antagonist toxicosis. Due to the short half-life of factor VII, prolongation of the PT precedes a prolongation of the aPTT in cases of vitamin K antagonist ingestion, but often they will both be markedly prolonged if there is clinical evidence of hemorrhage [23]. Patients with an

inherited coagulopathy may have a prolongation of the PT and/or aPTT, but specific clotting factor analysis is necessary to determine which clotting factor is affected (see Chapter 69). Mild-to-moderate prolongations in the PT and/or aPTT may be seen with ruptured abdominal masses [22] and should be addressed prior to surgery. A coagulation profile can be considered in cases of traumatic hemoperitoneum, but may be less helpful unless a consumptive coagulopathy or coagulopathy secondary to massive transfusion is suspected, and/or surgery is necessary for definitive hemostasis (see Chapter 163).

While more advanced diagnostic imaging may need to be delayed until the patient with hemoperitoneum is cardiovascularly stable, a focused assessment with sonography for trauma (FAST) can often be performed simultaneously with resuscitative efforts provided ultrasound capabilities are available and the clinician is reasonably trained and comfortable with the exam [10,24] (see Chapter 182). While details of the protocol are beyond the scope of this chapter, an abdominal FAST evaluates each quadrant for evidence of free fluid within the abdominal cavity. FAST can be used to guide paracentesis efforts in order to obtain fluid for evaluation and can be performed serially to evaluate for progressive fluid accumulation. While initially developed for patients with blunt or penetrating trauma, FAST has since been evaluated in non-traumatized dogs and cats with suspected effusions [25]. Depending on the skill of the operator, other intra-abdominal pathology (such as a splenic or hepatic mass) may also be detected during a FAST scan [24]. A FAST scan does not take the place of a full abdominal ultrasound, but it can be performed quickly while patients are being stabilized by clinicians with limited ultrasound training [10,25].

If ultrasound is not available, a blind paracentesis can still be performed if hemoperitoneum is suspected (see Chapter 186). Some clinicians prefer to perform radiographs prior to abdominal fluid collection to prevent any confusion if free peritoneal gas is noted on the radiograph, but abdominocentesis may be done prior to radiographs if a closed system is used. Abdominocentesis may be performed with the patient standing or in lateral recumbency. To avoid the spleen, the area 2–3 cm caudal to the umbilicus and 2–3 cm to the right of the midline is a good place for a “blind” tap. The area is clipped and prepped. A needle (20–22 gauge, 1–1.5 inch depending on animal size) is attached to a syringe (3–6 mL) and advanced into the abdominal cavity perpendicular to the body wall and gentle suction is applied [26]. If no fluid is obtained, suction can be maintained while withdrawing the needle, but the needle should never be redirected while in the abdominal cavity as laceration of structures could result. If a single tap is negative, a “four-quadrant” tap or a diagnostic peritoneal lavage (DPL) can be

performed [6]. Complications of abdominocentesis include vessel or organ laceration, inadvertent vessel or organ aspiration, and introduction of bacteria or gas.

Fluid obtained should be placed in a sterile tube and evaluated. A PCV/TP should be performed on the fluid, as often fluid can appear quite bloody but have a low PCV that is indicative of blood contamination only and not a true hemorrhagic effusion. A true hemorrhagic effusion should have a PCV that is at least 10–25% peripheral blood and not contain any other microscopic abnormalities such as bacteria or neoplastic cells [26]. Bloody fluid should also be checked to see if it clots within the tube. Clotting blood may indicate an acute (<1 h) hemorrhage or accidental aspiration of a vessel or the spleen. Acute (<1 h) hemorrhage may have platelets present, but more chronic hemorrhage should be devoid of platelets. More chronic effusions may have evidence of erythrophagocytosis. Microscopic analysis should be performed to check for bacteria or the presence of any other abnormal cells. With ruptured abdominal masses due to hemangiosarcoma, neoplastic cells are not usually seen [26].

Further diagnostics may need to be delayed until the patient has been stabilized. In cases of traumatic hemoperitoneum, thoracic and abdominal radiographs are recommended. Evidence of free peritoneal gas, spinal trauma, or concurrent thoracic trauma may be identified and require further investigation. In cases of spontaneous hemoperitoneum, abdominal radiographs may be useful to identify decreased abdominal detail or the presence of an abdominal mass, although all masses may not be visible radiographically. Three-view thoracic radiographs (metastatic check) are recommended to look for evidence of pulmonary metastatic disease in cases of spontaneous hemoperitoneum.

A full abdominal ultrasound can be considered to better evaluate the source of abdominal hemorrhage. One exception may be cases of heritable or toxic coagulopathies, where an ultrasound may be less helpful. In cases of traumatic hemoperitoneum, an ultrasound can determine if an organ is damaged to the extent that surgery is warranted (i.e. a fractured or avulsed kidney), or if the bleeding is oozing from vessels or organs that are more susceptible to medical management. In cases of spontaneous hemoperitoneum, ultrasound can determine if a mass is present and if so, what organ it is arising from.

The use of ultrasound in the evaluation of abdominal masses has limitations, however. Ultrasound alone cannot determine if a mass is benign or malignant. Some findings may lead the clinician to suspect one over the other, but care should be taken in overinterpreting ultrasound results. Some characteristics of masses on ultrasound (having a mixed echogenic appearance or “target lesions”) may lead the examiner to suspect a malignant tumor, but this is not pathognomonic for neoplasia

[27,28]. Multiple masses that could be interpreted as metastatic disease may be benign nodules and/or hematomas or omental blood clots. The finding of a single mass or multiple masses on ultrasound was not predictive in determining if there was malignancy or not in one study of dogs with hemoperitoneum [29]. Ultrasound-guided organ or mass biopsies or aspirates can be considered, but in cases of hemangiosarcoma these diagnostics are generally not helpful [21]. Abdominal ultrasound may be most helpful in planning surgery; many clinicians may feel comfortable performing a splenectomy but not have the tools or skills needed to perform a liver lobectomy.

More advanced imaging techniques such as contrast-enhanced ultrasound, computed tomography (CT) and MRI are becoming more available and may prove useful in the future in evaluating animals with traumatic hemoperitoneum as well as helping to predict if abdominal masses leading to spontaneous hemoperitoneum are benign or malignant [30,31].

In cases of hemoperitoneum believed to be due to a bleeding abdominal mass, an additional diagnostic dilemma faces clinicians and owners regarding the decision to move forward with surgery or not. Given the poor prognosis associated with bleeding abdominal malignancies, particularly hemangiosarcoma, owners are often reluctant to pursue major and costly surgery. Knowing the likelihood of a malignancy (or, better yet, the definitive diagnosis) prior to surgery would help in decision making. A few studies have shown an association between some hematological findings and the diagnosis of hemangiosarcoma in dogs with hemoperitoneum, such as a lower platelet count on admission and lower total protein values [7,32]. Another study showed that the mass-to-splenic volume ratio and splenic weight as a percentage of body weight may help predict benign versus malignant lesions (larger masses more likely to be benign) [33]. At this time, however, there is no test that will give a conclusive presurgical diagnosis other than clear metastatic disease.

Newer research is focusing on more specific markers of malignancy, such as TK1 [34] and serum collagen XXVII peptide [35], but it is not yet known how sensitive and specific these tests will be in distinguishing malignant from non-malignant causes of spontaneous hemoperitoneum and if they will be available as point-of-care testing to assist with real-time decision making.

Definitive Care and Prognosis

Definitive care recommendations (medical management versus surgical intervention) and prognosis will depend on the underlying cause of the hemoperitoneum, the response to resuscitative measures, hospital resources,

and owner resources. The only type of spontaneous hemoperitoneum where surgery would generally not be considered is that caused primarily by a coagulopathy. These cases are medically managed with transfusions (plasma and red cells) and, in very rare cases of vitamin K antagonists, with the appropriate antidote (vitamin K) (see Chapter 130). Inherited coagulopathies carry a variable prognosis depending on the severity of the deficiency and clotting factors involved [36] (see Chapter 69). With prompt and aggressive care, prognosis can be quite good [37].

Patients with traumatic hemoperitoneum may or may not require surgical intervention and should be closely monitored during resuscitation efforts. Small-volume hemorrhage or hemorrhage that stops with medical management likely does not require surgery. In most cases of traumatic hemoperitoneum, the hemorrhage is from the liver or spleen, either from avulsion of vessels or fractures within the organ [3]. If a patient does not stabilize with medical management, or has evidence of continued abdominal hemorrhage, surgical exploration should be considered. Additionally, there may be other indications for surgical intervention in trauma patients such as abdominal wall penetration or hernia, diaphragmatic hernia, urinary bladder rupture, rupture of a hollow viscus, or bile peritonitis.

Patients should be stabilized as well as possible prior to surgery, but the optimal timing of surgery following a traumatic event is controversial [38]. If stabilization is dependent on surgical intervention (i.e. control of hemorrhage), surgery may be necessary on a patient that still has some degree of hemodynamic instability. Anesthesia protocols must be carefully evaluated to minimize cardiovascular depression (i.e. the use of total intravenous anesthesia) and prep and surgical times kept as short as possible (see Chapters 190 and 191). The prognosis in cases of traumatic hemoperitoneum will vary widely depending on how severe the blood loss is and the significance of concurrent injuries. Stable animals with a small-volume hemoperitoneum and no other major injuries have a very good prognosis. Animals with significant blood loss, concurrent injuries, or who do not stabilize after initial treatment may have a less favorable prognosis [4,5].

In cases of spontaneous hemoperitoneum due to a bleeding abdominal mass, surgery is often necessary for definitive care (removal of the source of hemorrhage), although depending on the likelihood of a malignancy, owners may be reluctant to pursue surgery and may opt for palliative medical care or humane euthanasia. The goal of surgical intervention is to remove the source of the bleeding to control hemorrhage and evaluate for evidence of gross metastasis. Due to the elusive nature of hemangiosarcoma, it is recommended that the entire

mass be submitted for histopathology [9]. Medical management of a bleeding abdominal mass is usually palliative only. A blood transfusion may temporarily stabilize a patient long enough for the family to have some time with their pet. Yunnan baiyao may have some temporary effect in slowing bleeding, has been shown to have some *in vitro* antineoplastic effects, and may be considered where surgery is not an option but owners are not yet prepared to euthanize [39].

The prognosis with surgical intervention for spontaneous hemoperitoneum is variable. Short-term, perioperative mortality rates can vary depending on the cause and degree of cardiovascular compromise prior to surgery. One study reported that 63.1% of dogs with hemangiosarcoma, 87.5% of dogs with splenic hematoma, and 100% of dogs with splenic torsion or hepatocellular carcinoma

survived to discharge from the hospital after surgical intervention for acute non-traumatic hemoperitoneum [9]. The long-term prognosis for dogs with bleeding abdominal masses is generally grave if the mass is found to be malignant. Median survival times of 2–3 months have been reported for dogs with splenic hemangiosarcoma treated with surgery alone [20]. One study showed a 1-year survival of just 6.25% [40]. Adjuvant treatment such as chemotherapy can offer some increase in life expectancy, but generally only by a few months [20].

Cats with spontaneous hemoperitoneum, regardless of the underlying cause, generally have a less favorable prognosis, with or without surgical intervention [1,2]. If the underlying cause of the spontaneous hemoperitoneum is not a malignancy, and the patient survives the perioperative period, the prognosis can be quite good [8,9].

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85

Splenic Disease

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Splenic Disease in the Emergent Patient

Splenic diseases, specifically ruptured splenic masses causing spontaneous hemoperitoneum (SH), are a common reason for dogs to require emergency care [1–4]. Non-neoplastic conditions, including traumatic injury to the spleen [5] and splenic torsion [6], may also be encountered by emergency veterinarians albeit less frequently. Cats are generally less likely to present with overt symptoms attributable to splenic disease compared to dogs but important splenic diseases (e.g. mast cell disease) are recognized in this species also [7].

Splenic diseases can be broadly considered as either causing hemodynamic compromise, usually due to acute hemorrhage, or being relatively occult in nature with few obvious overt symptoms. Given the insidious nature of some splenic diseases, plus the fact that animals may die prior to obtaining a definitive diagnosis, the true prevalence of splenic disease is difficult to estimate.

Splenic Masses in Dogs

Splenic masses are the most common variety of splenic disease encountered in dogs (Web Figure 85.1). The mass usually causes few obvious clinical signs itself and it is not until the mass bleeds or ruptures that the patient acutely decompensates. The hemodynamic consequences of acute hemorrhage are then typically overt and include collapse, altered mentation, tachycardia, tachypnea, and pallor [4]. If left untreated, death from exsanguination may occur, and swift accurate identification of hemorrhage is vitally important in the acutely collapsed dog.

The reported prevalence of malignancy in dogs is variable but it is frequently identified in over 50% of

submitted biopsies [1–3]. Hemangiosarcoma (HSA) is the most common malignancy in dogs, reported to occur in up to 73% of cases [1,2]. Hemangiosarcoma metastasizes readily and is associated with a poor long-term prognosis for those dogs that survive the perioperative period, even with postoperative chemotherapy [8]. In comparison, benign masses, including hematomas and hemangiomas, are generally associated with a better long-term prognosis, especially if splenectomy alone is completely curative for the specific tumor.

Despite the frequent acute onset of clinical signs in dogs with splenic masses, in retrospect, more subtle historical clues are sometimes evident. Owners may describe a recent history of vague signs that could be misinterpreted as “off days” in the older dog due to osteoarthritis or natural aging. In a proportion of cases, this likely represents minor self-limiting episodes of hemorrhage that resolve without intervention. Hypovolemia due to chronic hemorrhage also stimulates thirst so a relative polydipsia may also be recognized in some dogs [9]. Physical examination changes including abdominal distension, detectable fluid wave, palpable splenomegaly, abdominal pain and periumbilical hemorrhage (termed Cullen’s sign in people [10]) may be identified in addition to perfusion abnormalities (see Chapter 84). In contrast, incidental splenic masses are typically identified only when dogs are examined by veterinarians for unrelated reasons.

Ventricular arrhythmias may also be noted with splenic masses independent of heart disease [11] (see Chapter 53). The cause of ventricular ectopy is rarely definitely identified in individual dogs but could represent tissue hypoxia secondary to hypovolemia or anemia, metastases to the myocardium, or catecholamine excess [11]. Antiarrhythmic therapy (e.g. lidocaine) may be required in some cases although maximizing oxygen

delivery through fluid resuscitation or blood product administration should also be considered.

The initial priority in hemodynamically unstable dogs is obtaining vascular access to collect blood samples for point-of-care testing and to facilitate resuscitation with fluids or blood products. Identification of a low-normal packed cell volume with disproportionately low total protein should prompt a search for acute hemorrhage in the collapsed dog. Regenerative anemia may be noted over time in dogs with splenic masses associated with chronic bleeding. Schistocytes may be seen on blood smear evaluation, suggesting microangiopathic disease (e.g. HSA, DIC). Coagulation abnormalities may be noted in dogs with splenic masses and SH, including a moderate consumptive thrombocytopenia, prolongation of prothrombin and activated partial thromboplastin times, and a hypocoagulable-hyperfibrinolytic tendency on viscoelastic monitoring [12] (see Chapter 70). Hyperlactatemia, as an indicator of systemic hypoperfusion, was associated with the extent of hyperfibrinolysis in one study of dogs with SH [12] (see Chapter 68). In dogs with chronic effusions, pseudoaddisonian-like electrolyte changes (i.e. hyperkalemia and hyponatremia) may also be noted associated with increased renin-angiotensin-aldosterone activity and the dilutional effect of increased water consumption [9] (see Chapter 115).

Splenic masses, with or without abdominal effusion, are usually readily identified with ultrasonography [13]. The ultrasound appearance can be a variable, with solitary and multiple nodules present with or without evidence of cavitation (Figure 85.1). Ultrasound-guided abdominocentesis can be performed to confirm hemorrhage, although blind abdominocentesis is also easily and safely performed in most patients (see Chapter 186).



Figure 85.1 Ultrasound image of a splenic mass with multiple areas of cavitation. Reproduced with permission of Trisha Oura, DVM DACVR, Cummings School of Veterinary Medicine at Tufts University.

The completeness of an abdominal ultrasound examination can be compromised in larger, deep-chested dogs, especially for more cranial abdominal organs. Computed tomography (CT) may enable better visualization of abdominal organs in such cases (e.g. dogs > 25 kg) [14] but the availability of this in emergency practice currently limits its relevance. One study identified that 8.7% of dogs with splenic HSA had concurrent right atrial masses, although pericardial effusion was uncommon [15]. Pericardial effusion can be identified with some accuracy by emergency veterinarians using a FAST approach (see Chapter 182) after training [16], but accurate identification of atrial masses requires operator skill and experience. Thoracic radiographs are usually recommended prior to surgery, if patient stability allows, to stage the extent of disease preoperatively.

Splenectomy, often on an emergent basis, is invariably recommended for dogs with splenic masses. Given the potential urgency of the situation (i.e. to achieve hemostasis), pre-operative aspiration or biopsy of splenic masses is rarely performed. Combined ultrasound-guided fine needle aspiration and needle core biopsy could be considered in more stable patients, however [17].

The inability to accurately predict the nature of the mass with respect to malignancy prior to surgery poses a clinical challenge regarding accurate prediction of prognosis. Certain characteristics are recognized more commonly with malignancy, including increased patient age [18], certain breeds of dog (e.g. golden retrievers, Labrador retrievers, German shepherd dogs) [4], presence of hemoperitoneum [19], lower mass-to-spleen ratio [20], lower splenic weight [20], lower total protein [18], lower platelet count [18], and the requirement for transfusion [4]. It is important to note, however, that there can be considerable overlap between these characteristics and the final histopathological diagnosis. The number of lesions visualized with ultrasound was not reported to distinguish benign from malignant splenic masses well in dogs with SH [21]. The neoplastic biomarker thymidine kinase shows promise as a method of identifying malignancy prior to surgery, although it is currently not available as a point-of-care test, limiting its applicability to the emergency situation [22].

Factors associated with poor short-term survival for dogs undergoing splenectomy for splenic masses include preoperative thrombocytopenia, anemia, intraoperative ventricular arrhythmias [3], and blood product administration [4,23]. The most common reasons for short-term death in a study of dogs undergoing splenectomy for splenic masses were uncontrolled hemorrhage and thrombotic complications, specifically portal system thrombosis (PST) and pulmonary thromboembolism [3]. Acute PST is described as an uncommon complication of splenectomy in dogs [24] and people [25–27]. In



Figure 85.2 Necropsy image showing demarcation between areas of normal small intestine and ischemic intestine following the development of a portal system thrombus 24 hours after splenectomy in a dog.

people, a hypercoagulable tendency and ligation of the splenic vein creating a low-flow “cul de sac” are believed to contribute to postoperative PST [27]. Pre-operative viscoelastic evidence of hypercoagulability was common in hemodynamically stable, non-anemic dogs undergoing splenectomy for splenic masses [28]. The specific circumstances necessary for PST to occur in individual dogs are currently unknown and likely multifactorial in nature.

The potential role of thromboprophylaxis in some dogs with splenic masses is as yet uncertain. Dogs that develop PST following splenectomy tend to develop an acute onset of abdominal pain, cardiovascular collapse associated with massive fluid losses through the GI tract secondary to mesenteric ischemia, tachypnea, and abdominal effusion. The thrombus may be identified with ultrasound and demarcation of normal and abnormal tissues may be visualized at necropsy (Figure 85.2). The prognosis for these dogs is generally poor in the authors’ experience although more chronic portal system thrombosis may be associated with improved outcome [24].

Splenic Torsion

Splenic torsion is an uncommon but important disease typically affecting male, large-breed dogs (e.g. Great Danes, German shepherd dogs) (Web Figure 85.2) [6]. The exact mechanism underpinning torsion of the splenic pedicle is unclear. Logically, increased laxity of the gastrosplenic ligament is believed to develop, providing the circumstances necessary for torsion to occur [29]. This also explains the association between splenic

torsion and gastric dilation-volvulus (GDV) in dogs [30], leading to the recommendation to perform prophylactic gastropexy in all dogs undergoing splenectomy for this disease. The risk of GDV development following splenectomy for other conditions (e.g. splenic masses) appears less likely based on the current literature [31,32] although an association was documented in one study [33] (see Chapter 82).

Splenic torsion typically results in an acute onset of symptoms, consistent with those seen in the acute abdomen, including collapse, abdominal pain, and cardiovascular instability [6]. More chronic cases of splenic torsion have been associated with hematological abnormalities, namely anemia [34,35] and moderate-to-severe thrombocytopenia [35,36]. Dogs with chronic splenic torsions may be erroneously diagnosed with IMHA and ITP. Splenectomy should be curative and immunosuppression is not necessary in these cases. The origin of thrombocytopenia in dogs with splenic torsion is not completely understood but likely reflects platelet sequestration and/or DIC [36].

Splenic torsion can usually be diagnosed with ultrasonography [37]. Ultrasound characteristics have all been described previously, including marked splenomegaly, a mottled splenic echogenicity, a lacy or “starry sky” appearance to the spleen, splenic vascular thrombosis, ischemia at the hilus, and a marked hyperechoic triangular region at the hilus between the splenic veins and splenic parenchyma (Figure 85.3) [37,38]. Radiography is generally too non-specific to definitively diagnose this condition (e.g. loss of serosal detail, splenomegaly) [39] but CT does enable its identification with potentially increased accuracy compared to ultrasonography [40].

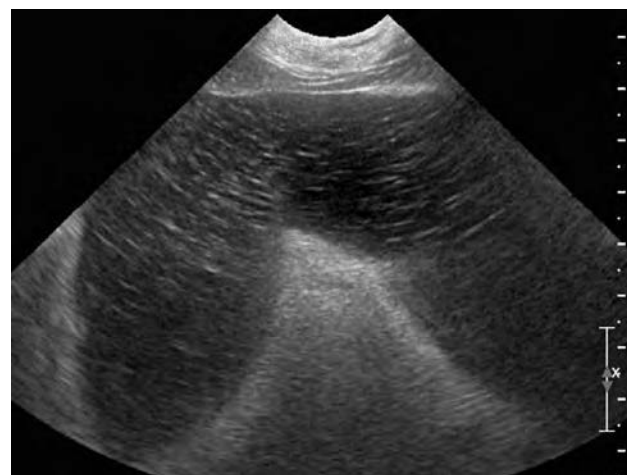


Figure 85.3 Ultrasound image of the speckled “starry sky” appearance of the spleen in a dog with splenic torsion. Reproduced with permission of Trisha Oura, DVM DACVR, Cummings School of Veterinary Medicine at Tufts University.

Splenectomy is recommended for all cases of splenic torsion. Prompt fluid resuscitation, with the potential for blood product administration if anemia or thrombocytopenia is present, is required in dogs with evidence of hemodynamic embarrassment prior to anesthesia and surgery (see Chapters 170 and 176). The splenic pedicle should not be untwisted prior to splenectomy in an attempt to limit the introduction of necrotic products into the systemic circulation [41].

The prognosis for dogs that are promptly diagnosed with splenic torsion is considered excellent based on the current veterinary literature [6].

Splenic Trauma

Traumatic hemoperitoneum has been reported to occur in 23% of dogs suffering blunt trauma [42]. In contrast to spontaneous hemoperitoneum, these cases less commonly require surgical intervention and the origin of the hemorrhage (e.g. spleen, liver) is rarely identified with certainty. A smaller number of dogs may experience ongoing uncontrolled hemorrhage following trauma. In these cases, exploratory laparotomy may be indicated to achieve surgical hemostasis [43]. In these cases total or partial splenectomy may be required for hemostasis if evidence of splenic injury is identified [41].

Splenic Infarction

Splenic infarction, not associated with splenic torsion, is a relatively uncommon clinical entity in dogs, usually occurring in animals with several concurrent disease processes. The associated diseases likely induce a hypercoagulable state and include cardiac disease, liver disease, kidney disease, neoplasia, corticosteroid excess, and sepsis [44]. Regionally important infectious diseases (e.g. *Bartonella*) should also be considered in individual cases [45]. Splenic infarctions are generally managed conservatively with thromboprophylaxis and due consideration for the underlying primary disease rather than via splenectomy (see Chapter 71).

Splenic Abscesses

Splenic abscesses are seldom seen in practice [46,47] but can be considered on the differential diagnosis list for systemically sick dogs with signs including, but not limited to, fever, abdominal pain, vomiting, and lethargy. The patient's clinical picture will usually suggest an infectious or inflammatory disease process. The origin of the abscess likely will remain undetermined but

prior foreign bodies [48] and leishmaniasis [49] have been reported as causes in dogs. Ultrasonography will be necessary to identify splenic changes and fine needle aspiration can yield samples to definitively identify the presence of an abscess on cytology. Splenectomy is the treatment of choice along with culture-guided antimicrobial therapy.

Miscellaneous Conditions Causing Diffuse Splenomegaly in Dogs

Uniform splenomegaly can be due to congestion, extramedullary hematopoiesis, and splenitis [50]. Splenic congestion is most commonly identified in dogs following administration of certain pharmacological agents (e.g. acepromazine) [50] but may also be a feature of portal hypertension. Extramedullary hematopoiesis (EMH) occurs in patients with underlying anemia and/or thrombocytopenia. In this instance, EMH can be distinguished cytologically from neoplasia based on fine needle aspirated samples [51].

Splenitis describes diffuse inflammation of the splenic tissues and usually is a sign of systemic infectious disease (e.g. borreliosis, ehrlichiosis, Rocky Mountain spotted fever, systemic fungal disease) [50]. In these circumstances, therapy is directed at addressing the primary pathology.

Feline Splenic Disease

Overall, cats are less commonly seen on an emergent basis with splenic disease. Spontaneous hemoperitoneum in cats has been reported to have an approximately even distribution with respect to malignant and non-malignant causes [52] (see Chapter 84). Splenic masses, specifically HSA, were identified as the most common cause for SH in cats, especially in older cats, but this is a rare disorder in comparison to the dog [52]. Lymphoma and mast cell tumors are more commonly identified in the spleen of cats [7], although these tumors seldom result in hemoperitoneum.

Postoperative care of cats with mast cell tumors can be challenging, where handling of the spleen can result in mast cell degranulation and profound hemodynamic instability. This degranulation results in vasodilatory shock (see Chapter 155), which will necessitate a combination of fluids and vasoactive agents to improve systemic perfusion.

Long-term survival is possible in cats surviving the perioperative period following splenectomy for mast cell tumors [53].

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86

Pancreatitis

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Introduction

Pancreatitis is a common inflammatory disorder of the exocrine pancreas and is currently broadly classified as acute, acute recurrent, and chronic. The clinical severity varies from mild and self-limiting to fatal. The nomenclature used in the veterinary literature can be confusing because the underlying pathological lesion(s) (e.g. necrosis, suppurative inflammation, chronic active inflammation) cannot be differentiated clinically and histopathology is rarely performed [1]. Many authors have therefore suggested the adaptation of the consensus definitions used in human medicine to clinically classify cases based on severity of disease (Table 86.1) [2–4]. Whether mild or severe, acute or chronic, pancreatitis is a common condition in small animal emergency medicine. Because clinical signs of acute pancreatitis (AP) can be similar to surgical diseases and since severe pancreatitis can lead to severe illness and death, recognition and appropriate treatment are essential in the emergency setting.

Table 86.1 Atlanta human classification scheme for assessing the severity of acute pancreatitis (AP) cases, adopted by veterinary authors in the field [1,56].

	Description
Mild AP	No organ failure, no local or systemic complications, resolves in the first week
Moderate AP	Transient organ failure or exacerbation of co-morbidities. May resolve without intervention or may require prolonged specialist care
Severe AP	Persistent organ failure (>48h), increased risk of mortality

Pathophysiology

The causes of pancreatitis in dogs and cats are usually unknown although a number of risk factors have been proposed (Box 86.1). The co-localization of zymogen granules and lysosomal proteases inside acinar cells leads to the final central pathway – the activation of trypsinogen to trypsin [5–7]. Mechanisms are in place to prevent inappropriate, early activation of trypsin but these become overwhelmed in patients with pancreatitis [6,7]. Activated trypsin subsequently activates other pancreatic enzymes, propagating autodigestion of the gland [4,7]. The ensuing inflammation can be contained locally and cause complications like pancreatic necrosis, acute fluid collections, extrahepatic biliary duct obstruction (EHBDO) and peritonitis, or can lead to distant systemic effects, propagating the systemic inflammatory response syndrome (SIRS) [3–5,8,9]. Disseminated intravascular coagulation (DIC) and multiple organ dysfunction syndrome (MODS) are potential consequences of a fulminant, uncontrolled inflammatory response [10,11] (see Chapter 159).

If the animal survives the inflammatory response of AP, the process can be completely reversible unless the initial trigger persists [6]. Even with complete resolution, AP can return as acute recurrent disease, which can ultimately resolve or may become a chronic process. The chronic form is progressive and irreversible with the potential consequences of exocrine pancreatic insufficiency (EPI), diabetes mellitus (DM) or both [2,5,12].

History, Signalment, and Clinical Signs

The majority of dogs and cats that develop pancreatitis are older than 5 years, but animals of any age can be affected [10,13,14]. Certain canine breeds are considered at increased risk (see Box 86.1) but only one study in cats

Box 86.1 Proposed risk factors associated with the development of acute and chronic pancreatitis. Many links are anecdotal and unproven at the cellular level [10,12,15,18,20,24,26,58,91,92,93].

Genetic predisposition

- Acute disease
 - Yorkshire Terriers
 - Miniature Schnauzer
- Chronic disease
 - CKCS
 - Boxers
 - English Cocker Spaniels
 - Border Collies
 - Toy/non-sporting dogs

Lifestyle

- Obesity (dogs)

Dietary

- High-fat low-protein diets
- Inappropriate food (dogs)

Concurrent disease

- Dogs
 - Diabetes mellitus and DKA
 - Hyperadrenocorticism
 - Hypothyroidism
 - Prior gastrointestinal disease (cats)
 - Cholangiohepatitis
 - FIP
 - Toxoplasmosis

- IBD
- Diabetes

Drugs/toxins

- Azathioprine
- Potassium bromide
- L-asparaginase
- Sulfonamides
- Zinc
- Clopramine
- Chlorothiazide
- Organophosphates

Clinicopathological

- Hypertriglyceridemia (dogs)
- Hypercalcemia (cats>dogs)

Infectious

- Babesiosis
- Leishmaniasis*

Ischemia

- Hypotension
- Hemorrhagic shock

Other

- Pancreatic duct obstruction
- Trauma
- Abdominal surgery

* It is uncertain whether it is the treatment for leishmaniasis or the infection itself that is responsible for AP. CKCS, Cavalier King Charles spaniel; DKA, diabetic ketoacidosis; FIP, feline infectious peritonitis; IBD, inflammatory bowel disease.

identified a breed association (Siamese) [13,15–17]. Acute, acute recurrent disease, and chronic processes with regard to pancreatitis are clinically and historically indistinguishable [5,16,18]. Clinical examination findings are non-specific and vary depending on the severity of disease and whether there are signs of the systemic inflammatory response or multiple organ involvement (see Chapter 159).

Presenting complaints in dogs include anorexia, vomiting, lethargy, and weakness, and a smaller proportion have diarrhea; cats are more frequently presented for anorexia and lethargy [3,10,19,20]. Clinically, dogs are commonly dehydrated; one study reported that 51% of dogs were moderately dehydrated and 46% of dogs were dehydrated and hypoperfused (see Chapter 153) [10]. Icterus due to EHBDO was noted in 26% of dogs with severe acute pancreatitis (SAP) in one study [10]. Aspiration pneumonia (see Chapter 37) or acute respiratory distress syndrome, if present, may cause respiratory distress. Pyrexia is relatively common in dogs (~32%) but this is an uncommon sign in cats and hypothermia

is reported more frequently in this species [10,17,20]. Clinical appreciation of abdominal pain was reported in 58% of dogs in one study [10]. Rectal examination may reveal melena or hematochezia. Reported neurological abnormalities include disorientation, stupor, twitching and seizures, but these are uncommon [10]. Physical examination findings in cats are usually indistinct and include dehydration, lethargy, icterus, and hypothermia [13,16,17,21].

Diagnosis

The presumptive diagnosis of pancreatitis is made through careful integration of historical, clinical, clinicopathological, and diagnostic imaging findings. The initial assessment in many cases will be that of an acute abdomen (see Chapter 6), and as such the initial work-up is focused on ruling out a surgical disease. A definitive diagnosis requires histopathology, but this is rarely clinically justifiable.

Most clinical pathology findings are, in isolation, non-diagnostic. In cats, co-morbidities such as hepatic lipidosis, inflammatory bowel disease, and inflammatory liver disease are frequently identified, especially associated with chronic disease; these co-morbidities may confound the clinician's assessment [13,16,22,23]. Common hematological results in dogs include leukocytosis, neutrophilia, left shift, and thrombocytopenia [10]. In contrast, cats more frequently have anemia and leukopenia [10,17,24]. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are often prolonged in severe cases (see Chapter 70) [20]. Azotemia is often prerenal, but severe cases may present with evidence of acute kidney injury (see Chapter 94) [25]. Cholestasis may be associated with EHBDO in both species, or be due to concurrent primary hepatic disease in cats [13].

In dogs, two pancreatic ducts enter the duodenum in different locations. In the majority of dogs, the pancreatic ducts do not join the common bile duct before emerging into the duodenum. Cats differ in that there is more commonly one pancreatic duct that joins the common bile duct before entering the duodenum. A small proportion of cats may have a second smaller pancreatic duct that enters the duodenum separately. Uncommon variations in dogs include arrangements that are similar to cats in that only one duct exists, with this duct joining the common bile duct prior to entering the duodenum. Variability in pancreatic duct anatomy could in part explain differences in canine and feline susceptibility to EHBDO [26].

Mild hypoalbuminemia is also reported in cats [24]. Hypocalcemia has been associated with poorer outcomes and is reported more frequently in cats than in dogs [6,10,17,20]. Hypokalemia is common in cats despite a lack of overt gastrointestinal signs and is likely due to prolonged anorexia (see Chapter 109) [17]. Amylase and lipase are infrequently elevated in cats with pancreatitis and are not specific markers in either species. Only 26% of dogs with fatal acute pancreatitis have lipemic serum [10,27–29]. Hyperglycemia is reported in both species and hypoglycemia in cats was associated with a suppurative form of AP in one study [2,17].

Canine pancreatic lipase immunoreactivity (PLI) testing is the most sensitive and specific serum assay currently available for dogs [30–32]. Studies report variable sensitivities (21–78%) and specificities (80–100%) but these generally improve with increasing severity of disease or when lowering ($>200\text{ }\mu\text{g/L}$ Spec cPL) or increasing ($>400\text{ }\mu\text{g/L}$ Spec cPL) the cut-offs for sensitivity and specificity, respectively [3,30–35]. The sensitivity of the test in chronic pancreatitis is thought to be lower than for acute disease [18,30]. The SNAP cPL, which only provides a semi-quantitative result (normal or abnormal), may have particular application in the emergency room

because of its rapid reading. The reported specificity is not as robust as the Spec cPL with the potential for “abnormals” to reflect pancreatic lipase concentrations within the equivocal range ($200\text{--}400\text{ }\mu\text{g/L}$), but it is highly sensitive so dogs with abnormal SNAP cPL should have further diagnostic testing to confirm or refute the suspicion of pancreatitis [30,31,36]. Canine PLI testing should be used as a screening test as opposed to a method for definitive diagnosis. A positive PLI should increase suspicion for AP. However, further testing, such as abdominal imaging, should be performed [37]. A negative SNAP cPL or Spec cPL makes AP less likely [31]. Feline-specific pancreatic lipase (Spec fPL) and SNAP fPL are also available for assisting with the diagnosis of pancreatitis in cats, with sensitivities reported to range from 79% to 100% and specificities from 67% to 100% [30,38,39].

Diagnostic Imaging

The role of abdominal radiographs in the initial work-up is primarily to rule out surgical diseases because the sensitivity of this modality for diagnosing pancreatitis is low (24%) [10]. Changes that can be identified in dogs include a widened pyloric-duodenal angle, displacement of the pyloric antrum toward the patient's left side and reduced serosal detail in the cranial abdomen [10,16,40]. These changes may not be seen in cats; hepatomegaly with abdominal effusion are the most common radiographic features in this species [13,17,21].

Abdominal ultrasound (US) is the imaging modality of choice for the diagnosis of AP. Characteristic changes in dogs and also seen less frequently in cats include hypoechoic areas within the pancreas, hyperechogenic peripancreatic mesentery, peritoneal effusion, and corrugation of duodenal wall with alterations to wall layering (Figure 86.1) [4,10,21,41–43]. Cats may also have dilation of the gall bladder and common bile duct, abnormal pancreatic margins or hepatomegaly with altered echogenicity [13,21,24,44]. Reported sensitivity of abdominal ultrasound for the diagnosis of AP is variable; studies in cats report lower sensitivities than in dogs (24–35% in studies of cats and approximately 68% in dogs), but it is operator dependent and improving with advancements in imaging quality, contrast-enhanced techniques, and heightened clinical suspicion for this differential [4,6,10,13,40,41,44]. Abdominal ultrasound has a higher sensitivity with more severe disease, so cases that are presented on an emergency basis represent a population where this test is even higher yield than non-emergent cases [30]. Ultrasonographic findings do not correlate with severity of disease [38,41,43,45].

Contrast-enhanced computed tomography (CECT) is currently the diagnostic modality of choice in human medicine [4]. There are reported comparable sensitivities



Figure 86.1 Abdominal ultrasonographic image of a dog with pancreatitis. The pancreas is hypoechoic to the surrounding hyperechoic peri-pancreatic fat. Reproduced with permission of Cathy Beck.

of CECT to ultrasound in cats, thus raising the question as to whether or not this modality is necessary in this species given the associated expense and limited availability [40]. A recent pilot study compared CT-angiography with US in dogs with pancreatitis and more abnormalities were identified in the former modality, but larger studies are needed to confirm this [46]. With the advances in CECT technology, these studies can be performed quickly in awake sedated animals. They may therefore become a more important tool for diagnosing AP, especially in large dogs where imaging of the cranial abdomen is often limited by size [47].

Fluid Analysis

If present, abdominal fluid should be collected for analysis (see Chapter 186). Abdominal effusion that occurs solely due to pancreatitis may have a variable nucleated cell count and protein concentration. Glucose and lactate peritoneal plasma differences have been described to differentiate septic and non-septic abdominal effusions, but these studies did not evaluate the accuracy in discriminating septic cases from non-septic effusions when the cell count in the non-septic effusion was high [48,49]. Therefore, care must be taken when using such tests to determine the likely etiology of effusion and the approach to treatment (surgical versus medical). Moreover, low numbers of inflammatory cells in abdominal effusion does not rule out pancreatitis [17].

Measurement of lipase in abdominal fluid when compared to plasma may be useful; a two-fold greater concentration of lipase in abdominal fluid when compared to serum or plasma suggests an increased likelihood of

pancreatitis, although larger studies are needed [50]. Peritoneal concentration of cPLI was investigated for its ability to discriminate AP from other types of abdominal diseases in one study [51]. A cut-off value of 500 ug/L (measured by Spec cPL) in peritoneal fluid demonstrated good sensitivity (100%; 95% confidence interval (CI) 80.7–100) and specificity (94%; 95% CI 76.7–99.7) for this purpose [51]. Reduced specificities with this test could result from other inflammatory abdominal diseases causing secondary pancreatitis [51]. Therefore, measurement of peritoneal cPLI can only be considered a complementary diagnostic test in AP.

Biopsy and FNA

Surgical biopsy is not commonly performed (especially on an emergency basis) because of higher costs and the potential to worsen clinical signs [51]. It is, however, the only definitive means of diagnosis and should still be considered if there is suspicion of a neoplastic or infectious process. Fine needle aspiration is less invasive, but a low incidence of obvious gross lesions, the inability to predict pathological distribution and the often localized disease can make this a low-yield procedure [42,52–55].

Scoring Disease and Assessing Severity

The revised Atlanta classification of human acute pancreatitis is a non-invasive scoring scheme that has recently been adopted by experts in the veterinary field to categorize the severity of acute pancreatitis [3–5,56]. The severity of the disease is classified as mild, moderate or severe acute pancreatitis and allows for patients to be stratified into categories associated with different mortalities (see Table 86.1) [5,56]. Scoring systems specific for pancreatitis in dogs have been investigated (clinical severity index for dogs with pancreatitis), but evaluation in a larger cohort is necessary [57]. Establishment of a severity scoring system in dogs and cats with pancreatitis would allow early recognition of patients requiring critical care. This approach has been shown to improve outcome in humans, thus warranting further studies in the veterinary field [3].

Treatment

Specific therapy targeting pathophysiological pathways in AP is currently only experimental and has so far shown little promise [58,59]. Many treatments have not demonstrated survival benefits (nasogastric suctioning, H₂ blockers, fresh frozen plasma, parenteral nutrition,

and peritoneal lavage) [60]. The mainstay of treatment remains largely supportive and is aimed at treatment of underlying condition(s) when present.

Early treatment considerations should include removing any factors that could precipitate the disease (see Box 86.1). A major contributor to the progression of mild acute pancreatitis to severe acute pancreatitis (SAP) is the disturbance of pancreatic microcirculation and it is therefore prudent to restore and maintain hydration and perfusion early in treatment, bearing in mind that markers of global perfusion may not reflect microcirculatory status of the pancreas [6,61,62].

There is no evidence to support a recommendation on the type of fluid therapy; selection should be made with reference to the acid–base and electrolyte status of the patient (see Chapters 167, 168, and 169). Cases with a hypochloremic metabolic alkalosis from protracted vomiting and ileus may benefit from normal saline (0.9%). Low acinar pH promotes trypsin activation and therefore acidemic patients may benefit more from a buffered solution such as lactated Ringer's solution (LRS) [1,63]. The use of colloids is controversial and may be warranted in selected cases but there is no specific indication in patients with pancreatitis [64]. This also applies to frozen or fresh frozen plasma where previously reported benefits of replacing circulating alpha-macroglobulins and ameliorating the inflammatory response have not been reflected by survival outcomes in human or veterinary medicine and its routine use can no longer be recommended [1,6,65,66].

Analgesia is indicated in cases with abdominal pain (see Chapters 190 and 191). A reasonable first-line therapy for mild pain is buprenorphine (10–20 mg/kg IV q6–8h), particularly because it does not cause contraction of the sphincter of Oddi (see Chapter 193) [1,6]. For cases that are refractory to buprenorphine, the benefits of using pure mu-opioids should be balanced against the potential for gastrointestinal ileus. Alternatives or adjunct pain management therapies include lidocaine, which also has proposed prokinetic and anti-inflammatory effects (1–2 mg/kg IV, 25–50 mg/kg/min IV CRI), and ketamine for its lack of effect on GI motility and for its potential anti-inflammatory effects (0.5–1 mg/kg, 2–10 mg/kg/min CRI) [6,67]. If a patient experiences increasing levels of pain refractory to treatment, acute fluid collections within the pancreatic tissue may be responsible, requiring percutaneous drainage [6].

Repeated nasogastric suctioning to relieve gastric distension with fluid is argued by some authors to cause esophagitis, but a study comparing nasoesophageal tubes and nasogastric tubes did not report worse complication rates (including regurgitation) in dogs with nasogastric tubes [6,68]. There is no association between nasogastric suction and increased pain relief or improved outcome in humans and so the necessity of such a procedure

needs to be weighed against the argued potential risk of esophagitis [69].

Maropitant is a NK-1 receptor blocker that acts as an antiemetic both centrally and peripherally; blockade of this receptor could theoretically reduce capillary leak and pain via amelioration of substance P production [1,6,70]. In addition to this, there are conjectural reasons to avoid other commonly used antiemetics like metoclopramide. An unproven disadvantage to dopamine blockade with metoclopramide is the loss of beneficial amelioration of inflammation, demonstrated in experimental models [1,6,71]. Dolasetron or ondansetron can be added as second-line antiemetics if control of emesis is not achieved with maropitant [3]. Antiemetics should be provided even in the absence of overt nausea to facilitate early voluntary eating [1]. If ileus is a concern, prokinetics such as metoclopramide, ranitidine or cisapride can be implemented, in addition to antiemetics.

There are no reports investigating the efficacy of gastric acid suppression in dogs with AP [6]. There are, however, theoretical benefits of increasing gastric pH to decrease exocrine pancreatic stimulation and to reduce further mucosal injury already established by hypovolemia or peritonitis [1]. Proton pump inhibitors such as omeprazole or pantoprazole can be used; pantoprazole has also been shown in experimental rodent models of AP to ameliorate inflammation through hydroxyl radical scavenging [6,72]. Histamine-2 antagonists, such as famotidine, may also help decrease gastric acidity.

Corticosteroids have traditionally been considered contraindicated because of the concern regarding their causative link with pancreatitis. They are no longer thought of this way and have instead become increasingly considered for the management of severe AP refractory to conventional treatment or where critical illness-related corticosteroid insufficiency (CIRCI) is suspected [6,73,74].

There is sufficient evidence that nutrition plays an important role in the treatment of AP [75–78]. The optimal timing, route, and type of nutrition remain unclear [79]. Human recommendations include early enteral nutrition in cases of SAP whereas there is no evidence that forcing early nutrition in cases of mild AP is necessary (unless inappetence is reaching 5 days) [76–78,80]. It is thought that the possible benefits of enteral feeding through SAP include improved enteral health, reduced bacterial translocation, reduced vomiting and regurgitation, reduced immunosuppression, and improved outcome [3,4,76]. The historical notion of “resting” the pancreas to prevent exocrine pancreatic stimulation has fallen out of favor [81,82]. Prepyloric feeding is well tolerated and the benefits over parenteral nutrition are well studied [19,79,80,83,84]. It is unclear whether feeding a low-fat diet is necessary in cases without hypertriglyceridemia, but feeding a low-fat diet if the patient is lipemic

is still advocated by most authors [6,79,85]. A nasogastric or nasoesophageal feeding tube can be sufficient in the short term, but full caloric requirement using human or veterinary convalescent liquid diets is difficult to achieve through these narrow tubes. After 3 days, a higher protein content food will need to be continued so an esophageal tube will need to be placed or whey protein can be supplemented to the liquid diet if the patient seems close to achieving adequate voluntary intake [1].

The recommendation of using a low-fat diet does not apply to cats given their higher tolerance and requirement for dietary fat, but consideration must be given to the possibility of concurrent IBD in cats, where a highly digestible, fat-restricted diet is preferable [79].

Supplementing feeding with glutamine has gained interest because of the theoretical benefit on enterocyte health and lymphocyte function, but there are insufficient data to support its use at this time [86,87]. The supplementation of probiotics has not been evaluated in dogs and cats and is currently not widely recommended, which mirrors human guidelines [79].

Pancreatic infections are rarely documented in dogs and cats [4]. The routine use of antimicrobials in the treatment of AP is not recommended, but may be justified in select cases failing to respond to conventional treatment (see Chapter 200). The concern for bacterial translocation is another potential indication for antibiotics use [1]. Clindamycin and metronidazole have been shown to reach therapeutic levels within the pancreas in dogs with AP and can be considered if the unlikely complication of pancreatic abscessation is suspected [4,88,89]. Broad-spectrum antimicrobials can be considered when there is evidence of poor gut mucosal integrity (melenas, hematochezia) and especially in patients with hypoperfusion. Human recommendations for

pancreatic infections are to trial medical management first and delay surgical interventions [59]. High mortality rates are reported with surgical management of canine pancreatic infections and necrotizing pancreatitis, so aggressive medical interventions should be attempted in most veterinary patients prior to pursuing surgical intervention, as is recommended in humans [3,90]. Surgery in cases with EHBDO is, however, warranted and a good outcome is possible [89,90].

Close monitoring of cardiovascular status, fluid balance, and indicators of progression into MODS and multiple organ failure (e.g. gastrointestinal tract and renal function) should be practiced (see Chapter 159).

Prognosis and Owner Communication

Mortality rates of AP range from 27% to 58% in dogs and 41% to 80% in cats [1,4,13,14,21]. Higher mortality rates in cats are associated with concurrent hepatic lipidosis and hypocalcemia [13,21]. Length of hospitalization in dogs and cats with AP can be very variable and cost can be significant for prolonged hospitalization in sicker animals.

There is no evidence that dogs with dietary indiscretion as an underlying cause of AP will have recurrence (in the absence of repeated episodes of dietary indiscretion), but there is low-level evidence to feed a low-fat diet for 4 weeks following the episode of AP [15]. Hyperlipidemic dogs may have an underlying lipid disorder, which will require follow-up, and patients with diabetes mellitus or exocrine pancreatic insufficiency will require ongoing management. Supplementation of exocrine pancreatic enzymes for 3–4 weeks may be considered in severely affected dogs or dogs demonstrating signs of exocrine pancreatic insufficiency (steatorrhea) [1].

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Peritonitis

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Introduction

The peritoneal cavity is a sterile potential space lined by a single layer of mesothelial cells known as the peritoneum. The portion covering the abdominal organs, termed the visceral peritoneum, is continuous with the portion covering the abdominal wall, termed the parietal peritoneum. The peritoneal lining has a vast surface area (100–150% of BSA), which can result in substantial production and absorption of fluid into and from the abdomen, respectively [1]. Fluid production is guided by hydrostatic and oncotic pressures of the abdominal vasculature, as well as the mesothelial reflection coefficient

or “leakiness” of the mesothelium [1,2]. Lymphatics in the diaphragm also drain fluid into the thoracic duct from the peritoneal cavity.

Peritonitis is defined as inflammation of the abdominal lining and most commonly results from bacterial contamination secondary to an organ rupture. However, sterile inflammatory conditions of the abdomen are also recognized (Box 87.1). Irritation or trauma to the peritoneal lining causes direct cellular damage and subsequent release of lysosomal enzymes, kinin, and histamine. Peritoneal capillaries and the mucosal lining allow white blood cells, fibrin, fibronectin, and fluid to enter the abdominal cavity. Stimulation of the sympathetic nervous system inhibits

Box 87.1 Causes of peritonitis in dogs and cats.

Secondary septic peritonitis

Penetrating abdominal trauma

Gastrointestinal leakage
Perforating foreign body
Perforating ulcers
Gastric or intestinal rupture
Neoplastic perforation
Intestinal ischemia
Surgical dehiscence
Feeding tube leakage

Urogenital

Ruptured prostatic abscess
Ruptured pyometra
Ureteral rupture with urinary infection
Bladder rupture with urinary infection
Ruptured kidney abscess

Hepatobiliary

Ruptured infected gall bladder
Hepatic abscess
Pancreatic abscess

Abdominal lymph node abscessation
Splenic abscess
Body wall abscess

Iatrogenic

Peritoneal dialysis
Surgical contamination
Percutaneous drainage catheters
Barium leakage

Sterile peritonitis

Pancreatitis
Uroabdomen
Bile peritonitis
Hemoabdomen
Chyloabdomen
Surgical materials
Effusive feline infectious peritonitis
Metastatic neoplasia

Iatrogenic

Peritoneal dialysis (secondary to dialysate)

peristalsis which prevents movement of contaminants within the peritoneal cavity. In addition, the omentum gravitates to the areas of inflammation to increase oxygen tension, deliver white blood cells and absorb bacteria, debris, and foreign material. Because the decision to pursue emergent surgical versus medical management often hinges on suspected or documented septic versus sterile process, a thorough understanding of both is critical.

Etiology

Bacterial peritonitis is commonly characterized as primary (spontaneous), secondary (intraperitoneal leakage of bacteria), or tertiary (recurrent after treatment) [3]. Human and veterinary studies have documented that primary peritonitis is often monobacterial, whereas secondary peritonitis is commonly polybacterial [4].

Primary septic peritonitis is thought to occur secondary to hematogenous spread and is rare in small animals [3,5]. In cats, primary peritonitis is most commonly associated with feline infectious peritonitis. There is some evidence that primary bacterial peritonitis is more prevalent in cats than in dogs, and anaerobic gastrointestinal microbes are the most common isolates [6]. Overwhelmingly, secondary bacterial peritonitis from gastrointestinal leakage is the most common category recognized in veterinary medicine. In cats, this is frequently due to underlying neoplasia, and in dogs secondary to perforation or surgical dehiscence [6].

Immune Response

Both local and systemic signs of illness are recognized in dogs and cats with peritonitis. Vasoactive mediators such as serotonin, histamine, and microbial endotoxins mediate local inflammation, resulting in vasodilation and exudative fluid in the abdominal cavity. Systemic signs of inflammation ensue when pathogen-associated molecular pattern molecules (PAMPs) such as bacterial endo- and exotoxins bind leukocyte pattern recognition receptors (PRRs), resulting in potent leukocyte activation. This promotes the transcription of leukocyte genomic NF- κ B and the production of potent cytokines (IL-1, IL-6, IL-8, IL-10, IL-13, HMGB-1). A balance of proinflammatory and anti-inflammatory cytokines directs the clinical manifestations of sepsis, with a dysregulated inflammatory response often resulting in organ failure and high mortality rates [7].

Signalment and History

Patient signalment gives important contextual clues to prioritizing differentials for any disease process and

must precede every case presentation or interclinician communication. Beyond the fact that neoplastic processes prevail in older patients compared to younger ones, species differences exist in the clinical presentation of certain diseases (such as pancreatitis in cats versus dogs). Bacterial cholangiohepatitis is a common cause of sepsis, icterus, and abdominal pain in cats, but is very uncommon in dogs. In contrast, biliary mucocele with biliary tract rupture is a surgical emergency and has high disease prevalence in the Shetland sheepdog.

A concise but detailed patient history is critical in the emergent patient, with specific questions aimed at identifying key information regarding acute abdominal illness. A systematic approach to the patient history is recommended to assure that nothing is missed. This includes presenting complaint, last time patient was normal, progression of signs, systemic manifestations, any current or previous medications, changes in the past 6 months, medical/surgical history, and pet's current diet [8]. For example, a young, previously healthy Labrador Retriever with an acute abdomen and vomiting, who is 2 weeks post-op from a cruciate repair and on NSAIDs, will trigger the clinician's suspicion for duodenal perforation. It cannot be overemphasized that both the clinical and historical pictures are critically important, especially in complex cases with co-morbidities.

It is important to recognize that non-specific signs of peritonitis such as vomiting, inappetence, and lethargy are common in both dogs and cats. Further confounding the clinical picture are species differences in external manifestations of abdominal pain. Unfortunately, it is common that acute abdominal conditions are underdiagnosed and treated empirically as gastroenteritis until signs of sepsis fulminate days later.

Physical Examination

A triage examination should be performed on every emergent patient upon presentation. This involves rapid evaluation of the cardiovascular, respiratory, and neurological systems and determining if the patient is in shock and requires immediate further assessment (see Chapter 2). The patient with peritonitis will commonly present with abdominal pain and any combination of signs relating to abdominal pathology: gastrointestinal signs (vomiting, regurgitation, diarrhea), abdominal distension, cardiorespiratory derangements, restlessness, lethargy, or collapse.

Most causes of peritonitis will lead to clinical manifestations of cardiovascular shock if unrecognized or untreated. The pathophysiology of shock in the patient with peritonitis can be multifactorial and most commonly includes hypovolemia and sepsis/systemic inflammatory response syndrome (see Chapters 152 and 159).

It is imperative to recognize the signs of shock in dogs and cats, as well as the species differences between the two (see Chapter 152). Signs of shock in adult dogs include tachycardia, hyperdynamic or weak pulses, rapid or slow capillary refill time (>2 sec or <1 sec), and tachypnea. Dull mentation and recumbency may sometimes be present but it is not uncommon for a septic abdomen to “walk in the door.” Signs can be quite different in cats; it is unclear why, but cats often do not show signs of hyperdynamic shock. Clinical features in this species include tachycardia or bradycardia (a heart rate of 160 or lower for a cat in hospital should always be taken seriously). Prolonged capillary refill time or peripheral pallor in a non-anemic cat, poor pulse quality, hypothermia, and abdominal pain (not a consistent finding) are other key features. Icterus in a sick cat with signs of cardiovascular instability can be a cardinal feature of sepsis or systemic inflammation in this species [6,9,10].

Although identification and treatment of shock take priority, it is imperative that a comprehensive physical examination is performed on every patient presenting with an acute abdomen secondary to peritonitis. Once the patient is more stable, an assessment for co-morbidities, as well as the extent of disease, should be pursued. This includes a standing thoracic auscultation with close evaluation for new murmurs, oral examination, basic neurological assessment including cranial nerves and spinal palpation, fundic and anterior chamber evaluation, palpation of lymph nodes and joints, evaluation of skin and mucosa for evidence of hemostatic derangements, and a rectal examination. The urogenital tract in intact male dogs can be a significant source of systemic disease and should be thoroughly evaluated.

Diagnostics

Diagnostics that will identify the source of abdominal pain and systemic derangements requiring intervention are recommended in any patient presenting with an acute abdomen. Most emergently, this includes a patient-side blood gas profile comprising acid–base, electrolytes, PCV, TS, renal, and blood gas analysis, followed by abdominal imaging. Additional laboratory submissions typically include a complete blood count, serum biochemistry, urinalysis, and canine pancreatic lipase, as indicated, for a comprehensive evaluation of the acute abdomen patient.

Abdominal imaging is indicated in any patient presenting with an acute abdomen. Most commonly, this is initiated with orthogonal abdominal radiographs, followed by ultrasound. A horizontal beam radiograph can be particularly helpful for identification of free gas, which indicates perforation of a hollow viscous organ, penetrating trauma, or rupture of a gas-forming abscess, and is always a surgical emergency. Free gas is normally present

postoperatively for several days and in that instance may not be an indicator of an emergent pathology. Animals with a confirmed uroabdomen should have preoperative contrast radiography performed to localize the leakage site and plan appropriately for surgery. Thoracic radiographs should be performed to rule out concurrent disease, such as infectious, neoplastic or traumatic illnesses.

By definition, the patient with peritonitis will present with abdominal effusion, which should prompt the clinician to perform an abdominocentesis and rapid fluid analysis (see Chapter 186). Rapid ultrasonographic identification of free effusion and ultrasound-guided abdominocentesis can be performed using the focused assessment with sonography for trauma (FAST) technique, which is currently under investigation for non-traumatic causes as well [11]. Chapter 182 provides further details.

Lack of ultrasound capability is not incapacitating for the detection and treatment of patients with septic peritonitis. If abdominal effusion is suspected (often on radiographs), a sterile diagnostic abdominocentesis should be performed with the patient in left lateral recumbency using a 22 gauge needle and 3cc syringe in a location 1–2cm caudal and 1–2cm left lateral to the umbilicus (the most gravitationally dependent portion) (see Chapter 186). If fluid retrieval is unsuccessful with one-site abdominocentesis, a four-quadrant abdominocentesis should be performed. This is best accomplished with the patient in dorsal recumbency and the abdomen shaved and sterilely prepared. Four sites, centered at the umbilicus and medial to the mammarys, are sampled in a similar fashion as a single-site abdominocentesis. Caution should be exercised to avoid the superficial epigastric vessels with this procedure. Lastly, in patients where a four-quadrant tap also results in poor fluid retrieval, a diagnostic peritoneal lavage (DPL) may be performed. It is important to note that fluid retrieved following DPL may be cytologically evaluated, but indicators of sepsis such as glucose and lactate comparisons to peripheral blood are unreliable due to the dilutional effect of fluid instilled in the abdomen.

Allotment of any free fluid obtained should be performed as follows.

- Small amount into sterile glass tube or culturette for PCR and/or culture and susceptibility testing.
- A drop placed on a glass slide for direct smear (Wright stain).
- A drop used for lactate and glucose test strips on portable meters.
- Small amount into EDTA tube for total nucleated cell count (TNCC), RBC, PCV, TP, and cytology.
- A small amount into a plain red top tube for biochemical analyses.

Key characteristics of different abdominal effusions are summarized in Table 87.1.

Table 87.1 Fluid analysis findings in patients with peritonitis [8,12].

Diagnosis	Fluid cytology	Fluid analysis	Intervention indicated
Uroabdomen	Suppurative inflammation, presence of bacteria if UTI is present	Fluid creatinine:serum creatinine >2.0 Fluid [K ⁺]:serum [K ⁺] >1.4 (dogs) or 1.9 (cats)	Depending on location of urinary tract rupture: emergency surgery, bladder/urethral catheterization, percutaneous drainage, or combination
Hemoabdomen	Hemorrhage (with erythrophagocytosis if subacute or chronic)	Hemorrhagic effusion with PCV/TS dependent on chronicity and peripheral PCV/TS	Surgery usually not necessary in traumatic hemoabdomen; surgery indicated in spontaneous/neoplastic
Bile peritonitis	Suppurative inflammation with bile pigment within macrophages or in the background; may be septic if bacteria in biliary tree	Fluid bilirubin:serum bilirubin >2.0	Emergency surgery
Pancreatitis	Non-septic suppurative inflammation		Medical management; rarely surgery may be necessary if abscess present
Septic peritonitis	Septic suppurative inflammation with intracellular microbes	Fluid TNCC >13,000/μl Serum glucose:fluid glucose >20 mg/dL Fluid lactate:serum lactate >1.5 mmol/dL	Emergency surgery

PCV, packed cell volume; TNCC, total nucleated cell count; TS, total solids; UTI, urinary tract infection.

Treatment

Treatment for peritonitis varies significantly and depends on the inciting pathology. While diagnostics will guide the clinician to surgical or medical management for definitive care, there are some commonalities of therapy for all animals with peritonitis. Surgical management of peritonitis is beyond the scope of this chapter, but is indicated on an emergent basis in all patients with a septic abdominal effusion, free abdominal gas, uroabdomen or bile peritonitis. Pain management, treatment of a coagulopathy, ensuring proper perfusion and fluid balance, maintenance of an acceptable hemoglobin concentration and appropriate antimicrobial usage must be considered in all critically ill patients, but especially in the context of the perioperative patient with peritonitis.

Several techniques exist for abdominal closure following laparotomy for septic peritonitis. The abdomen may be closed primarily, with or without closed suction drains, or may be treated with open abdominal drainage in cases of severe contamination in which the peritoneal cavity cannot be sufficiently decontaminated in surgery. Where facilities are equipped, the use of vacuum-assisted closure has also been reported [13,14]. Both open abdominal closure and vacuum-assisted closure are advanced techniques that require specialized facilities and close monitoring of systemic signs and albumin levels for optimal outcomes.

Fluid Therapy

A significant, imperative goal in the treatment of critically ill patients is to ensure proper perfusion to the tissues. Fluid therapy plays a major role in the treatment of these unstable patients. Normalization of lactate, arterial blood pressure, and vital signs such as heart rate, mucous membrane color and capillary refill time should be an early and important goal in these cases. See Section 5 for further details regarding types and amounts of fluids for resuscitation.

Antimicrobial Therapy

Antimicrobial treatment of the patient with peritonitis should be the rule rather than the exception if bacterial peritonitis is suspected or confirmed. Broad-spectrum, four-quadrant, intravenous antimicrobial therapy should be instituted without delay, and samples for culture and susceptibility testing should be obtained as soon as possible. Chapter 200 discusses the use of antibiotics in this context in greater detail.

Pain Management

The treatment of pain in small animals suffering from peritonitis should be early, aggressive and multimodal, as indicated for individual patients (see Section 7).

Appropriate analgesia is necessary to avoid the physiological effects of pain, as well as to facilitate handling and examination of the patient. Pure mu-opioid agonists such as hydromorphone, fentanyl or methadone are excellent choices for treatment of animals with severe pain. Multimodal analgesia utilizes more than one class of drug in order to facilitate analgesia. A combination of fentanyl or morphine, lidocaine and ketamine given as a constant rate infusion is an excellent choice for patients with peritonitis. Perioperative epidural administration of morphine or lidocaine can also improve patient comfort dramatically. Lidocaine patches can be used for incisional pain when applied to the surgical site. Additionally, some clinicians instill local anesthetics into the peritoneum intraoperatively or via an indwelling soaker catheter.

Analgesic administration must be balanced with the possible side-effects of the drugs themselves. Opioids may cause cardiac and respiratory depression, ileus, and urine retention in some patients. This is dose related and can be mitigated by using multimodal analgesia to reduce the dose of opioids administered. In addition, prokinetic drugs may offset the adverse gastrointestinal effects of these drugs.

Due to the hemodynamically compromised nature of the septic patient, non-steroidal anti-inflammatory drugs and corticosteroids are contraindicated.

Antiemetics, Antacids, and Prokinetics

Almost all cases of peritonitis will require drugs that modulate the gastrointestinal tract. Because of the peripherally generated nausea in patients with peritonitis, antiemetics such as maropitant, ondansetron, dolasetron, metoclopramide, and chlorpromazine are reasonable therapeutic choices (see Chapters 13 and 74 for further details). Maropitant is a substance P antagonist that works in both the chemoreceptor trigger zone and the emetic center and is the only veterinary-approved drug in this class [15,16]. Ondansetron and dolasetron are serotonin antagonists that are also extremely effective centrally acting antiemetics. Chlorpromazine is only moderately less effective than the aforementioned antiemetics, but as a phenothiazine derivative and relative of acepromazine, it should be used with caution in hemodynamically unstable patients. Metoclopramide has the added benefit of being a prokinetic as well [16]. Often, a combination of drugs is necessary in patients with peritonitis.

Prokinetic drugs are useful in animals with peritonitis as these patients often have multiple reasons for gastrointestinal ileus. Vomiting and regurgitation as well as inability to tolerate enteral nutrition can increase both morbidity and mortality. Metoclopramide and erythromycin or azithromycin can be administered either as intermittent doses or as constant rate infusions (more effective method for

metoclopramide). Ranitidine has both a prokinetic function in the proximal GI tract and H₂ antagonism, making it a good choice in patients where both therapies are desirable.

Antacid administration is controversial in patients with peritonitis. Antacids can help to counteract the detrimental effect of decreased splanchnic blood flow on the gastric mucosa. Additionally, they facilitate the healing of gastric ulcerations if such are present. There are significant side-effects to decreasing gastric acidity including decreased gastric absorption of oral drugs, interference with metabolism of some oral drugs and enabling enhanced bacterial growth in the gastric lumen. The latter detrimental effect can worsen the effect of aspiration pneumonia, should this occur. Proton pump inhibitors are most effective at raising gastric pH (lowering acid load) [17,18]. In several comparative studies, the proton pump inhibitors (omeprazole and pantoprazole) outperformed the H₂ antagonists (famotidine or ranitidine).

Nutrition

It has been recognized that instituting early postoperative nutrition in patients with septic peritonitis results in significant reduction in hospitalization length [19]. Enteral nutrition has anti-inflammatory properties and facilitates enterocyte replication and return to function. Various techniques and nutritional strategies exist for providing early, safe, and adequate enteral caloric support for the critically ill small animal patient and the enteral route is recommended whenever possible [20,21]. Parenteral nutrition strategies can also be employed in patients where enteral feeding is not tolerated, as some studies have shown that parenteral as well as enteral nutrition improve patient outcomes [19,22].

The authors recommend that nutritional planning begin at the time of hospitalization. The placement of an esophagostomy feeding tube at the time of surgery is a valuable and proactive tool to ensure that nutrition is not delayed. Alternatively, nasogastric or nasojejunal feeding tube placement may also be considered in patients where nutritional support is anticipated to be temporary. Nutrition should be initiated within 24 hours postoperatively if the patient is hemodynamically stable. The daily caloric requirement may be calculated using the formula ($RER = 70 \times BW_{kg}^{.75}$) and nutrition initiated at 25% of RER on the first day to ensure enteral tolerance. This may be increased to 50% on day 2, and 75–100% by day 3.

Prognosis

Patients with septic peritonitis often require intensive surgical and medical management for several days, occasionally weeks. The overall prognosis depends on the

underlying cause, systemic health of the patient, and effective surgical and medical management. Reported survival rates range between 31% and 85% [5,10,23–25]. Prospective studies on septic peritonitis in veterinary medicine are scarce, but retrospective analyses have not

substantiated associations between antibiotic selection, timing, and outcome [25,26]. This needs to be interpreted with caution, however, and the authors still recommend and practice early antimicrobial therapy and source control to optimize patient chance for survival.

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Postoperative Complications Presenting to the Emergency Service

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Introduction

Emergency clinicians are often asked to evaluate animals that have undergone recent surgery or invasive procedures. The time following their procedure can be variable (e.g. hours to weeks), along with the overtness of their complication. Minor issues (e.g. surgical incision issues, splint or bandage changes, adjustments in analgesia plan) are typically straightforward, while evidence of systemic compromise may require more thorough investigation.

Postoperative problems or presenting complaints can be separated into those directly related to the procedure itself (surgical site complications) and indirect complications more related to perioperative management, hospitalization, or even identification of previously unrecognized diseases (e.g. hypoadrenocorticism). A detail-oriented approach to these cases is the key to successful accurate characterization of postoperative issues, enabling appropriate therapy to be instituted.

The animal may have undergone a procedure at another facility, meaning the emergency clinician may have limited access to their medical records. In these situations, reliance on the owner's knowledge or understanding of the procedure may have to suffice until records become available. Formulation of a diagnostic plan is determined by the history, physical exam, appreciation of anticipated complications, and the animal's trend following discharge.

Physical examination findings should be considered in the context of the patient's timeline from time of discharge to the present. If a fever was present at the time of discharge, for example, and is still present, the problem may have been in motion during hospitalization. New findings such as indicators of cardiovascular instability including tachycardia, tachypnea or bounding pulses prompt more emergent intervention. Potential clues towards underlying infection include, but are not limited to, a new heart murmur, fever or icterus. Findings

that cannot easily be accounted for as a complication directly related to the procedure may still be related (e.g. pneumonia following aspiration event under anesthesia). In some cases, multiple coinciding complications may be present (e.g. infected surgical implant with a bloodstream infection). A careful objective approach is especially important if the primary clinician or surgeon is unavailable to provide insight.

Surgical Site Complications

Surgical site complications directly involve the procedure and, depending on the nature of the procedure, may range in importance from those easily remedied to potentially life threatening without intervention. Incisional problems (e.g. swelling, discharge or dehiscence) are commonly encountered and usually obvious to owners (Figure 88.1). Owners are also usually cognisant of



Figure 88.1 A pit bull who was presented to the emergency service after being found dead after an ovariohysterectomy.

issues with bandages or splints, or poor locomotor ability (e.g. following orthopedic surgery).

Surgical wounds are classified as clean, clean-contaminated, contaminated, and dirty [1]. Concurrent issues including diabetes, hyperadrenocorticism or chronic glucocorticoid administration may be complicating factors in non-healing wounds. Certain wounds, such as traumatic shearing injuries, bite wounds, and impaling injuries, carry a higher risk of contamination. Dirty wounds often require long-term wound management and bandage changes, increasing the potential for hospital-acquired infections that may be resistant to commonly prescribed antimicrobials. Open fractures of a high grade (comminuted with soft tissue injury) are also susceptible to infections [2]. Open fractures stabilized with implants also can carry long-term concerns for infection risk. Strategies to limit exposure to at least those avoidable infections should start with the first visit to the emergency service by expediently cleaning and protecting open fractures to prevent further contamination.

Incisional complications include inflammation, suture reaction, seroma, incisional infection, and dehiscence. The animal may be more bothered by the wound itself rather than being systemically compromised. The presence of other symptoms (e.g. inappetence, fever) may actually indicate a separate issue. The wound should be assessed early following triage and addressed promptly to limit development of hospital-acquired infection. Fever is a serious clinical sign in these postoperative situations. Point-of-care ultrasound can be used to examine for pockets of fluid or cellulitis, confirm regional extent of the lesions, and aid sampling fluid for cytological analysis. Cytology confirms infection if intracellular bacteria are visualized. If infection is not confirmed via cytology, the wound can be managed as a seroma. If infection is confirmed, the wound is better managed with reoperation since this allows for inspection of the deeper layers of closure, debridement, and lavage. Bacterial culture and sensitivity should be obtained, and broad-spectrum antibiotics should be initiated. Clean and otherwise healthy surgical wounds that have simply dehisced due to mechanical trauma (chewed sutures) can usually be flushed, debrided, and closed routinely.

Non-healing surgical wounds also require exploration although not necessarily in the operating room. Planning and patience are important components of chronic wound management since they are not usually amenable to a quick solution. Infected wounds may benefit from debridement and flushing, and certainly are not ready for closure until infection is controlled. Interim care of infected wounds may require open wound management with wet-to-dry, dry-to-dry, wound vacuum-assisted closure (VAC) [3] dressings and topical debriding and

antimicrobial dressings. Systemic antibiotics should be selected based on the most likely causative organism, especially if previously prescribed antibiotics proved to be ineffective (see Chapter 200). Bacterial biofilms harbor and protect bacteria from access for culture and sensitivity, and are an important cause of chronic non-healing. Infected wounds should be generously flushed with sterile saline and debrided [4]. Please see Chapter 166.

Dehiscence of soft tissue surgeries involving abdominal viscera can be serious causes of morbidity and mortality even with reoperation. Perforated gastrointestinal surgical sites and abdominal wall dehiscence all require prompt identification and surgical repair. Bile leakage from biliary tract surgery or urine leakage from urinary tract surgery are also important sources of peritonitis, albeit typically sterile yet caustic in nature initially. By the time animals present with dehiscence or complications of these surgeries, several opportunities may have arisen to initiate complicating infection as well. If abdominal sepsis is present, cautious selection of antibiotics while waiting for culture and sensitivity should ideally include those with efficacy for the individual hospital's known pattern of bacterial resistance (see Chapter 87).

Diagnosis of peritonitis is supported by identification of free intra-abdominal effusion on ultrasound, but definitive diagnosis requires cytology and potentially comparison of paired effusion and blood samples. A fluid sample should be obtained aseptically via abdominocentesis (see Chapter 186). Suture lines and drains should be avoided since these are sometimes contaminated with bacteria that may have little association with the peritonitis. In the presence of fever and/or cardiovascular instability, prior history of gastrointestinal surgery makes abdominal sepsis likely with identification of intracellular bacteria in the abdominal fluid. A finding of fluid glucose at least 20mg/dL (1.1mmol/L) lower than blood glucose was historically considered a reliable means of diagnosing abdominal sepsis [5], but this appears more questionable in the postoperative setting [6]. Reoperation is indicated with attention to simultaneous resuscitation and prompt initiation of appropriately chosen antibiotics.

Bile peritonitis is likely with a prior history of biliary tract surgery, evidence of bile pigments on cytology of abdominal effusion and abdominal bilirubin levels greater than serum bilirubin concentration [7]. Bile leak can also occur into the peritoneal cavity with dehiscence of a prior duodenal surgery in the region of the attachment of the common bile duct, so observation of bile pigment in abdominal effusion with a history of duodenal surgery is suggestive of intestinal dehiscence. Uroabdomen is likely with a prior history of urinary tract surgery and abdominal effusion with potassium and creatinine levels greater than blood levels.

Animals presenting with peritonitis usually have signs of acute abdomen (see Chapter 6). Survey abdominal radiographs will document loss of abdominal detail, and free air either if surgical exploration has been recently performed or there is evidence of a bowel rupture. Mesenteric torsion and more commonly GDV should be considered as a cause of acute abdomen, especially in large-breed dogs following anesthetic procedures. Acute pancreatitis clinically can appear similar to septic peritonitis (see Chapter 86). The dog with acute necrotizing pancreatitis (ANP) may present febrile with acutely painful abdomen. Cytology of abdominal effusion is suppurative with pancreatitis, but bacteria are not present. ANP is an important cause of acute abdominal signs, but it is not a surgical disease unless severe biliary obstruction results. However, dogs with ANP can be critically ill, requiring aggressive intensive care with a guarded outcome.

Dogs which have undergone surgeries involving the portal system (splenectomy, liver lobectomy) may suffer acute collapse from thrombosis [7]. Disruption of any part of Virchow's triad (hypercoagulability, altered blood flow, endothelial injury) can precipitate thrombosis. Acutely occlusive portal system thrombosis (PST) may result in sudden cardiovascular collapse with rapid decompensation and death [7]. Splenectomy has been shown to be an important cause of acute portal vein thrombosis (PVT) and should be considered in dogs with a history of splenectomy and now presenting with sudden collapse, acute vomiting, bloody diarrhea, and abdominal distension [8]. Acute portal hypertension will result in serosanguineous abdominal effusion that is low in protein and hypocellular. This laboratory value differentiates PVT from hemoabdomen due to a slipped ligature. Treatment of PVT usually requires anticoagulation (see Chapter 71) in addition to aggressive fluid therapy and potentially blood products. Portal system thrombosis that extends into the mesenteric veins will likely require surgical intervention. Prognosis with acute thrombosis of the portal system is usually guarded and in some cases death is unavoidable [7].

Animals with portosystemic shunts may suffer a variety of complications following procedures to decrease blood flow through the shunting vessel, although these are less with progressive gradual ligation methods (e.g. ameroid constrictor). Portal system thrombosis can result simply from alteration of blood flow. Acute portal hypertension has a presentation similar to that of acute PVT. Emergent removal of the occluding method is indicated or else attempts to resuscitate will be unsuccessful and uncontrolled acute portal hypertension may result in death. Seizures have also been documented following shunt ligation, and may result in patient death or euthanasia.

Ovariohysterectomy (OHE) is a commonly performed procedure with complications similar to those of other abdominal surgeries, including incisional inflammation or infection, wound dehiscence and potentially viscera herniation (see Figure 88.1). Failure to protect the surgical incision from trauma inflicted by the animal is a common cause of incisional instability and wound breakdown. Hemorrhage is the leading fatal complication, and bleeding into the abdominal cavity following OHE can occur with injury to the ovarian or uterine vessels during manipulation of the ovarian ligament or uterine body [9]. In the absence of documented coagulopathy, emergent reoperation for uncontrollable hemorrhage post OHE is indicated, both for inspection of the blood vessels associated with the surgery and containment of bleeding. Prior to transfusion, a citrated plasma sample should be obtained and frozen to later document von Willebrand factor deficiency or other inherited clotting disorders.

Acute azotemia following genitourinary tract surgery can result from several complications, including leakage of urine into the peritoneal cavity (uroabdomen), obstruction of urine flow due to compression or inflammation of the ureters or urethra, urethral obstruction by cystic calculi that were inadvertently missed during cystotomy, or acute kidney injury. Any reason for acute azotemia may result in oliguria or anuria, but abrupt anuria should prompt consideration for surgical misadventure. Other important causes for acute azotemia and diminished urine output include surgically misplaced ligatures, or inflammation resulting in severe compression and restriction of urine flow (Figure 88.2). In cases of inadvertent placement of a ligature about the ureters, prompt removal of the constriction of the suture is often adequate to salvage renal function. In cases of severe

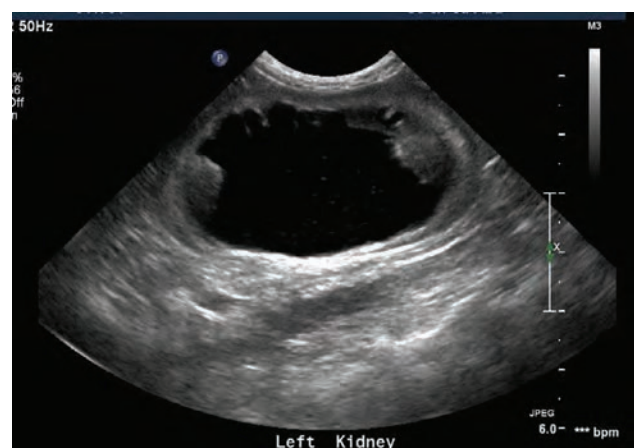


Figure 88.2 An ultrasound image of a hydronephrotic kidney that developed following inadvertent ligation of the ureter during a cystotomy.

inflammation or stricture, other strategies such as stenting may be required to improve patency [10,11].

Surgery site complications resulting in uroabdomen or urinary obstruction require stabilization of hyperkalemia and metabolic derangements prior to reoperation. With uroabdomen, the placement of a peritoneal catheter [12] or drain is usually sufficient to allow urine drainage and to stabilize electrolytes, along with careful fluid therapy. Refractory hyperkalemia may benefit from more specific therapy (e.g. insulin-dextrose, calcium gluconate) (see Chapter 109). A sterile urinary catheter should be placed into the urinary bladder for emptying prior to insertion of the peritoneal catheter to avoid injury to the bladder. To better characterize the cause of obstructive azotemia, contrast studies can be pursued. Intravenous pyelography may be risky in animals that have urinary obstruction and cannot clear the contrast medium. If surgery site complications accounting for azotemia are fully considered and ruled out, other causes for new azotemia would include AKI due to toxic insult (e.g. NSAIDs, aminoglycosides), perioperative hypotension, or multiorgan failure associated with sepsis. Resolution of AKI with appropriate supportive measures is possible but may necessitate prolonged hospitalization and potentially dialytic therapies (see Chapter 94).

Associated Complications

Aspiration pneumonia is a common complication in dogs after general anesthesia (see Chapter 37) [13]. Witnessed events such as regurgitation or vomiting during induction or recovery can usually be identified, but silent regurgitation and aspiration may occur unwitnessed. Esophageal disease may increase the risk of aspiration. Aspiration pneumonia has been reported in dogs following unilateral arytenoid lateralization surgeries, brain surgeries, and laparotomies [14–16]. Animals with pneumonia may present with signs referable to

respiratory compromise and infection, so tachypnea or dyspnea in the presence of a new fever should prompt obtaining thoracic radiographs. Broad-spectrum antibiotics should be chosen based both on whether the recent history included administered antibiotics, and the pattern of the individual hospital's pattern of resistance (see Chapter 200). If the animal is stable enough, sampling the respiratory tract with transtracheal aspirate or BAL is ideal to provide antimicrobial sensitivity. It is important not to delay antimicrobial therapy if a culture cannot be performed in a timely fashion.

Thromboembolic events are widely reported in human medicine, with deep venous thrombosis (DVT) described prominently. In animals, DVT is rarely described, but thromboembolic events have been reported, including pulmonary thromboembolism (PTE) [17], splenic vein thrombosis [18], PVT [7] and aortic thromboembolism [19,20]. Echocardiography may identify right ventricular enlargement or, with reasonable high suspicion for PTE, a definitive diagnosis can be determined with CT angiography. Anticoagulation is indicated for PTE, or potentially thrombolysis in consultation with cardiology in extreme cases (see Chapter 62).

Conclusion

Animals may present to an emergency service following a surgery or invasive procedure for evaluation for problems that directly relate to the surgery site or for complications that stem from management and events that surrounded the surgery. Surgery site complications may involve the surgery wound, bandaging, pain associated with the surgery, dehiscence or hemorrhage. Life-threatening surgery site complications include GI dehiscence, hemorrhage, and acute azotemia due to urinary obstruction or uroabdomen. Presence of fever suggests infection and warrants investigation. Other perioperative complications include aspiration pneumonia, thromboembolism, and AKI.

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Biliary Disease

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Introduction

Patients presenting as emergencies with underlying biliary disease can have a wide variety of presenting signs, reflecting the number and diversity of underlying disease processes. Some patients may present collapsed with evidence of decompensated hypovolemic or distributive shock whereas others may present much earlier in the course of their disease and be relatively stable on initial evaluation. As with all emergency patients, empirical stabilization and diagnostic tests often need to be performed concurrently. Biliary disease may occur secondary to a range of primary hepatic diseases that can lead to intrahepatic cholestasis or to diseases of the extrahepatic biliary system as summarized in Box 89.1. This chapter will focus on diseases of the extrahepatic biliary system and the reader is referred to the chapter on hepatic disease (Chapter 90) for more information on these conditions.

Box 89.1 Causes of biliary disease.

- Cholelithiasis
- Choledocholithiasis
- Cholecystitis
 - May be emphysematous
- Gall bladder infarction
- Biliary neoplasia
 - Biliary cystadenoma
 - Biliary carcinoma
- Parasitic biliary disease
 - Uncommon – some species of fluke infect the biliary tree and liver of cats
- Gall bladder mucocele
- Gall bladder torsion
- Gall bladder rupture
 - Secondary to trauma, neoplasia, cholecystitis

Overview of Anatomy and Physiology

The canine extrahepatic biliary system is composed of the gall bladder, cystic duct, hepatic ducts, common bile duct, and major duodenal papilla. Bile flows from the bile canaliculi into the interlobular ducts, and into the lobar ducts before leaving the liver. Lobar ducts drain into hepatic ducts, through which bile passes into the common bile duct [1]. The gall bladder lies within a fossa between the right medial and quadrate lobes of the liver. The gall bladder is drained by the cystic duct and is the portion of duct before the hepatic ducts enter into the common bile duct, which terminates near the minor pancreatic duct at the major duodenal papilla. In a medium-sized dog, the common bile duct is approximately 5 cm long and 2.5 mm in diameter and empties into the duodenum 1.5–6 cm distal to the pylorus at the major duodenal papilla after coursing intramurally for approximately 2 cm [1]. The circulation to the gall bladder and common bile duct is via the cystic artery and it is derived from the left branch of the proper hepatic artery. This circulation must be preserved when performing decompressive or rerouting surgery of the biliary tract. Injury to this vessel can result in acute necrotizing cholecystitis and bile peritonitis.

Functionally, the biliary system is responsible for draining waste products (including bilirubin) from the liver into the duodenum. It also plays an important role in digestion as bile emulsifies fats and, due to its alkaline nature, neutralizes acid in partially digested food. Bile contains a number of substances including bile salts (the sodium and potassium salts of bile acids), cholesterol, lecithin and phospholipids as well as bilirubin and biliverdin. In health, the gall bladder acts as a storage organ for bile, with gall bladder contraction being stimulated by the hormone cholecystokinin (CKK). CKK is released from the duodenal mucosa in response to fatty acids and

amino acids entering the duodenum and hence gall bladder emptying is co-ordinated with the need for digestion.

On a daily basis, the vast majority of bile salts are reabsorbed into the portal circulation in the distal ileum, with only a small amount being lost in the feces. Loss via the biliary system is the principal route for cholesterol excretion from the body. Metabolites of bilirubin and biliverdin are responsible for the color of the feces.

Presenting Signs and Initial Physical Examination

The diagnosis always begins with a thorough history and physical examination and biliary disease is no exception to this. Common presenting signs include lethargy, inappetence, vomiting and diarrhea, and abdominal pain of varying intensity. Some patients may simply present collapsed. A history of recent trauma is of particular note as patients with sterile bile peritonitis secondary to rupture of the gall bladder following blunt abdominal trauma typically present 7–10 days after the incident [2,3].

On physical examination, signs are variable. Icterus is common with severe biliary disease but may not be present with mild or early disease. Similarly, icterus may have a prehepatic or hepatic cause as well as biliary (posthepatic) disease (see Chapter 11). Initial examination should always focus on the major body systems and with biliary disease none or all of these may be affected. The cardiovascular system is most commonly affected, with signs of hypovolemic or distributive shock occurring with many causes of biliary disease. Respiratory disease is less common but may occur, for example, secondary to aspiration pneumonia or respiratory compensation for metabolic acid–base disturbances. Neurological signs may occur although are less common with posthepatic (biliary) as opposed to hepatic disease. Abdominal palpation may reveal focal or diffuse pain and evidence of free abdominal fluid may be present.

Diagnostics

An initial diagnostic database should include a PCV/TS, metabolite panel (including electrolytes, venous blood gas, glucose, and lactate) and blood smear; a range of abnormalities may be found dependent on the diagnosis. Urgent clotting tests (PT and aPTT) are recommended in all emergency patients where biliary disease is being considered and will help identify disseminated intravascular coagulation (DIC) as well as determining the presence and severity of coagulopathy in animals with biliary obstruction. A full hematology and biochemistry panel should be performed in most cases with particular

attention paid to indicators of liver function (albumin, blood urea nitrogen, cholesterol, bilirubin, and glucose) as well as the liver enzymes.

Classically, the increase in AlkP and GGT is much more dramatic than the increase in ALT in biliary disease, with the reverse being true for primary hepatic disease [4]. Bilirubin will typically be elevated, with clinical jaundice occurring once serum bilirubin concentrations exceed around 2 mg/dL (35 μ mol/L). Hypercholesterolemia is common with cholestasis, with marked elevations in cholesterol occurring with biliary obstruction. Further laboratory testing may include dynamic bile acid testing, pancreatic lipase immunoreactivity, and thromboelastography (TEG) with the addition of thyroid hormone evaluation in cats.

A free fluid (FAST) scan is the initial “kennel-side” imaging test of choice in patients suspected of having biliary disease (see Chapter 182). If free fluid is identified, abdominocentesis should be performed and the fluid analysed (see Chapter 186). Evaluation of the bilirubin gradient (i.e. the difference between the bilirubin in the abdominal fluid and in a concurrently obtained serum sample) can diagnose biliary tract rupture in patients where this is a differential. The fluid should also be examined cytologically to look for signs of sepsis (intracellular bacteria within neutrophils). If free fluid is not present, ultrasound is still an important imaging technique for evaluating the internal architecture of the liver, gall bladder, common bile duct, and pancreas, although the user should be aware of their skills in this regard. Radiography is less helpful generally although free fluid may be suspected. CT is becoming increasingly available; its use for evaluating the abdomen of veterinary emergency patients is still being explored but it may be expected to identify many of the same problems as are currently diagnosed via ultrasound.

Stabilization

As with all emergency patients, initial stabilization should be based on the major body systems assessment as described elsewhere (see Chapter 2). Points to note specifically in patients with biliary disease are described below.

Cardiovascular System

Patients with biliary disease may be either hypovolemic and/or dehydrated *or* they may have a normal fluid balance. Fluid therapy should be tailored to the patient's physical examination. Concern is often expressed regarding the use of lactate-containing fluids (e.g. Hartmann's or lactated Ringer's solution) in patients with hepatobiliary disease as lactate is metabolized within the

liver. As the liver's capacity to metabolize lactate is large, this concern is rather overstated and these fluids need only be avoided if the animal is in fulminant liver failure (i.e. is also exhibiting hypoglycemia and coagulopathy) (see Chapter 167).

Respiratory System

Patients with icterus rarely have marked respiratory abnormalities. If concurrent severe respiratory abnormalities are present, they should be worked up as a separate problem. Aspiration pneumonia should be considered if the animal has been vomiting secondary to the biliary disease (see Chapter 37).

Neurological System

Neurological abnormalities are relatively common in animals with severe hepatic disease (hypoglycemia and hepatic encephalopathy) but much less common in patients with biliary disease. If neurological signs are present, blood glucose should be measured as a matter of urgency and supplemented as appropriate. The reader is referred elsewhere for management of patients with hepatic encephalopathy (see Chapter 90).

Acute Medical Therapy

Medical therapy may be the primary treatment for some causes of biliary disease, including cholecystitis and parasitic disease. Cholecystitis is treated with supportive care (fluid therapy and nutrition), analgesia, and antimicrobials. Antimicrobial therapy should ideally be chosen based on bacterial culture of bile (see Chapter 200). Samples may be obtained by percutaneous aspiration of biliary contents under ultrasound guidance; risks of this approach include bile peritonitis and vasovagal collapse and the risk:benefit ratio should be carefully considered. Empirical treatment with antimicrobials effective against anaerobes and common enteric bacteria may be justified in many cases [5,6]. Treatment of parasitic biliary disease requires use of anthelmintics [7].

Patients with gall bladder mucocele present with a wide range of clinical signs; it may be an incidental finding during abdominal ultrasound or the patient may present with bile peritonitis following rupture. The optimal treatment for gall bladder mucocele is undetermined; surgery is necessary if rupture has occurred but if the patient is stable, medical therapy with choleretics such as ursodiol and SAME in combination with antimicrobials may be attempted and may be effective in some cases [8]. Medical therapy is rarely successful for patients with cholelithiasis.

Along with specific medical treatment, administration of parenteral vitamin K should be considered in all patients with biliary disease. As a fat-soluble vitamin, absorption of vitamin K is depressed in patients with biliary obstruction and there is a potential for development of a coagulopathy (see Chapter 70). Monitoring of clotting tests (particularly PT) is recommended and empirical supplementation with a low dose of vitamin K (0.5 mg/kg once daily) may be used.

Surgery

The diseases that lead to a need for surgery of the extrahepatic biliary system in dogs and cats are primarily acquired conditions and include extrahepatic biliary tract obstruction (EHBTO), gall bladder mucoceles, traumatic injury, and cholecystitis. The main goal of surgery is to confirm the underlying disease process, establish a patent biliary system, and minimize perioperative complications.

When dealing with emergency patients, the clinician should critically evaluate their surgical skills and ability to perform some of the definitive procedures that may ultimately be required. Many of these (for example, cholecystoduodenostomy and cholecystojejunostomy) are technically challenging procedures that are best performed by a surgeon with appropriate training and experience. If this is not available immediately, it may be in the best interests of the patient to undergo damage control surgery (see Chapter 189), for example, placement of a temporary biliary diversion tube, until relevant surgical expertise can be accessed. Damage control surgery (DCS) may also be beneficial for the patient even if appropriate survival expertise is available immediately as it may reduce anesthesia and surgical time at a very early stage of the patient's treatment and help reduce complication rates and improve outcome. The evaluation of this is still in its infancy, especially in veterinary patients.

If definitive surgery is performed, a number of techniques may be used, depending on the disease process, and these are briefly described below along with an overview of DCS.

For a complete description on indications, stages, techniques, and outcomes-related DCS, see Chapter 189.

There are two conditions of the extrahepatic biliary tract that may make an animal systemically ill enough to justify the implementation of DCS. Extrahepatic biliary tract obstruction and bile peritonitis, especially septic bile peritonitis, may require DCS to provide either temporary biliary drainage or peritoneal drainage, respectively. During stage I DCS, for extrahepatic biliary tract disease, it is important not to damage the cystic duct, common bile duct, or cystic artery as this would prevent

stage III DCS, definitive repair, from being successful. A temporary cholecystostomy tube can be placed in cases of suspected extrahepatic biliary tract obstruction. Tube placement may be accomplished via laparotomy. A pigtail or Foley catheter is inserted into the apex of the gall bladder and a purse-string suture is placed around the base of the catheter to minimize leakage. The tube should exit the abdomen just caudal to the costal arch, and is secured to the skin using a purse-string and finger trap. The tube is connected to a sterile collection system (Figure 89.1). In the case of bile peritonitis, the abdomen is lavaged thoroughly during stage I DCS, a peritoneal or omentum tissue culture is performed, and a closed suction drainage catheter system is placed to temporarily drain the peritoneal cavity and leaking biliary system until definitive surgery can be performed (Figure 89.2). The gall bladder, cystic duct, common bile duct, and cystic artery are never ligated, transected, or damaged during stage I DCS as doing so may prevent successful definitive repair [9–11].

For stage III DCS, definitive surgical intervention may be in the form of a cholecystectomy, cholecystoenterostomy, choledochotomy, choledochal tube stenting, or a combination of procedures. A cholecystectomy should never be performed until patency of the extrahepatic biliary tract has been assessed and confirmed [9–11]. Removal of the gall bladder in a patient with a bile duct obstruction is contraindicated and could be



Figure 89.1 A 5-year-old female spayed whippet sustained penetrating trauma to the abdomen (ran onto a stick), resulting in a laceration to the common bile duct. Primary repair was attempted but was unsuccessful and the patient presented to the referral clinic with septic bile peritonitis. At that time, the patient was not stable enough for definitive biliary diversion so a temporary tube cholecystostomy was placed (locking loop catheter) and the abdomen was left open. Cholecystoduodenostomy was performed 48 hours later and the abdomen was closed. Source: Courtesy of Richard Coe.



Figure 89.2 A 3-year-old female spayed Labrador recovering from abdominal exploratory after being hit by a car 8 days earlier. Six days post trauma, she presented to an emergency clinic for vomiting, abdominal pain, and icterus and was diagnosed with septic bile peritonitis. An abdominal exploratory was performed, the ruptured gall bladder was removed, the abdomen lavaged, and multiple closed suction abdominal drains were placed for continued removal of abdominal fluid and contaminants and for postoperative peritoneal fluid evaluation. The patient made a complete recovery after being discharged 4 days after surgery.

a life-threatening surgical error. Indications include any primary disease of the gall bladder (cholecystitis, cholelithiasis, mucocele, neoplasia, infarction) or if severe structural changes have occurred secondary to other diseases or conditions.

Before performing a cholecystectomy, patency of the EHBT must be assured. This is done via a duodenotomy or from a cholecystotomy after removal of the gall bladder contents. Assessing the patency of the biliary tract after completing the cholecystectomy defeats the purpose as the lack of a patent system may indicate the need for a cholecystoenterostomy.

There are two techniques for initiating a routine cholecystectomy. The first involves dissection of the gall bladder out of the hepatic fossa and the other begins with identification and isolation of the cystic duct and cystic artery [7,9]. The authors prefer, in most cases, to isolate the cystic duct and artery first. This is performed by applying gentle traction to the gall bladder and hepatic fossa in a cranial direction. Mixer or right angle forceps are used to gently dissect dorsally around the cystic duct and artery. Two encircling sutures or one encircling and one distally placed transfixation suture are used to securely close the cystic duct and ligate the cystic artery. In most cases, the artery and duct are included in the same ligature. If they can be separated from each other, individual ligation is more secure. A third encircling suture, hemostat, or clip is placed distal to the last suture

and the cystic duct is transected immediately proximal to this. The end of the cystic duct that is still connected to the gall bladder is used as a handle to apply gentle traction to the gall bladder to facilitate its removal from the hepatic fossa.

Dissection of the hepatic visceral peritoneum from the gall bladder can be initiated with Metzenbaum scissors, electrosurgery, or blunt dissection. The further away the dissection plane is from the liver, the less hemorrhage will occur. Once a plane is established, the index finger or tips of a hemostat wrapped in gauze square are used to carefully remove the gall bladder from the hepatic fossa. In chronic cases where the serosa of the gall bladder is adhered to the serosal hepatic surface, electrosurgery or a vessel sealing device may be used to remove a small rim of liver parenchyma with the gall bladder to minimize the risk of rupturing the gall bladder wall during cholecystectomy. Hemorrhage from the hepatic fossa can be controlled with direct pressure applied to a lap sponge or by application of a hemostatic agent (Gelfoam, Vetigel, or Surgicel).

If a duodenotomy was used to assess patency of the biliary ducts, a small amount of sterile saline can be flushed gently into the common bile duct to assess the

security of the ligatures placed on the cystic duct remnant. Aggressive flushing and excessive manipulation of a catheter in this area have led to rupture of the bile ducts and should be avoided [10].

Cholecystoenterostomy, choledochotomy, choledochal tube stenting, and other surgical interventions are reported elsewhere [9,11].

Prognosis

The prognosis for patients with biliary disease is very dependent on the underlying diagnosis. For patients with extrahepatic biliary obstruction disease requiring surgery, survival rates are reported to be around 70% when a population of dogs with a variety of diseases are considered and only 50% when a subset of dogs with bile peritonitis were evaluated; septic bile peritonitis appears to carry a particularly poor prognosis [12–14]. Feline patients also have a poor prognosis [15]. Several factors may contribute to this, with arguably the most important being the presence of sepsis/SIRS and multiorgan dysfunction (see Chapter 159).

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Acute Liver Failure

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Introduction

Acute liver failure (ALF) is an uncommon but life-threatening emergency that occurs in patients with rapid deterioration of liver function. It is most commonly defined in people as decreased liver function with evidence of a coagulopathy (international normalized ratio [calculation used to standardize prothrombin time] of ≥ 1.5) and any degree of mental alteration or encephalopathy in a patient without pre-existing liver disease [1–4]. In people, this can be further subdivided into hyperacute, acute, and subacute, depending on the amount of time that elapses between the initial signs of icterus and signs of encephalopathy, but there is debate whether this helps determine prognosis.

There are many known causes of ALF in dogs and cats, with neoplasia, toxins, and infectious causes being the most common [5–7]. Hepatic lipidosis is a common cause of ALF in cats and dogs with portosystemic shunts can also present with signs of encephalopathy. A patient that presents in ALF is the quintessential emergency patient as alterations in every organ system can occur and progress rapidly. Prompt recognition of ALF, early intervention, and knowledge of sequelae and treatment options are imperative for a positive outcome. Referral to a 24-hour care or referral specialty hospital is indicated. Financial aspects of intensive monitoring, treatment and care must also be discussed with the owners.

Pathophysiology

The liver is responsible for carbohydrate, protein and fat metabolism, synthesis of clotting factors and other cellular proteins, metabolism of hormones and essential nutrients, promoting biotransformation, and metabolism of drugs and other toxic blood-borne products. The liver is made up of lobules, with the portal vein, hepatic

artery, and bile duct in the periphery and the central hepatic vein in the center (Figure 90.1). Blood flows from the portal vein and hepatic artery to the central vein. The area closest to the central vein, the centrilobular area or zone 3, has the lowest oxygen content [8]. It also has the highest level of cytochrome p450, making it especially sensitive to toxic insults (Figure 90.2). The portal tract (area of portal vein, hepatic artery, and bile duct) is the site of liver progenitor cells. Damage to this area limits the liver's regenerative response.

Depending on the cause of ALF (see below), the hepatocyte undergoes necrosis and/or apoptosis. This leads to release of cytosolic proteins (e.g. alanine aminotransferase (ALT), aspartate aminotransferase (AST)) and diminished glutathione levels. Decreased glutathione levels make the liver more susceptible to oxidative injury and decrease its ability to conjugate and detoxify some

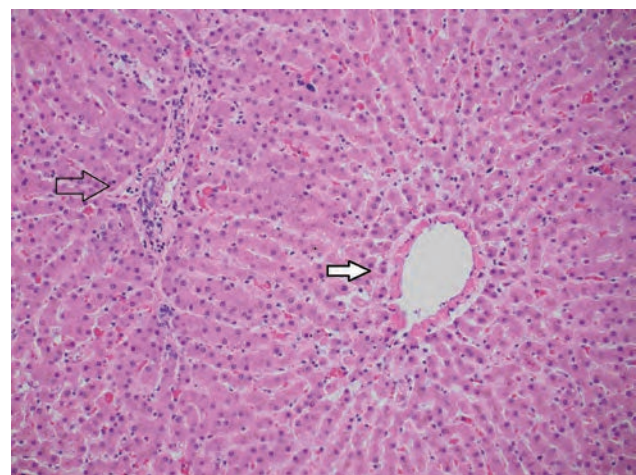


Figure 90.1 Normal liver – white arrow points to central vein or centrilobular area, black lined arrow points to portal tract (portal vein, hepatic artery, bile duct). Reproduced with permission of Bradley Turek.

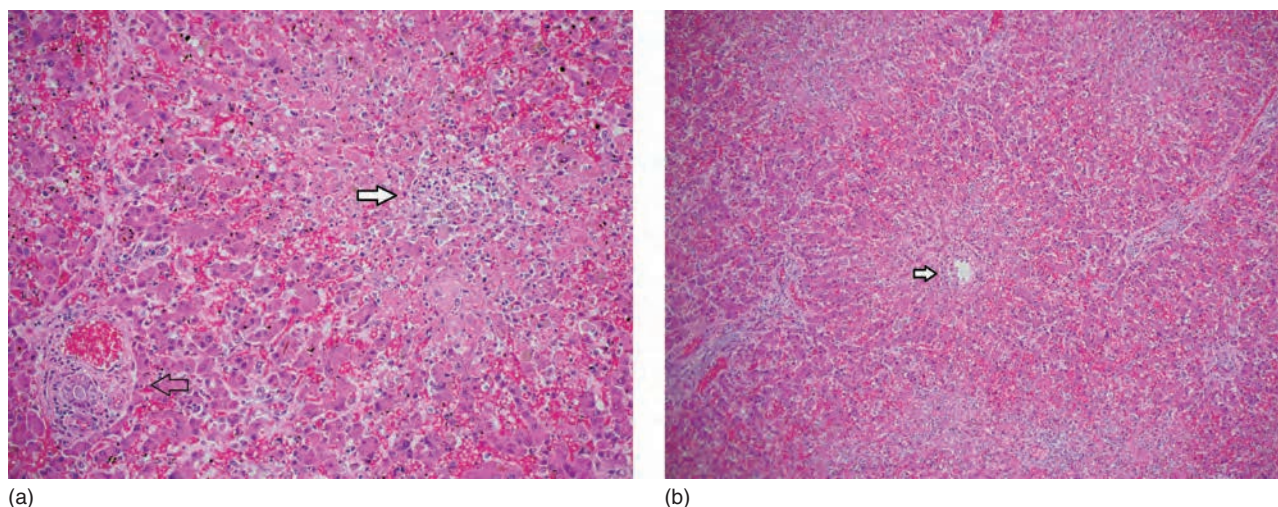


Figure 90.2 (a,b) Same patient, different magnification. Acute hepatic necrosis showing centrilobular hepatocellular degeneration (white arrow). Thin black lined arrow shows portal tract. Reproduced with permission of Bradley Turek.

toxins. There can also be impaired bilirubin transport systems leading to cholestasis and hyperbilirubinemia. Decreased gluconeogenesis, impaired hepatic insulin and glycogenolysis, along with possible sepsis (see below), lead to hypoglycemia.

Decreased ability of the liver to detoxify ammonia by the urea cycle leads to elevated ammonia levels, which causes signs of hepatic encephalopathy (HE). There are many proposed mechanisms and substances leading to the development of HE, but elevated ammonia levels is still thought to be extremely important [9–12]. Gastrointestinal bacteria produce ammonia from degradation of amines, amino acids, and purines. Ammonia enters the astrocyte, combines with glutamate and is converted to glutamine by glutamine synthetase. Glutamine is osmotically active and leads to cellular swelling. Elevated ammonia levels also lead to changes in neurotransmitter synthesis and release, altered brain glucose metabolism, and changes in the mitochondria. Astrocyte swelling leads to cerebral edema and increased intracranial pressure.

Changes induced by elevated ammonia, increased levels of inflammatory mediators, and loss of cerebral blood flow autoregulation contribute to increased intracranial pressure. This can progress to brain herniation. There are known risk factors in humans for cerebral edema and brain herniation. These include a higher-grade encephalopathy, serum ammonia level greater than 150–200 $\mu\text{g/dL}$ (normal 15–45 $\mu\text{g/dL}$), rapid progression of liver injury to hepatic encephalopathy, infection/systemic inflammatory response syndrome (SIRS), and need for renal replacement therapy or vasopressor support [4].

Decreased function of Kupffer cells, the liver macrophage, results in decreased metabolism and clearance of endotoxin, infectious organisms and other substances brought to the liver by the portal system. Decreased perfusion to the gastrointestinal (GI) tract can also lead to bacterial translocation. These can lead to toxins or pathogens entering the systemic circulation and causing sepsis.

Patients in ALF will also have varying degrees of a coagulopathy. The majority of coagulation factors and thrombopoietin are synthesized in hepatocytes. In patients with liver failure, there is decreased synthesis of procoagulant (factors II, V, VII, and X) and anticoagulant factors (antithrombin, activated protein C, protein S). There are also impaired fibrinolytic systems and defective function and number of platelets. This, along with a short half-life of some factors and increased consumption, can lead to a coagulopathic state (see Chapter 70). However, due to the decrease in both pro- and anticoagulant factors, there is “rebalanced hemostasis” where the risk of spontaneous clinical bleeding, as well as thrombosis, is minimal. However, this can shift quickly if there is infection, SIRS, renal failure or neoplasia, to increase the risk of hemorrhage [13–18].

Presenting Complaint and Clinical Signs

Most dogs and cats will present due to anorexia, vomiting, diarrhea, polyuria/polydipsia, lethargy to collapse, and/or abdominal pain. Owners may or may not appreciate icterus. Signs of encephalopathy, such as altered mentation or seizures, may also be present. Questioning

the owners about any possible toxins, drug exposure, and current owner or pet medications, including supplements, is imperative.

Patients in ALF can present with varying degrees of clinical signs, with alterations in all four major organ systems assessed on initial presentation. Abdominal palpation may reveal hepatomegaly, abdominal pain or presence of a fluid wave.

Cardiovascular Signs

Acute liver failure is characterized as a state of vasodilation with increased cardiac output, decreased systemic vascular resistance and decreased mean arterial pressure [1–4,19–21]. Secondary infections, sepsis or SIRS can contribute to this, if present. Hypotension and hypovolemic shock are typically seen. Anorexia, protracted vomiting and diarrhea can also contribute to dehydration and hypovolemia. Clinical signs include pale mucous membranes, prolonged capillary refill time, poor pulse quality, and tachycardia. Cats can present bradycardic. If there is a component of sepsis, then hyperemic or brick-red mucous membranes and bounding pulses can also be present (see Chapter 159).

Respiratory Signs

Tachypnea to dyspnea and cyanosis can be seen due to compensation secondary to hypovolemia, acidemia, abdominal pain, aspiration pneumonia secondary to vomiting, or acute respiratory distress syndrome (ARDS) (see Chapter 4). Changes in neurological status can also impair the respiration; early intubation and protection of the airway is recommended in people with hepatic encephalopathy.

Neurological Signs

Animals in ALF typically have alterations in mentation that can quickly (within hours) change from depressed to comatose and/or seizures (see Chapters 3 and 21). Hepatic encephalopathy signs can also include hyperactivity, head pressing, hypersalivation, disorientation, circling, pacing, blindness, ataxia, muscle tremors, cranial nerve deficits, and conscious proprioceptive deficits [9,22,23]. In cats, ptialism is the most common sign. There is a hepatic encephalopathy grading system in place for people and one recognized for dogs (Box 90.1) [23]. There are potential precipitating factors to the onset of hepatic encephalopathy including SIRS, GI bleeding, hypokalemia, hyponatremia, diet change or indiscretion, furosemide treatment, azotemia, constipation, and alkalosis [10,11,23].

Box 90.1 Grading for hepatic encephalopathy.

Grade 0	No clinical signs
Grade 1	Mild impaired mobility, apathy or both
Grade 2	Severe apathy, mild ataxia or both
Grade 3	Hypersalivation, severe ataxia, head pressing, blindness, circling or any combination of these signs
Grade 4	Seizures, stupor or coma

Renal Signs

Acute kidney injury (AKI) can occur early in the course of disease or occur as signs of multiple organ failure ensue (see Chapter 94). In people, AKI is seen in up to 70% of patients with ALF [1–3,19]. There will most likely be a prerenal component in patients with azotemia, but due to the potential for renal insult, aggressive therapy and frequent monitoring are imperative. Many toxins that cause hepatic injury can also result in renal injury due to both organs having a high metabolic rate.

Patients can also have signs of a coagulopathy (melena, hematochezia, or hematemesis, petechiae, ecchymosis, epistaxis) and/or thrombosis (i.e. portal vein thrombosis and ascites).

Causes

There are many causes of ALF, with neoplasia and toxins being the most common (Box 90.2). Animals with congenital portosystemic shunts can present due to hepatic encephalopathy and are therefore included. There are case reports of zonisamide [24], mitotane [25], and manganese found in joint supplements [26] causing hepatic necrosis and many review articles of herbal supplements [27] causing acute liver injury. Many causes of chronic liver disease can present with acute symptoms (i.e. copper storage disease).

Acetaminophen is the most common cause of toxin-induced ALF in people and is a well-known toxin in dogs and cats (see Chapter 132) [4,8,28–31]. It is rapidly absorbed through the GI tract and is minimally protein bound. It can be conjugated with glucuronide or sulfate to non-toxic metabolites, or oxidized by cytochrome p450 into the toxic metabolite N-acetyl-p-benzoquinonimine (NAPQI). NAPQI, a free radical that damages hemoglobin and red blood cells, can be detoxified by conjugation with glutathione. NAPQI will accumulate in hepatocytes when glucuronide, sulfate, and glutathione levels are depleted. This then binds to the hepatic cell membrane,

Box 90.2 Causes of acute liver failure.**INFECTIOUS****Viral**

Canine adenovirus 1 (infectious canine hepatitis)
 Accidental parenteral injection of intranasal *Bordetella bronchiseptica*
 Herpes virus
 Feline corona virus (feline infectious peritonitis)
 Calicivirus (virulent systemic calicivirus)

Bacterial

Clostridium piliformis (Tyzzer disease)
 Leptospirosis

Parasitic

Leishmania
Platynosomum fastosum (cat, liver fluke)
Toxoplasma gondii
Diriofilaria immitis

Fungal

Coccidioidomycosis
Histoplasma

TOXIN

Acetaminophen
 Aflatoxin
Amanita mushrooms
 Androgenic anabolic steroids
 Arsenic
 Carbon tetrachloride
 Cyanobacteria (blue-green algae)
 Cycad palm (sago palm)
 Diazepam/oxazepam (orally; cat)
 Halothane
 Herbal supplements: Ayurvedic herbal products (*Atractylis gummifera*, *Callilepis lauerola*), chaparral; Chinese herbal products (Jin Bu Huan, Ma Huang, Dai-saiko-to, germander, greater celandine, green tea, black cohosh, saw palmetto, noni juice, etc.), Herbalife products, Hydroxycut, kava, Pyrrolizidine alkaloids

Herbicides, fungicides, insecticides
 Heavy metals: iron, copper, phosphorus, mercury
 Ketoconazole
 Lomustine (CCNU)
 Manganese (joint supplements)
 MDMA (Ecstasy)
 Metaldehyde snail bait (delayed but reported)
 Methotrexate
 Naphthalene (mothballs)
 Non-steroidal anti-inflammatory drugs/carprofen
 Paraquat
 Pennyroyal oil
 Phenazopyridine (cat)
 Phenobarbital
 Phenols/pine oils
 Phenytoin
 Primadone
 Selenium
 Stanzol (cat)
 Sulfonamide antibiotics
 Thiacetarsamide
 Tetracyclines
 Tree oil/melaleuca oil
 Vitamin A
 Xylitol
 Zinc
 Zonisamide

OTHER

Budd–Chiari-like syndrome
 Copper storage disease
 Heat stroke
 Hepatic lipidosis (cat)
 Portosystemic shunt
 Neoplasia – primary and metastatic
 Hypotension/ischemia
 Trauma (ischemia)

damaging the lipid layer and leading to cell death. It also covalently binds proteins and increases reactive oxygen species levels. This leads to zone 3 centrilobular hepatocellular necrosis. Acetaminophen undergoes enterohepatic recirculation.

Aflatoxin is most commonly produced by *Aspergillus flavus* and *parasiticus* [32,33]. The most common and potent toxin is aflatoxin B1. Dogs can ingest aflatoxin from contaminated dog food, moldy garbage or compost. Cats are more sensitive to aflatoxin, but there are no case reports of affected cats. Protein-bound aflatoxin enters the portal circulation after absorption in the duodenum. Unbound aflatoxin accumulates

in the hepatocyte and is metabolized by cytochrome p450 to aflatoxin 8,9 epoxide. This metabolite affects DNA polymerase and affects protein synthesis, leading to centrilobular necrosis, hepatocellular steatosis (fat accumulation), bile duct proliferation, cholestasis, and fibrosis.

Amanita phalloides mushrooms (death cap) are found in the north-eastern United States, Central and South America, Asia, Australia, Africa and Central and Western Europe. They are predominantly found in the spring, late summer, and autumn. *A. phalloides* contains three main groups of toxins, amatoxins, phallotoxins and virotoxins, with the amatoxin alpha-amanitin being

the most important [34–40]. This inhibits nuclear RNA polymerase II and leads to decreased concentrations of mRNA and decreased protein synthesis, with subsequent cell death. Massive centrilobular hepatic necrosis with vacuolar degeneration ensues. Hepatocytes, crypt cells, and proximal convoluting tubules of kidneys are most susceptible due to their high metabolic rate. There are three phases of toxicity: GI phase with GI signs, which occurs 6–24 hours post ingestion and lasts 12–36 hours; a latent period of about 12 hours; and then the hepatorenal phase during which there is progressive loss of liver and kidney function. Amanitin does undergo enterohepatic recirculation.

Cyanobacteria or blue-green algae are prokaryotic organisms found in ponds, lakes, slow-moving streams, and reservoirs. When there is a high nutrient content (especially nitrogen and phosphorus), the algae bloom or undergo massive replication. It is impossible to distinguish non-toxic from toxic algae. *Microcystis*, *Anabaena*, and *Planktothrix* can produce toxic microcystins. The microcystin toxin is hepatotoxic and must be ingested or aspirated. The toxin is absorbed from the small intestine into the liver to enter hepatocytes. Microcystins inhibit protein phosphatases 1 and 2A, and increase free radical formation, leading to cell lysis and apoptosis [41].

Cycad palm, or sago palm, are plants found in the southern United States and Hawaii. They also occur as houseplants and bonsai arrangements, making their availability more widespread. Of the three toxic compounds produced, the cycasin toxin is predominant and is metabolized by intestinal flora to its active compound, methylazoxymethanol [42,43]. Methylazoxymethanol undergoes enterohepatic circulation and if not metabolized, leads to decreased mitochondrial and ATP activity and decreased glucose-6-phosphatase. This leads to hepatocellular death and marked focal centrilobular and midzonal coagulation necrosis.

Oral diazepam can lead to acute, massive centrilobular necrosis and biliary hyperplasia in cats. It can occur 5–13 days after starting the medication and is thought to be due to the decreased glucuronide conjugation and glutathione deficiency in cats. The exact mechanism is unknown but is thought to be an idiosyncratic reaction [44–46].

Non-steroidal anti-inflammatory drugs (NSAIDs) (see Chapter 133) can lead to liver failure, but GI and renal toxic side-effects are typically seen. Carprofen (Rimadyl) is one NSAID that has been shown to lead to hepatocellular toxicity 5–30 days after initiation of therapy [47,48]. NSAIDs inhibit phospholipase A₂ and cyclo-oxygenase (COX)-1 and -2, leading to decreased prostaglandin production. COX-1 produces prostaglandins essential for renal and GI mucosal blood flow, reduces gastric

acid secretion and stimulates mucus and bicarbonate production by gastric epithelial cells, whereas COX-2 is activated during inflammation. Carprofen is a selective COX-2 inhibitor that should lead to less renal and GI toxicity. Hepatotoxicity from carprofen is thought to be an idiosyncratic, cytotoxic reaction leading to multifocal to extensive hepatocellular necrosis. Labrador retrievers were overrepresented in one study, but all Labradors recovered, as opposed to a 50% mortality rate in other breeds.

Xylitol is a 5-carbon sugar found in many sugar-free and oral care products due to its low glycemic index and ability to prevent caries in people. In dogs, it is absorbed from the GI tract within 30 minutes of ingestion and causes a large dose-related release of insulin. Hypoglycemia can be seen 30 minutes to 12 hours post ingestion. It can also lead to hepatotoxicity and elevated liver enzymes less than 4–24 hours post ingestion. An animal can have one sign of toxicity without the other. The exact mechanism of hepatotoxicity is unknown but there are two proposed theories [49,50]. One is that xylitol leads to hepatic ADP, ATP and inorganic phosphate depletion and the other is that it causes the production of reactive oxygen species during its metabolism. Either leads to centrilobular necrosis.

Leptospirosis is caused by the *Leptospira* spirochete. There are many serovars, with some being more hepatotoxic. Younger dogs are more commonly affected [51]. Animals can be exposed to *Leptospira* organisms in infected urine, via animal bites or through ingestion of infected soil or water. There can also be placental transfer or sexual transmission. Leptospirosis can lead to profound hepatic dysfunction. There can be leptospiral toxins leading to subcellular damage; however, it is thought that hepatotoxicity results from the cholestasis of sepsis rather than direct hepatocellular damage. The degree of bilirubin elevation seems to correspond to the severity of hepatic necrosis [51].

Hepatic lipidosis occurs when the feline hepatocyte accumulates lipid vacuoles. This leads to decreased function of the hepatocyte, and, if severe, liver failure. There is primary or idiopathic and secondary hepatic lipidosis. Secondary lipidosis is due to another disease process leading to anorexia [52].

Portosystemic shunts are aberrant vessels that go from the intestines directly into the systemic circulation, bypassing the liver for detoxification of products of metabolism. Without the portal vein bringing blood from the intestines to the liver, the liver also loses its nutrient supply. This can lead to hepatic atrophy and insufficiency. Many dogs with congenital portosystemic shunts present due to signs of hepatic encephalopathy [9,23,53].

Diagnostic Tests

Any animal presenting with derangements in any of the four major organ systems should immediately have an intravenous catheter placed and a minimum emergency database performed, including packed cell volume, total solids, serum electrolytes, blood glucose, and lactate. A non-invasive oscillometric blood pressure measurement, pulse oximeter reading, and electrocardiogram should also be performed (see Chapter 2). The diagnostic work-up (Box 90.3) for an animal presenting in ALF can be very extensive, depending on the potential for toxin exposure.

Routine diagnostic tests including complete blood count, serum chemistry panel, and urinalysis should be submitted. A complete blood count may reveal a regenerative or non-regenerative anemia, thrombocytopenia, elevated or decreased white blood cell count, target cells, and/or acanthocytes. Values that assess liver function (glucose, albumin, BUN, bilirubin, and cholesterol) should be evaluated. Signs of liver failure include low albumin, low blood glucose, low cholesterol (although cats may have an elevated cholesterol [52]), low BUN (concurrent GI bleeding may increase this) and elevated total bilirubin. A urinalysis should be evaluated for specific gravity pre-fluids if possible, and to evaluate for any cellular or granular casts indicating renal tubular injury, or ammonium biurate or urate crystals indicative of a portosystemic shunt.

Blood typing, cross-match, ammonia levels, bile acids, and a coagulation panel (including fibrin degradation products (FDP) and D-dimers) should be submitted once liver failure is suspected.

More specific tests for coagulation, including thromboelastography, protein C, fibrinogen and/or antithrombin levels, can also be considered. Prolongation of PT/PTT is typically seen, but TEG can reveal a normal or hypercoagulable state. Evidence of disseminated intravascular coagulation may also be present (see Chapter 70).

On triage, a focused assessment with sonography for trauma (FAST) scan should be performed on the thoracic and abdominal cavity to evaluate the presence of free fluid (see Chapter 182).

Chest x-rays should be performed to determine heart and vessel size and to evaluate for pulmonary metastatic disease, aspiration pneumonia, atelectasis, pulmonary infiltrates or pleural effusion. Abdominal radiographs can determine liver size. Abdominal ultrasound should be performed to evaluate liver architecture and any portosystemic shunts, neoplasia, ischemia or decreased blood flow to the liver, the presence of abdominal effusion, and also to evaluate other abdominal organs. If peritoneal effusion is present, abdominocentesis should be performed and fluid analysis and cytology is warranted (see Chapter 186). Ultrasound-guided liver aspirate and/or biopsy can be considered based on ultrasound and

Box 90.3 Diagnostic tests for acute liver failure.

Initial evaluation:

Packed red blood cell volume, total solids, venous blood gas, lactate, glucose, electrolytes (sodium, potassium, chloride, ionized calcium)**
Indirect oscillometric blood pressure**
Pulse oximeter reading**
Electrocardiogram
FAST – thoracic/abdominal

Full work-up:

Complete blood count**
Serum chemistry panel**
Urinalysis**
Ammonia level**
Bile acids, fasting
Arterial blood gas (if signs of respiratory distress/hypoxia)
Urine culture and susceptibility testing
Blood type
Coagulation panel including FDP, D-dimers**
Cross-match
Thromboelastography**
Protein C level
Antithrombin level
Fibrinogen level
Thoracic radiographs
Abdominal radiographs
Abdominal ultrasound
Abdominocentesis, if indicated
Echocardiogram
Leptospirosis serum titers*
Leptospirosis PCR urine/blood*
Liver aspirate/biopsy
Acetaminophen level*
Toxicology screen – blood, gastric contents/vomitus, urine, stool, specific sample of toxin, liver and/or kidney biopsy*
Copper levels – serum, urine*
Blood cultures*
Intravenous catheter cultures*

* Based on clinical suspicion.

** Indicates tests requiring serial evaluations.

FAST, focused assessment with sonography for trauma; FDP, fibrin or (fibrinogen), fibrinogen degradation product; PCR, polymerase chain reaction.

clinical pathology results. Echocardiography can help evaluate cardiac function and volume status.

Leptospirosis titers and/or urine and blood PCR should be performed, if suspected, and appropriate zoonotic precautions taken.

Toxicological testing can be submitted on gastric contents/vomitus, stool, urine, liver biopsy samples, dog

Table 90.1 Biochemical tests and frequency for ALF.

Biochemical test	Frequency	
Emergency database (EDB)	4–6 hours	Electrolytes, PCV, TS
Lactate (if not part of EDB)	4–8 hours	
Blood glucose	2–4 hours	
Urinalysis	12–24 hours	Monitor specific gravity and presence of renal tubular casts
CBC	24 hours	Monitor WBC and platelet counts
Serum chemistry panel	24 hours	Monitor total bilirubin, BUN, liver enzymes
Coagulation panel	12–24 hours or post transfusion	
TEG	24 hours	
Ammonia level	12–24 hours	Depending on neurological status

BUN, blood urea nitrogen; PCV, packed cell volume; TEG, thromboelastography; TS, total solids; WBC, white blood cell.

food samples (if dog food contamination is suspected) or ingested mushroom or plant specimens for the possible toxins (see Chapter 127).

Culture and susceptibility samples on urine, blood, effusion, intravenous or urinary catheter tips should be taken and saved or submitted, if there is concern for infection.

Advanced imaging such as magnetic resonance imaging (MRI) can be considered if the neurological signs are not thought to be due to hepatic encephalopathy. The risks of general anesthesia, as well as the choice of anesthetics, must be considered.

Due to the dynamic nature of ALF, many tests will need to be repeated frequently (Table 90.1).

Emergency Stabilization and Treatment

The main aspects of treatment of patients with ALF include restoration of vascular volume, maintaining arterial blood pressure and systemic perfusion, decreasing ammonia levels if elevated, preventing and treating increased intracranial pressure/cerebral edema, sepsis and multiple organ dysfunction syndrome (Box 90.4). Due to the dynamic nature of these patients, frequent monitoring and reassessments are imperative.

If the patient has recently ingested a hepatotoxic agent, induction of emesis followed by activated charcoal is recommended as long as there are no contraindications

(see Chapter 127). For toxins that undergo enterohepatic recirculation, repeated doses of activated charcoal should be given every 6–8 hours. Hospitalization and monitoring are still recommended, as there still may have been absorption of the toxin.

It is imperative that the animal with suspected hepatotoxicity stops all current medications, not only those known to be hepatotoxic, since there is always the potential for an idiosyncratic reaction. Other methods of decontamination, such as intralipid therapy, hemodialysis, charcoal hemoperfusion, etc., can be considered depending on the toxin (see Chapter 129).

Based on initial triage assessment, initial resuscitation may require both isotonic crystalloids and colloids. One-quarter to one-half of a shock bolus of crystalloids +/- colloids should be started upon triage (see Chapters 167 and 168). Resuscitation should continue until volume status, perfusion parameters and acid–base status have improved, being careful not to fluid overload. Ideally, maintaining the mean arterial pressure (MAP) between 60 and 75 mmHg, in order to maintain cerebral perfusion pressure (CPP) between 60 and 80 mmHg, is recommended [1,2,4,5]. Vasopressor therapy is often required due to the vasodilatory state. Although there is some controversy over which vasopressor is best, norepinephrine is generally the vasopressor of choice in people due to minimal changes in CPP [1–5,19]. Vasopressin is contraindicated if severe intracranial hypertension is suspected. Adrenal cortical insufficiency has been shown in people with ALF. Administration of dexamethasone can be considered if hypotension persists despite volume correction and vasopressor therapy. A change in survival has not been shown in people given corticosteroids [3–5,19].

Blood glucose should be monitored frequently (i.e. every 2–4h) and significant hypoglycemia should be treated with a 0.5 g/kg IV dextrose bolus diluted and given slowly. An addition of 2.5–5% dextrose to the fluids should then be started.

Electrolyte and acid–base disturbances are commonly seen and are associated with a worsening prognosis in people [3–7,10]. Hypophosphatemia is common and should be treated, but hyperphosphatemia can also be seen (see Chapter 110). The presence of metabolic acidosis, hyperlactatemia, hypokalemia, and hyponatremia may be associated with worsening cerebral edema [6,23] (see Chapters 108 and 109).

Signs of infection, sepsis, and/or SIRS are common in people with ALF. These are also associated with worsening coagulopathy and neurological status. The most common foci include the lung, urinary tract, blood, and catheter insertion sites. Prophylactic antibiotics that cover gram-positive, gram-negative, and anaerobic bacteria are recommended if evidence of sepsis is present

Box 90.4 Treatments for acute liver failure.

Acute ingestion of hepatotoxin	Cryoprecipitate 1–2 mL/kg
Induction of emesis	Platelet-rich plasma
Gastric lavage	Packed red blood cells 10–15 mL/kg
Activated charcoal +/– repeated doses	Vitamin K1 0.5–1 mg/kg SC q12–24h
Intralipid therapy	Gastrointestinal protectants
Extracorporeal detoxification	Proton pump inhibitor
Cardiovascular	Omeprazole 0.5–1 mg/kg PO q24h
Restore intravascular volume – crystalloids/colloids	Pantoprazole 1 mg/kg IV q12h
Maintain arterial blood pressure – vasopressors (e.g. norepinephrine 0.05–0.5 µg/kg/min IV CRI)	H2 blocker
Neurological	Famotidine 0.5–mg/kg IV q12h
Hepatic encephalopathy	Ranitidine 0.5–mg/kg IV q12h
Ampicillin 22 mg/kg IV q8h	Prostaglandin analog misoprostol 2–5 µg/kg PO q8h
Metronidazole 7.5 mg/kg IV q12h	Sucralfate 250 mg–1 g PO or slurry q6–8 h
Lactulose orally/enema 1.5 mL/kg diluted to 30% q6–8h	Infection/sepsis
Avoid stimulation/agitation	Start coverage for gram-positive, gram-negative, anaerobic if signs of infection/sepsis post culture and susceptibility samples
Increased intracranial pressure	Cefazolin 22 mg/kg IV q8h
Mannitol 0.5–1 g/kg IV over 20 min	Ampicillin 22 mg/kg IV q8h
Hypertonic saline 3–5 mL/kg over 3–5 min (keep sodium 145–155 mEq/L)	Enrofloxacin 10–15 mg/kg IV q24h (dogs)
Board to elevate head 15–30°	Ceftazadine 40–50 mg/kg IV q6–8h
Minimal neck restraint/avoid jugular venipuncture	Cefotaxime 25–50 mg/kg q4–6h
Maintain oxygenation	Clindamycin 10 mg/kg IV q12h
Avoid glucose and electrolyte imbalances	Metronidazole 7.5–10 mg/kg IV q12h
Sedation – low-dose benzodiazepine, propofol, barbiturates	Hepatoprotectant/antioxidant
Seizures	N-acetylcysteine 140 mg/kg IV loading then 70 mg/kg IV q6h for 4 doses
Low-dose benzodiazepine (midazolam/diazepam 0.1–0.25 mg/kg IV); controversial	S-adenosyl-L-methionine 17–22 mg/kg PO q24h; 40 mg/kg loading then 20 mg/kg q24h dogs; 180 mg q12h for 3 days then 90 mg q12h for 14 days cats
Levetiracetam 60 mg/kg IV loading then 20 mg/kg IV q8h	Silymarin/silibinin 8–20 mg/kg PO divided q8h
Propofol 0.5–1 mg/kg IV then 0.05–0.4 mg/kg/min CRI	Metabolic
Phenobarbital 16 mg/kg IV divided into 4 doses over 12–24h (monitor for need for intubation/ventilation)	Correct electrolyte and acid–base disturbances
Respiratory	Correct hypoglycemia – avoid hyperglycemia
Supplemental oxygen	Enteral/parenteral nutritional support
Mechanical ventilation	Vitamin B complex 1 mL/L of fluids
Antimicrobials (see below)	And/or thiamine 10–20 mg/kg IM/IV/SC
Renal	Nursing care
Restore intravascular volume	Artificial tears OU q6h
Maintain arterial blood pressure	Keep sternal or turn q6h if recumbent
Consider continuous renal replacement therapy	If seizures, keep cage well padded
Hemorrhage	Prevent decubital ulcers if down/recumbent using soft bedding
Fresh frozen plasma 10–15 mL/kg	Maintain aseptic techniques when placing, checking, rewiring catheters
Fresh whole blood 20 mL/kg	Keep coat clean and dry, removing/cleaning/drying any urine or stool on coat

CRI, constant-rate infusion; IV, intravenous; OU, each eye (*oculus uterque*); PO, by mouth (*per os*); SC, subcutaneous.

or there is high suspicion, once culture and susceptibility samples are taken [1–5,10–12,23] (see Chapter 200). Change or de-escalation of antibiotics should occur once culture and susceptibility results return. Nephrotoxic antimicrobials should be avoided.

Elevated ammonia levels and hepatic encephalopathic signs should be treated with ammonia-lowering strategies, if possible, before signs of cerebral edema/increased intracranial pressure ensue. Antimicrobials that inhibit ammonia-producing bacteria and lactulose therapy to interfere with ammonia synthesis and uptake and decrease colonic pH are the two mainstays of treatment in veterinary medicine [6,9–11,22]. Ampicillin (22 mg/kg IV q8h) and metronidazole (7.5 mg/kg IV q12h) are the antimicrobials of choice in small animals. Neomycin can be nephrotoxic and is not used as commonly, but is also effective and carries less risk when given orally. Lactulose, a non-digestible synthetic disaccharide, is controversial in people due to a lack of proven clinical benefit and also due to concerns for abdominal distension pre-liver transplantation [1–3,19]. However, lactulose (1–5 mL/kg diluted to 30%) is commonly used in small animals and can be given as an enema, after a cleansing enema, in patients with depressed mental status. Assessment of the neurological system must be performed every 1–2 hours to monitor for progression of signs.

Worsening neurological signs or concerns of increased intracranial pressure (ICP) should be treated with mannitol (0.5–1 g/kg IV slowly over 20–30 min) [1,2,4–6,10,19] or hypertonic saline (7.5%, 3–5 mL/kg over 3–5 min) (see Chapter 22) [1–5,19,54]. Other treatments include using a board to elevate the head up to 30°, minimal neck restraint/no jugular venepunctures, avoiding glucose and electrolyte imbalances, maintaining oxygenation and sedation. Therapeutic hypothermia is used in people refractory to other methods of decreasing ICP, but this is typically done before liver transplantation [1–4,19].

Propofol or fentanyl constant rate infusions are the drugs of choice in people for sedation and analgesia, respectively. Propofol is thought to decrease cerebral blood flow and cerebral metabolism, thus decreasing intracranial hypertension [19]. Seizures are then treated with low doses of benzodiazepines (this is controversial), levetiracetam (loading 60 mg/kg then 20 mg/kg q8h), propofol (0.5–1 mg/kg IV then 0.05–0.4 mg/kg/min CRI) or phenobarbital (16 mg/kg divided into 4 doses over 12–24h) [9,10,22]. Barbiturates are typically avoided due to decreased metabolism and can necessitate intubation and ventilation. In people, however, barbiturates can be used to decrease ICP if neurological signs are severe. Mechanical ventilation and monitoring of systemic blood pressure are required if CRIs are needed. Flumazenil (0.02 mg/kg IV), a benzodiazepine receptor antagonist, has been helpful in people with severe HE, but this has not been proven in small animals [6,9,22].

Treatment of coagulation abnormalities is recommended only if there is clinical bleeding or an invasive procedure needs to be performed [1–6,9,13,15,22]. However, vitamin K1 (0.5–1 mg/kg subcutaneously once to twice a day) should be started. In people, even those undergoing liver transplantation, the amount of transfusions has majorly decreased and this has been associated with an increase in survival. However, fresh frozen plasma, cryoprecipitate, fresh whole blood, and/or platelet rich plasma (see Chapter 176) should be given if signs of bleeding (GI, cavity, venipuncture sites, or mucosal) occur or before invasive procedures (i.e. central catheter placement, liver biopsy, etc.). The exact target platelet count or clotting times have not been determined. Fresh whole blood or packed red blood cells should be given if the animal has clinical signs attributable to anemia.

Gastrointestinal bleeding should be prevented and/or treated with GI protectants [9,22] such as proton pump inhibitors (pantoprazole 1 mg/kg IV once daily) or H2 blockers (famotidine 0.5 mg/kg IV once or twice a day, ranitidine 0.5 mg/kg IV twice a day). Prostaglandin analogues (misoprostol 2–5 µg/kg orally three times a day) and sucralfate (0.25–1 g orally or as a slurry three to four times a day) can be added unless there are changes in neurological status.

Worsening azotemia, hyperkalemia, and/or anuria may require hemodialysis if non-responsive to correction of volume status and arterial blood pressure (see Chapter 94). Continuous renal replacement therapy (continuous veno-venous hemodialysis) is preferred over intermittent hemodialysis [1,2,4,19]. This has been shown to prevent alterations in blood pressure and intracranial pressure when used in people with ALF. This can also improve ammonia levels and volume overload states.

N-acetylcysteine (NAC) is used to replenish glutathione levels and thus help detoxify hepatotoxins. It has also been shown to have complex antioxidant, cardiovascular and immunological effects [1–3,5,9,19,22,46]. It is used in acetaminophen-induced liver failure, and is also commonly used if the cause is unknown. NAC should be started as soon as possible at 140 mg/kg IV in D5W or orally as a loading dose, then 70 mg/kg IV for four doses every 6 hours.

Cimetidine can be considered in cases of acetaminophen toxicity [29,31]. It inhibits cytochrome p450, leading to decreased formation of NAPQI. However, a recent study showed that adding cimetidine to NAC in patients with acetaminophen toxicity did not improve the hepatoprotective action compared to NAC alone [55]. Cimetidine should be given within the first 16 hours [30].

S-adenosyl-L-methionine (SAMe) is also used to replenish glutathione levels and is an anti-inflammatory and antioxidant [5,9,22,30,31,44]. It is only available

orally, with published doses of 40 mg/kg loading dose followed by 20 mg/kg a day in dogs and 180 mg twice a day for 3 days, then 90 mg twice a day for 14 days in cats or 17–22 mg/kg once daily.

Silymarin (extracted from the seeds of *Silybum marianum* or milk thistle, silibinin the active compound) has been shown to be protective in *A. phalloides* intoxication and is used as a hepatoprotectant for other toxins. Silymarin (8–20 mg/kg PO divided q8h) has membrane-stabilizing effects by inhibiting lipid peroxidation, strong antioxidant effects and it increases glutathione levels. In patients with *A. phalloides* toxicity, it inhibits the uptake of amatoxins into hepatocytes and may stimulate nuclear polymerase A which amanitin inhibits. Penicillin G is used with silymarin in *A. phalloides* toxicity [1,2,5,9,22,34,37].

Denamarin contains both SAME and silibinin. It is available in multiple sizes based on weight.

Nutritional support is imperative and has been proven beneficial in the treatment of patients with ALF. This is especially true for cats with hepatic lipidosis. The initiation and route of nutritional support are very dependent on the cause of ALF, duration of signs prior to presentation (i.e. anorexia for 1 week versus no anorexia) and rapidity of deterioration. Enteral nutrition is superior due to the protective and trophic nature for enterocytes and GI mucosa. This can be achieved with oral, nasoesophageal, nasogastric or esophageal tube feedings. E tubes can deliver higher amounts of calories with fewer side-effects, but require general anesthesia for placement. If there is any contraindication to enteral feedings then total parenteral nutrition should be instituted as early as possible. The amount of protein is typically restricted initially and plant or dairy sources of protein are chosen over meat-based protein [1,2,4–6,10,56].

Liver assist devices [57] or extracorporeal techniques of detoxification such as hemoperfusion with coated charcoal filters, plasmapheresis, or molecular adsorbant recirculating systems (MARS) have been used in the treatment of ALF in people (see Chapter 129). MARS is a non-biological liver assist device that uses albumin dialysis to extract both water-soluble and protein-bound toxins. It has been shown to improve hepatic

encephalopathic signs and hyperbilirubinemia, but an improvement in survival is unproven.

Prognosis

There are no prospective studies in small animals on ALF. There are many case studies or case reports on specific toxicities or causes, with mortality rates varying considerably. There is a recent retrospective study on ALF in dogs [7]. In this study, hyperbilirubinemia and coagulopathy were the inclusion criteria, but not hepatic encephalopathy due to the retrospective nature of the study. The authors found that survivors had a higher ALT, were more likely to maintain a normal albumin level and did not develop ascites or clinical bleeding during hospitalization. The exact cause of death was not discussed, but progression with worsening coagulopathy, encephalopathy, GI and renal dysfunction was rapid. Overall survival was 14%.

In people, the most common cause of death is intracranial hypertension with brain herniation and circulatory failure. It is hard to extrapolate survival rates between people and small animals due to liver transplantation, which increases survival to about 90%, and increased availability to ongoing treatment and liver assist devices. Prognosis and survival are dependent on etiology, acetaminophen and shock having a $\geq 50\%$ survival without transplant, while other etiologies have a $\leq 25\%$ survival without transplant [1]. In people, there are a few prognostic systems (King's College Criteria, Clichy, etc.) used to determine emergent need for liver transplantation and thus poor prognosis. These have not been evaluated in small animals, nor has another system been developed.

Conclusion

Acute liver failure is an uncommon but life-threatening disease seen in small animals. It is characterized by rapid progression of hepatic dysfunction leading to worsening coagulopathy, encephalopathy, and MODS. Early recognition to institute aggressive therapy, including hepatoprotectants, is needed for a positive outcome. Overall survival may still be poor to grave.

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Feeding Tube Complications

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Introduction

Inadequate food intake is a common problem in critically ill patients regardless of the underlying condition. Because malnutrition can occur quickly in these animals, it is important to provide nutritional support, preferably by the enteral route. The goals of nutritional support in these patients are to treat malnutrition when present but, just as important, to prevent malnutrition in patients at risk. Rather than focusing on improving appetite, which is commonly the only attempt at nutritional support, a more appropriate approach would be to simply ensure adequate nutritional intake, by placement of a feeding tube. Feeding tubes commonly used in dogs and cats include nasogastric or nasoesophageal, esophagostomy, gastrostomy, and jejunostomy feeding tubes. The enteral route should be used because it is the safest, most convenient, and most physiologically sound method of nutritional support.

Ensuring the successful nutritional management of critically ill patients involves making an appropriate nutritional assessment and implementing a feasible and effective nutritional plan. Central to the successful recovery of critically ill patients receiving nutritional support is the avoidance of complications, which by themselves could be detrimental to patient well-being but also will lead to feeding interruptions that can contribute to the development of malnutrition. Therefore, the management of these patient involves taking steps to minimize the risk of complications and being able to effectively deal with any complications that may arise related to feeding. This chapter explores the most common complications associated with tube feeding and the contributing factors that are believed to lead to their occurrence.

Complications Associated with Placement of Feeding Tubes

Regardless of the specific feeding tube selected for nutritional support, it is vital that placement of feeding tubes

is first learned with close guidance from an experienced clinician. Complications encountered during placement of feeding tubes include nasal injury, nasal hemorrhage (if tube was nasogastric or nasoesophageal), laceration to esophageal vessel or jugular vein (esophagostomy tube), inadvertent placement of feeding tube into the airways (nasogastric, nasoesophageal, esophagostomy tubes), injury to the trachea (e.g. tracheal laceration), interference with the glottis and injury to nerves leading to Horner's syndrome. Although these complications are uncommon, they can be serious enough to be life-threatening.

One of the most serious complications associated with placement of feeding tubes near the upper airways is inadvertent tracheal intubation. As the placement of nasogastric and nasoesophageal tubes is done on conscious animals, tracheal intubation is a significant risk. This can be avoided by careful technique and confirmation of correct placement within the esophagus or stomach before use. It is also possible that a previously correctly placed tube can be vomited and then inadvertently pass into the trachea. For this reason, it is important to confirm that the tube is still in the correct place prior to each feeding. Confirmation that a feeding tube is not within the trachea can be performed via radiography, fluoroscopy, or measurement of end-tidal CO₂. Instillation of sterile saline into the tube to elicit a cough can also be used to determine if the tube lies within the airways. As the placement of esophageal feeding tubes should be done under general anesthesia, the animal should already have its airway secure via endotracheal intubation. This will prevent the possibility that a feeding tube could be inadvertently placed within the trachea.

Following placement of a tube, it should be secured in place. Nasoenteral tubes (e.g. nasogastric, nasoesophageal) can be secured with single ligatures through pieces of tape near the nares and on the head. For esophagostomy tubes, the incision should be secured with a purse-string suture that apposes the incision stoma around

the tube and then a tension-relieving securing suture (e.g. Chinese finger trap, Roman sandals) is applied. The surgical site should be surgically prepared again prior to suturing as the skin may have become contaminated during tube placement. This will reduce postplacement stoma infection. The tube should be checked for no free movement through the stoma, as movement in and out of the stoma will prevent proper healing of the stoma.

Complications associated with percutaneous gastrostomy tube placement (either endoscopy-guided or blind techniques) include laceration of internal organs (e.g. spleen) with trocar or tube placement device, stomach rupture during insufflation of stomach and malposition of the stomach when secured to body wall. Complications occurring during placement of jejunostomy tubes have not been described, but because of the small diameter of these tubes, overly tight securing sutures (e.g. Chinese finger trap, Roman sandals) may occlude these tubes due to cumulative increase in resistance. It is advised that flow of the tube is checked throughout the procedure of securing it.

Complications Associated with Feeding Tube Use

The most common complication encountered with feeding tubes is tube blockage. For this reason, the consistency of the diet to be fed via a tube should be carefully tested with the tube prior to use. Tube blockages are best prevented by using pure liquid diets when the tube size is smaller than 8 Fr and by flushing the tube following each feeding using a small volume of water (i.e. 5 mL). If a blockage does occur, flushing and applying suction using warm water may dislodge the blockage. Alternatively, a combination of pancreatic enzymes and sodium bicarbonate in water should be injected into the clogged feeding tube and left for a few minutes before attempting flushing again with water to release the blockage [1]. Other compounds such as carbonated drinks may also be attempted but this has been shown to be less effective than water in an in vitro experiment [1].

Vomiting and regurgitation may occur with nasoesophageal tubes but this may be less frequently encountered than with esophagostomy feeding tubes. Patients that are experiencing frequent vomiting as a pre-existing condition prior to tube placement may require an alternative feeding technique or have vomiting controlled with antiemetic therapy before implementation of tube feeding. Regurgitation and reflux esophagitis may occur if the tube is inadvertently placed (across the lower esophageal sphincter) into the stomach. However, this complication is rarely reported and believed to be more common with large-bore feeding tubes such as

esophageal tubes than with narrower nasoesophageal tubes. A recent study comparing complications associated with nasoesophageal versus nasogastric feeding tubes found no difference in rates of complications [2].

Complications associated with esophagostomy feeding tubes are relatively uncommon and typically minor to moderate [3,4]. There was no difference in complication rate or severity in one retrospective study comparing esophagostomy tubes to percutaneous endoscopic gastrostomy tubes [5]. Serious complications such as inadvertent placement in the airway or mediastinum or damage to the major vessels and nerves can be avoided by proper placement technique and verifying tube position radiographically. Midcervical placement minimizes the risk of gagging and partial airway obstruction [3].

A perhaps more serious, albeit less frequent complication is the accidental administration of food into an intravenous catheter (termed “enteral misconnection”) which can cause anaphylactic shock and death. In order to prevent enteral misconnections, all feeding tubes should be clearly labeled. Additional measures to prevent inadvertent feeding into intravenous catheters include the implementation of enteral feeding safety devices. This entails capping every feeding tube with special adaptors that are non-Luer Lock compliant and that can only be connected to special color-coded safety enteral syringes or tubing. These precautionary measures can be cost-effective (i.e. are relatively inexpensive) but can be quite effective in preventing serious, if not fatal, medical errors associated with feeding [6,7]. Although these are not yet adopted universally in human medicine, there is growing pressure in making such measures mandatory [6,7].

Complications Encountered After Placement of Feeding Tubes

As previously mentioned, the use of feeding tubes can be associated with regurgitation and vomiting. In some cases, the tube itself may be vomited, which requires replacement or removal (Figure 91.1). As many critically ill patients are debilitated, the development of aspiration pneumonia or acute pneumonitis is a major concern (see Chapter 37). Management of nausea and vomiting in these patients is important. In patients that develop tachypnea or dyspnea, careful physical examination followed by thoracic imaging may be indicated. Further assessment via pulse oximetry or blood gas analysis may further clarify pulmonary compromise. In patients that are suspected to have aspirated, performance of bronchoalveolar lavage may confirm the development of pneumonia and bacterial culture with antimicrobial susceptibility testing may guide antimicrobial use (see Chapter 200).



Figure 91.1 A complication seen with esophagostomy tubes includes complete displacement of the tube following vomiting, in which the tube tip exits through the mouth. In these cases, the tube should be removed and a new tube placed. Simply flipping the tube back into the esophagus is not recommended as the stoma becomes contaminated with manipulation of the tube. A new stoma is required.

Another common complication associated with placement of esophageal, gastrostomy, and jejunostomy tubes is peristomal inflammation and stoma site infections. Peristomal cellulitis, infection or abscess have been well described [3–5,8] (Figure 91.2). In one study, stoma site complications were noted in 46% of patients with gastrostomy tube placements, but all dogs in this study



Figure 91.2 The tube stoma site should be checked every few days to ensure no infection is present. The picture shows purulent discharge from the stoma site of an esophagostomy tube. This tube should be removed and the wound area cleaned. If a feeding tube is still required, a different site should be used.

had chronic kidney disease which may have resulted in compromised immunity and healing [9]. Peristomal inflammation may be due to suture reactions and can be managed with thorough cleaning and application of topical antimicrobials⁴ while more severe cellulitis or abscessation may require systemic antimicrobial therapy and tube removal [10]. These risks can be minimized by ensuring the tube is secured properly and the stoma site is kept clean and protected [10]. During placement of feeding tubes, it is worth remembering that overly tight purse-string sutures can lead to tissue necrosis at the stoma site and subsequent cellulitis or abscessation.

If the stoma site is found to have severe infection, it is advised that the tube be removed and the infected site cleaned although debridement may not be required as adequate drainage is usually encountered. A bacterial culture with antimicrobial susceptibility testing is recommended. If the patient still requires tube feeding, an alternative feeding tube should be considered. Although not commonly done, esophagostomy tubes can be placed on the right side (as opposed to the recommended left side of neck) in cats and small dogs. In larger dogs, it may not be possible to place esophagostomy tubes on the right side.

In terms of metabolic complications associated with feeding, a very rare but potentially serious complication may be seen in cases of severe starvation (i.e. weeks of complete anorexia) in cats, whereby refeeding can trigger severe metabolic derangements. This so-called refeeding syndrome is thought to result from rapid shifts of key intracellular electrolytes (e.g. potassium, phosphorus, and magnesium) from the intravascular to intracellular space, mediated by a surge of insulin following introduction of carbohydrates. Although there is no definitive strategy to prevent its occurrence or predict which patients may develop refeeding syndrome, the most recommended feeding strategy is to first address fluid and electrolyte abnormalities, consider supplementation with thiamine and phosphorus before initiating a very slow and gradual introduction of low carbohydrate feeding (e.g. 10% of resting energy requirements on the first few days). For further information on refeeding syndrome, the reader is referred elsewhere [11].

Conclusion

With the recognition that nutrition support is an important aspect of critical care, patients with decreased food intake should be managed with assisted enteral nutrition. The placement of feeding tubes is the most effective way to initiate enteral feeding. As with any intervention in the critical care patient, complications may arise. Complications may arise during placement, or

develop following use and placement of feeding tubes. Although the risk of these complications can be reduced with proper planning, good technique, and equipment, the clinician should be aware of the development of

complications and act expediently to deal with them. With good management, disruption to feeding schedule can be minimized and the benefits of enteral nutrition on patient outcome can be appreciated.

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Anorectal Disease

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Introduction

Anorectal disease is a less common but potentially life-threatening cause of emergency room visits in dogs and cats. Perforation, prolapse, anal sac disease, rectal neoplasia, and perianal fistulae are the most frequently encountered anorectal abnormalities for the small animal veterinarian. Rapid recognition of emergent diseases affecting the anorectal region may prove life-saving.

Anatomy

The rectum begins at the pelvic inlet and ends at the level of the external anal sphincter where the anus begins, generally ventral to the second or third caudal vertebra. The majority of the rectum is within the peritoneal cavity, which extends well into the pelvic canal. The peritoneal reflection extends to the level of the pelvic diaphragm which is composed of the coccygeus and levator ani muscles that support the caudal rectum. The caudal rectum and anus are retroperitoneal. The caudal rectal artery supplies the majority of blood to the canine rectum; the middle and caudal rectal arteries supply the cat's rectum. The anal sacs sit between the external and internal anal sphincters. The external anal sphincter is innervated by the caudal rectal branches of the pudendal nerves in both species.

Perforation

Perforation is the most serious emergency affecting the rectum and anus. Perforation occurs secondary to penetrating trauma, usually from projectiles such as bullets or arrows or from bite wounds. Perforations from foreign bodies, and those associated with pelvic fractures, enemas, colonoscopy, and biopsies are less common.

Rectal perforation is a life-threatening emergency that can be overlooked in a patient with multiple traumatic injuries. It should be suspected in any animal with penetrating injuries affecting the pelvic, thigh, or perineal regions, and in animals with pelvic fractures. Leakage of rectal contents into the peritoneal or retroperitoneal spaces rapidly leads to bacterial proliferation and activation of multiple inflammatory pathways. Fecal material and mucin worsen peritonitis. Blood and avascular tissue provide an excellent medium for bacterial growth. These factors complicate and potentiate tissue injury associated with gunshot or bite wounds. Concurrent injury to the urethra results in urine leakage and potentially severe electrolyte and acid–base abnormalities.

Clinical signs vary depending on the cause and location of the perforation and severity of the associated injuries. Animals with gunshot or bite wounds can be variably depressed, lethargic, and painful from these “primary” injuries alone. Animals may present with varying degrees of shock and require immediate treatment to restore perfusion (see Chapters 152 and 153). Injuries affecting the central nervous system, respiratory system, and cardiovascular system are the most immediately life threatening (see Chapter 2).

Animals with perforations secondary to colonoscopy, colonic biopsy or enemas may have few initial clinical signs, despite the presence of a pneumoperitoneum (Figure 92.1). Affected animals may show signs of abdominal distension, especially if the colon is insufflated after the perforation has occurred. Fluid introduced into the peritoneal cavity disperses throughout the entire cavity in as little as 15 minutes. Sealing of the bowel or localization of the leak by the omentum and other bowel loops is unlikely. Animals will develop clinical signs as peritoneal contamination worsens and peritoneal inflammation progresses (see Chapter 87).

A diagnosis of anal or rectal perforation can be suspected based on the location of bite wounds or the path of a projectile injury. The peritoneal reflection extends

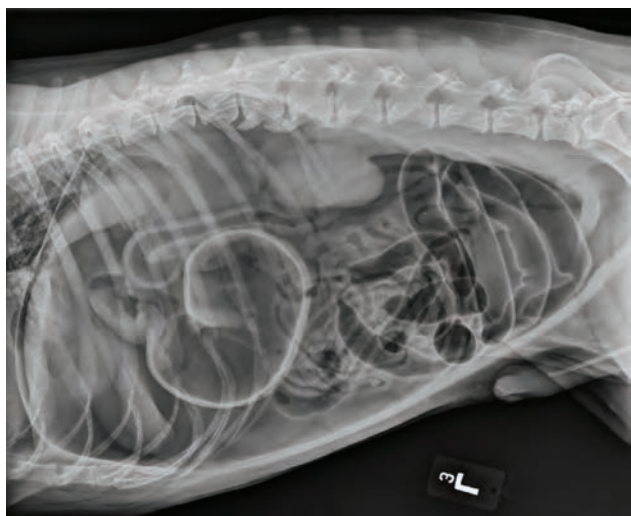


Figure 92.1 Pneumoperitoneum from colonic perforation secondary to colonoscopy in a dog.

quite caudally into the pelvis so even caudal rectal perforations can be associated with subsequent peritonitis.

After an initial emergency assessment of a critical patient is performed and resuscitation is commenced, a more thorough physical examination should include evaluation of the integrity of the rectum and anus. Probing of penetrating wounds, especially bites, is unreliable, as the probe does not always take the path of the original injury. Initially, a gentle digital rectal examination is performed. Any defect or palpable irregularity of the rectal wall increases suspicion for rectal perforation. A positive contrast enema using a sterile, iodine-based contrast agent injected through a Foley catheter in the distal rectum will confirm the perforation.

The presence of peritonitis can be assessed using ultrasound to scan the abdominal cavity and retrieve samples of fluid for analysis (see Chapters 87 and 182). Peritoneal fluid from animals with peritonitis will generally contain degenerative neutrophils and intra- and extracellular bacteria. A peritoneal fluid total nucleated cell count greater than 13 000 cells/ μ L was 86% sensitive and 100% specific for peritonitis in dogs and 100% sensitive and specific in cats [1]. The peritoneal fluid glucose and lactate concentrations should be measured and compared to those in the peripheral blood. A peritoneal fluid glucose concentration more than 20 mg/dL lower than that of peripheral blood was 100% sensitive and specific for peritonitis in dogs and 86% sensitive and 100% specific in cats. A peritoneal fluid lactate concentration 2 mmol/L higher than that of peripheral blood was 100% sensitive and specific for peritonitis in dogs but did not reach significance in cats.

Initial treatment of the patient with multiple traumatic injuries involves rapid patient evaluation, elimination of immediate threats to life, and initiation of resuscitation (see Chapter 2). A diagnosis of rectal or anal perforation is most often made during a more thorough examination following initial resuscitation measures. Septic shock is a likely sequel to rectal perforation, especially if presentation is delayed and there is substantial concurrent damage to surrounding tissues (see Chapter 159). Intravascular volume expansion with isotonic crystalloid fluids or a combination of crystalloids and synthetic colloids and blood products is required (see Section 5). The rate of fluid administration is dependent on the severity of the perfusion deficit and simultaneous injuries, for example, pulmonary contusions. Fresh or stored packed red blood cell transfusions may be required in cases with severe hemorrhage associated with either the rectal perforation injury (i.e. femoral or pudendal vessel injury) or other concurrent injuries (see Chapter 176). Treatment for septic shock is covered in more detail in Chapter 155. Broad-spectrum, bactericidal antimicrobials effective against gram-positive, gram-negative, and anaerobic bacteria are administered intravenously (see Chapter 200).

It is often not possible to completely stabilize animals with rectal perforation and sepsis until the underlying source or sources of contamination are addressed. An initial aggressive resuscitation and stabilization effort should be promptly followed by anesthesia and surgical exploration of the wounds and the abdomen if peritonitis is present. Surgical wound debridement begins superficially and extends sequentially into deeper tissue planes. Any tissues that do not actively bleed when incised are removed. The approach to the anal or rectal lesions depends on the location of the perforations. Caudal lesions can be accessed via a perineal approach. More cranial lesions can be accessed via a dorsal approach to the rectum. An incision is made from one ischiatic tuberosity dorsal to the anus and then to the opposite ischiatic tuberosity. The rectococcygeus muscle is transected. Placement of a urethral catheter aids in identifying the urethra during dissection of the ventral aspect of the rectum. Lesions of the cranial rectum are accessed via a ventral midline laparotomy combined with a pubic symphysiotomy.

The rectal and anal lesions are debrided to healthy bleeding tissue and sutured using 3/0 or 4/0 PDS in a simple interrupted, appositional suture pattern. In cases with rectal perforation and peritoneal contamination, two approaches may be necessary, one to access the rectal lesion(s) for repair and a second to allow copious lavage of the peritoneal cavity. When an abdominal approach is used, the omentum is employed to provide additional lymphatic and vascular support to the rectal repair.

Once the rectum or anus is repaired, the surgeon must address other projectile injuries and bite wounds (see Chapter 166). Once they are debrided back to healthy bleeding tissue, management options include primary closure with or without a drain, delayed primary closure, or leaving the wounds open to heal by second intention. Each set of wounds should be judged individually but in general, bite wounds or projectile injuries with associated rectal perforation should be left open initially because of the level of tissue damage and contamination.

Rectal Prolapse

Rectal prolapse usually occurs in dogs because of tenesmus secondary to anorectal, colonic, or, less commonly, urogenital disease. Rectal prolapse is less common in cats. Gastrointestinal parasitism, protozoal infection, colorectal neoplasia, and perineal hernia in older male dogs are the most common underlying causes. Foreign bodies, urinary calculi, and dystocia are less common causes. Prolapsed tissue becomes edematous and swollen as lymphatic drainage and venous return from the prolapsed segment are compromised. Prolonged venous stasis can lead to mucosal and eventually full-thickness necrosis of part or all of the prolapsed segment.

Affected animals present with a cylindrical rectal segment of variable length protruding from the anus (Figure 92.2). The appearance and health of the prolapsed segment depend on the severity and duration of the prolapse and self-trauma, if present. A rectal prolapse must be differentiated from a colonic or small intestinal intussusception protruding through the anus. A blunt probe or lubricated gloved finger is passed between the protruding tissue and the anus. Passage of an instrument or finger is not possible in animals with a rectal prolapse as

the prolapsed tissue converges with the anus. In animals with an intussusception, the instrument can easily be passed for some distance aborally.

A thorough history is obtained and a complete physical examination is performed on the animal. This should include careful abdominal and rectal palpation to detect possible causes of persistent tenesmus. Additional diagnostic tests, including a complete blood count, biochemical and electrolyte profile, fecal screen for parasites and protozoa, urinalysis, abdominal radiographs, and abdominal ultrasound may be necessary to diagnose an underlying cause of the prolapse. Gastrointestinal parasites do not shed eggs continuously, so at least three negative fecal flotation tests should be performed and the animal should be dewormed prophylactically.

Initial management of a prolapse with viable, healthy bowel wall involves treatment of the underlying cause, reduction of the prolapse under general anesthesia, and placement of a purse-string suture in the anus. The suture should be tied to occlude approximately 50% of the lumen of the anus and left in place for 3–5 days. An epidural anesthetic may be useful to prevent straining for the first 6–12 hours after recovery. In the author's experience, manual reduction and placement of a purse-string suture is unlikely to be successful in dogs with rectal prolapse that occurs after repair of a uni- or bilateral perineal hernia. In these dogs and in animals with recurrent rectal prolapse with viable tissue, a colopexy is the most effective treatment (Figure 92.3).

The animal is anesthetized and the ventral abdomen is clipped and prepared for aseptic surgery. A caudal ventral midline laparotomy is performed and the descending colon identified. The descending colon is gently pulled cranially while a non-sterile assistant reduces the



Figure 92.2 Rectal prolapse secondary to parasitism in a young dog. The rectal segment is healthy and does not require resection.

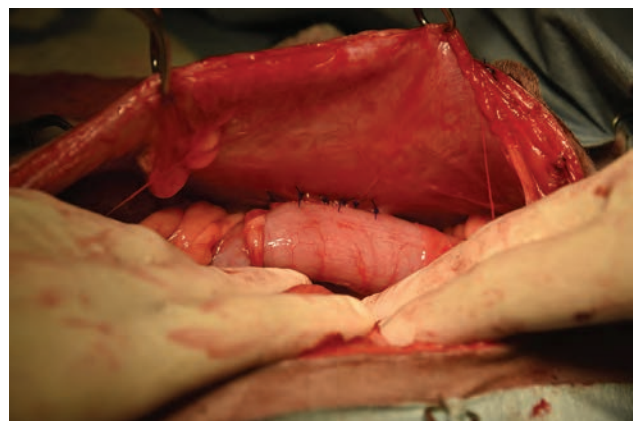


Figure 92.3 Colopexy performed to treat recurrent rectal prolapse in a dog. The colon is gently pulled cranially while the rectal prolapse is reduced by a non-sterile assistant. The descending colon is sutured to the left body wall.

rectal prolapse externally. The colon is held cranially and sutured to the left lateral body wall. Both incisional and suture-only colopexies have been reported [2]; both are effective. Whichever technique is used, the surgeon should attempt to avoid penetrating the colonic lumen as abscessation of the suture line may ensue.

Rectal resection and anastomosis is performed if the prolapsed rectal tissue is devitalized. The animal is anesthetized and an epidural anesthetic is performed. The animal is placed in sternal recumbency on a rectal stand. A syringe is placed in the lumen of the prolapse. Four full-thickness stay sutures are placed at 12, 3, 6, and 9 o'clock in the prolapse close to the anus. Both layers of the prolapse are incised 120–180° initially through visibly healthy tissue. The stay sutures prevent retraction of the tissues once the incision is made. The incised edges are sutured with a single layer of single interrupted sutures of 3/0 or 4/0 monocryl or PDS, depending on the size of the animal and thickness of the prolapsed tissue. The stay sutures are then removed and any remaining prolapse is reduced. Strictures, incontinence, dehiscence, leakage, and prolapse recurrence are potential complications.

Other Diseases

Anal Sac Diseases

The anal sacs are located at the 4 and 8 o'clock positions between the internal and external anal sphincters. Anal sac diseases occur more often in dogs than cats. Although not true emergencies, anal sac diseases are common reasons for owners to have their pets evaluated. Biting or licking at the anal area, tenesmus, pain on defecation, and scooting are all clinical signs indicating potential anal sac disease. One or both anal sacs may be impacted or infected, or may abscess and rupture. Impacted anal sacs are distended; palpation and expression via rectal examination is generally uncomfortable for the animal but not severely painful. Secretions from impacted anal sacs are generally a gray or gray-brown color. Infected anal sacs are generally more painful on rectal palpation and secretions are blood tinged and may contain purulent material. Infected anal sacs may rupture, resulting in marked swelling of the surrounding tissue, abscessation, and opening of one or more draining fistulae. Ruptured anal sacs should not be removed until after the associated inflammation has subsided to prevent damage to the external anal sphincter muscle and possibly the caudal rectal nerve(s). The abscessed area is flushed and cultured and the dog treated with systemic antibiotics. In some cases, the abscess will resolve and not recur; if clinical signs of anal sac disease persist or if abscessation recurs, anal sacculotomy is indicated.

Anal sac neoplasia is also not a true emergency, but is often overlooked in emergency cases if a thorough rectal examination is not performed. Apocrine carcinomas of the anal sacs are malignant tumors and can metastasize to the regional hypogastric and iliac lymph nodes and, less commonly, the lumbar vertebrae and lungs. Many of these tumors (25–90%) can produce a substance similar to parathyroid hormone, resulting in a paraneoplastic syndrome of hypercalcemia and hypophosphatemia and clinical signs of polydipsia and polyuria (see Chapter 73). The diagnosis of an anal sac tumor can be strongly suspected based on a thorough rectal palpation. Tumors can be large and completely efface the affected anal sac or can be small and feel like a pea attached to the cranial aspect of the anal sac. Rectal palpation should also include an evaluation of the hypogastric and iliac lymph nodes; palpable lymph node enlargement indicates likely metastatic spread. Further investigation includes a complete blood count, serum biochemical analysis, thoracic and abdominal radiographs, and abdominal ultrasound.

Rectal Neoplasia

Rectal tumors are a potential cause of tenesmus and hematochezia [3]. Tumors can involve the anus, rectum, or colon and can be benign (adenomas, also sometimes called polyps or adenomatous polyps) or malignant (adenocarcinoma, carcinoma). Tumors may cause constipation and also rectal prolapse secondary to severe tenesmus. In some instances, the tumor may protrude through the anus. The diagnosis may be suspected based on palpable masses or irregularities on rectal examination. Confirmation of the diagnosis requires a biopsy of the mass. This is often obtained during colonoscopy to evaluate the extent of the disease, decide on the likelihood of complete resection and surgical approach, and evaluate the large intestine for other masses. Appropriate investigation and staging of rectal tumors includes a complete blood count, serum biochemical analysis, thoracic radiographs, and abdominal ultrasonography.

Perianal Fistulae

Perianal fistulation is a condition seen predominantly in German shepherds where the perineal region is affected by multiple draining tracts. True fistulae between the rectum or anus and the perineal skin are rare. Although not a true emergency, these cases present to emergency clinics because of tenesmus, bloody discharge on the perineum, dyschezia, and constipation. Tenesmus and pain are particularly severe when the anus and distal rectum are severely affected by the disease.

The cause of this disease is unclear but evidence suggests an immune-mediated etiology [4]. Histology of

canine perianal fistula tissue is similar to humans with Crohn's disease and the condition often responds well to immunosuppressive treatment with cyclosporine. The diagnosis can often be made from the gross appearance of the lesions. A careful digital rectal examination, often requiring sedation, is performed to assess involvement of the anal sacs, anus, and rectum. Initial treatment includes oral cyclosporine (5 mg/kg PO q12h) and

a hypoallergenic diet [5]. Cyclosporine "trough" blood levels should be measured 2–4 weeks after commencing cyclosporine treatment to ensure adequate drug plasma concentrations. Blood is drawn immediately before administering the animal's morning dose of medication. Concurrent conditions, such as exocrine pancreatic insufficiency or inflammatory bowel disease, can inhibit adequate cyclosporine uptake.

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Constipation

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Introduction

Constipation is defined as infrequent, incomplete or difficult defecation, usually associated with dry, hard feces. If not treated appropriately, it can lead to obstipation which is severe constipation that is refractory to treatment and indicative of a permanent loss of function [1]. Constipation can occur in dogs and cats of any signalment, but is more common in the feline population.

Constipation, when considered simply, occurs due to partial obstruction (mechanical or functional) or voluntary lack of defecation (such as secondary to pain). In many cases constipation is simply a result of dehydration leading to dry feces as the body attempts to absorb excess water via the colon. While accounts of dehydration leading to constipation in the veterinary literature are purely anecdotal, even mild dehydration has been shown to cause constipation in humans. Once fecal water content falls below 75%, further small decreases in water content result in relatively large increases in stool viscosity [2]. The dry feces become difficult to pass due to partial mechanical obstruction and associated discomfort. Appropriate assessment of hydration status and treatment of dehydration are essential first steps in the management of any constipated patient.

While most descriptions of constipation in the veterinary literature focus on recurrent constipation or obstipation, patients will often have one or two isolated bouts of constipation without recurrence. Many first-time cases of constipation can be simple diagnoses, such as secondary to dehydration or ingestion of foreign material. In such cases, constipation may not recur. However, repeated episodes of constipation warrant a thorough diagnostic approach and client education to prevent progression to obstipation. An extensive list of differential diagnoses, such as that shown in Box 93.1, should be considered for all cases. Unfortunately, management of constipation, especially in the emergency setting, is an

Box 93.1 Causes of constipation.

Dehydration	Functional obstruction
Chronic renal failure	Idiopathic megacolon
Diabetes mellitus	Neuromuscular dysfunction (e.g. sacral spinal cord deformity of Manx cats, dysautonomia)
Hyperthyroidism	Electrolyte imbalance ($\downarrow K^+$, $\uparrow Ca^{++}$, $\downarrow Ca^{++}$, $\downarrow Mg^{++}$)
Vomiting/diarrhea	Metabolic disease (hypothyroidism, obesity)
Inadequate access to water	Drugs (opioids, diuretics, barium, phenothiazines, anticholinergics, antihistamines, iron, sucralfate)
Mechanical obstruction	Avoidance
Foreign material (bones, hair, cat litter, etc.)	Behavioral
Neoplasia	Change in environment
Rectal stricture	Soiled litterbox
Perineal hernia/rectal diverticulae	Decreased activity
Thickened colonic wall (neoplasia, inflammation)	Hospitalization
Extraluminal mass	Painful defecation
Pelvic fracture	Proctitis
Congenital anorectal disorders (e.g. atresia)	Perianal fistulae
Prostatic disease (mass, hypertrophy, cyst)	Anal sac disease
	Orthopedic disease

area where evidence for best practice in veterinary medicine is lacking.

History

Most pet owners will recognize constipation. Common clinical signs include decreased frequency of defecation,

increased frequency of attempts to defecate (trips to litter box for cats, trips outdoors for dogs), decreased stool volume, firm or dry stool, straining to defecate or vocalization during defecation. Rarely, patients may present for diarrhea due to their ability to pass only small amounts of colonic liquid around an obstructive fecal mass. Patients may also present for vomiting, often associated with straining to defecate. Straining to defecate in cats is easily confused with straining to urinate, and vice versa. Some cats presented for constipation may have lower urinary tract disease or urethral obstruction, while some presented for lower urinary tract disease may have constipation.

Physical Examination

Physical examination of the constipated patient should initially focus on assessment of hydration status and the severity of colonic distension and impaction. More focused examination to determine the underlying etiology should focus on neurological, orthopedic, perineal, and rectal examination.

The presence and severity of colonic impaction can be subjectively assessed by abdominal palpation in most patients. However, this may not be possible in obese or large dogs. The degree of colonic distension and the characteristics of impacted stool (soft versus firm versus hard) will help guide strategies for disimpaction of fecal matter. Abdominal palpation may also reveal lesions causing mechanical obstruction cranial to the pelvic inlet, such as a mass or foreign body.

Orthopedic pain may prevent an animal from defecating normally, leading to constipation. Thorough orthopedic examination is indicated to identify such a problem, particularly hip or stifle disease. The most commonly described orthopedic disease leading to constipation is pelvic fracture causing a narrowed pelvic canal, which has been well reviewed in cats [3–5]. Orthopedic examination findings in cats with pelvic fracture(s) may include pain on palpation of the hips and pelvis. Many cats with pelvic fractures have concurrent abnormalities due to the force of trauma required to fracture the pelvis, such as sacral fracture, coxofemoral luxation or femoral fracture [6]. Other signs of trauma, such as contusions, are often absent because they have resolved by the time the patient is presented for constipation.

A complete neurological examination should be performed in all constipated patients. Spinal cord lesions in the sacral segments (and possibly caudal lumbar) may lead to fecal retention and progressive constipation. One example is Manx cats with sacrocaudal dysgenesis that have been reported to develop megacolon [7,8]. Cats with this syndrome may show paraparesis, pelvic limb

ataxia with hyporeflexia, urinary incontinence, decreased anal sphincter tone and reflexes, or altered nociceptive responses in the perineal area and possibly pelvic limbs [9]. Similar neurological examination findings are present with other etiologies of sacral spinal cord disease.

Rectal and perineal examination should be performed in all constipated patients. However, rectal examination may be challenging in cats, small dogs, and fractious patients. For patients that will not tolerate rectal examination, the use of sedation should be strongly considered if the animal has recurrent or refractory constipation (see Chapter 192). Assessment of anal tone should always be evaluated before sedation. Rectal examination should focus on finding causes of mechanical obstruction such as intraluminal or extraluminal masses, strictures, or a narrowed pelvic canal secondary to previous fracture. The prostate should be palpated, if possible. Dorsal pressure allows for the assessment of lumbosacral pain. Perineal hernias may be identified, though they are more likely to be the result of chronic tenesmus rather than the cause of constipation. Perineal examination allows evaluation of perineal reflexes, external masses, wounds or fistulae. Anal sacs may be evaluated for masses or abscesses.

Diagnostics

Routine laboratory testing may be helpful in confirming the presence of dehydration and may identify underlying causes of constipation. Complete blood count, serum chemistry, and urinalysis should be performed in all patients with recurrent constipation. In addition to providing information regarding hydration status, these will assess for electrolyte abnormalities that may be contributing to constipation (see Box 93.1). They may also give clues to underlying diseases that may be responsible for dehydration. Thyroid function testing should be considered for patients in whom there is a clinical suspicion for hyper- or hypothyroidism.

Abdominal radiographs are a useful imaging modality in the emergency setting. They should be performed in all patients with recurrent constipation. The radiographic view should extend far enough caudally to include the entirety of the pelvis and colon. These serve to screen for causes of mechanical obstruction such as pelvic fracture or mass lesions. They can also provide information regarding the degree of colonic impaction and distension, which may prove useful in determining treatment and prognostic information. A maximal colonic diameter greater than 1.48 times the length of the L5 vertebral body is suggestive of megacolon in cats, though there is significant overlap of the maximal colon diameter between constipated cats and normal cats [10].

Treatment

Management of constipation in the emergency setting must be tailored to the individual patient. The approach to the patient with its first episode of constipation will be different from the approach to the patient with recurrent constipation. The severity of constipation will affect the nature of the treatment plan. The components of treatment include establishing proper hydration, disimpaction of feces, maintenance therapy, and treatment of the underlying cause. Ultimately, treatment of the underlying cause, if identified, is essential to preventing recurrence. In patients for whom an underlying cause is not identified, maintenance therapy will likely be required to prevent recurrence. Commonly used drugs and dosages for both disimpaction and maintenance therapy in veterinary medicine are shown in Table 93.1.

Disimpaction of Feces

Disimpaction of feces may be performed by use of rectal enemas or oral laxative therapy. Patients should be

rehydrated, if necessary, prior to any disimpaction attempts. In human pediatric medicine, there is no consensus regarding whether oral or rectal disimpaction is superior [11]. Oral disimpaction has the advantages of being less invasive and clearing the entire colon. Rectal disimpaction provides more immediate relief to the patient, though is generally less well tolerated. Disimpaction protocols in human pediatric medicine aim to clear the colon over 3–7 days [11]. Oral disimpaction using polyethylene glycol (PEG) 3350, a large molecular weight water-soluble polymer which works as an osmotic laxative, has a 95% success rate in children when used at 1–1.5 g/kg per day over 3 days [12]. Oral PEG 3350 has similar disimpaction rates to daily enemas with diocetylsulfosuccinate sodium (DSS) in children [13].

Enemas have historically been the preferred choice for disimpaction in veterinary medicine. Commonly used enemas include warm water (with or without petroleum jelly) and DSS (see Table 93.1). Note that sodium phosphate enemas should not be used as they may cause severe electrolyte derangements which may be fatal [14]. More recently, an oral approach to disimpaction of feces

Table 93.1 Commonly used therapeutics for management of constipation in veterinary medicine.

Drug	Dose/route	Notes
Disimpaction		
Warm water (+/- petroleum jelly) enema	10–20 mL/kg per rectum	
DSS enema 250 mg/12 mL gel	6–12 mL per rectum for cats and small dogs; 12 mL per rectum for medium and large dogs	
PEG 3350 (60 mg/mL solution)	6–10 mL/kg/h via NE tube	Median time to effect 8 h
Maintenance		
<i>Fiber supplements</i>		
Psyllium	1–4 tsp per meal	Approximately 6 g fiber per TBSP; adjust dose to achieve 2–3 soft, formed stools per day
Canned pumpkin	1–4 TBSP per meal	Approximately 0.3 g fiber per TBSP; adjust dose to achieve 2–3 soft, formed stools per day
<i>Osmotic laxatives</i>		
PEG 3350 granules	0.25–1.0 g/kg/day PO, divided q 12 h (1/16–1/4 tsp/kg/day)	Odorless, tasteless, easily added to food; adjust dose to achieve 2–3 soft, formed stools per day
Lactulose	0.5–1.5 mL/kg PO q 8–12 h	Adjust dose to achieve 2–3 soft, formed stools per day
<i>Colonic prokinetics</i>		
Cisapride	0.1–0.5 mg/kg PO q 8–12 h	5HT ₄ agonist
Ranitidine	1–2 mg/kg PO q 12 h	Acetylcholinesterase inhibitor
Misoprostol	2–5 µg/kg PO q 8–12 h	Only evaluated <i>in vitro</i>
Erythromycin	0.5–1 mg/kg PO q 8 h	Motilin agonist; effective in dog colon only <i>in vitro</i>

BID, twice a day (*bis in die*); NE, nasoesophageal; PO, by mouth (*per os*); TBSP, table spoon; TID, three times a day (*ter in die*).

in a small number of constipated cats has been described [15]. PEG 3350 in oral solution (60 mg/mL) was infused via nasoesophageal (NE) tube at a rate of 6–10 mL/kg/h. Significant defecation occurred in 5–24 hours (median 8 hours). While this technique appears to be effective, more data are required before it can be strongly recommended.

Some patients with severe obstipation will be refractory to oral and rectal disimpaction strategies. Manual disimpaction under general anesthesia will be required for these patients.

Maintenance Therapy

Maintaining proper hydration will help to limit episodes of constipation, especially in patients with underlying diseases that predispose to dehydration. Management of any underlying condition is the primary goal. One strategy that may be useful for maintenance of hydration is increasing water intake by increasing water content of the diet (feeding canned food or adding water to dry food) or providing enticing water sources (such as fountains for cats that prefer running water). In some patients, provision of subcutaneous fluids at home may be necessary.

Increasing dietary fiber content is the first line of maintenance therapy for dogs and cats with recurrent constipation. This is considered the starting point for maintenance therapy in human medicine as well [11]. Fibers are dietary components which cannot be degraded by mammalian digestive enzymes [16]. Instead, they are fermented by bacteria in the colon which results in production of short chain fatty acids (SCFA). SCFA have beneficial effects on colonic cell growth and motility. Fibers can be classified via their solubility in water (soluble versus insoluble) or via their fermentability by bacteria. In general, soluble fibers are more highly fermentable than insoluble fibers. The more soluble and fermentable fibers will produce large quantities of SCFA and decrease fecal bulk. The insoluble and poorly fermentable fibers absorb water and result in increased fecal bulk and softer stool, but result in little production of SCFA.

Dietary fiber may be increased by adding supplemental fiber to the animal's normal diet. Common sources of added fiber include psyllium (available in several over-

the-counter products) and canned pumpkin. While pumpkin may be more readily accepted by patients, it is inferior to psyllium as a fiber supplement. Several veterinary prescription diets are available with higher fiber content compared to maintenance diets. Little evidence is available to guide fiber strategies in veterinary medicine, but a psyllium-enriched dry diet is an effective treatment option for many cats with recurrent constipation [17]. However, animals with recurrent, severe constipation or obstipation may benefit from a low-fiber, low-residue type diet.

Oral laxative therapy may be used as an initial maintenance therapy or added for patients that do not respond to an increase in dietary fiber content. The most commonly used oral laxatives in veterinary medicine are lactulose and PEG 3350. Evidence in human medicine shows that PEG 3350 has superior efficacy to lactulose [11,18]. PEG 3350 has been shown to be palatable and effective in normal cats with no adverse effects [18]. Cats achieved soft, formed stools on doses of 0.8–3.8 g/day (approximately ¼ tsp to 1 tsp per day). With such a wide range of effective dosages, therapy must be tailored to the individual patient (see Table 93.1). Due to the ease of administration, PEG 3350 is the author's preferred oral laxative for use in dogs and cats, though there are no data comparing efficacy of different laxatives in veterinary medicine.

In patients that are suspected of having a colonic motility disorder (such as idiopathic megacolon of cats), colonic prokinetic agents are often necessary. Cisapride is the colonic prokinetic of choice [19], but other options are available (see Table 93.1).

Prognosis

The long-term outcome for the patient with constipation will vary widely depending on the underlying cause. Some patients will suffer from a single bout of constipation, and it will never recur. Others will have a lifelong struggle with recurrent episodes of constipation and require lifelong maintenance therapy. Most cases of constipation can be successfully managed medically, though surgical intervention may be necessary for animals with mechanical obstruction and some cats with idiopathic megacolon [3–5,20].

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F. Urogenital Disorders

Acute Azotemia

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Introduction

Azotemia is an increase in the concentration of nitrogen-containing substances in the blood, primarily BUN and creatinine. Since BUN and creatinine are both nitrogen-containing compounds, an increase in either compound by itself is therefore defined as azotemia. While azotemia is defined by any increase in BUN and/or creatinine, the term *uremia* is used to describe more severe azotemia, when adverse clinical manifestations are present. In current practice, BUN and creatinine are the most commonly measured “uremic toxins” or substances in the blood that are increased when the glomerular filtration rate (GFR) is compromised; however, these are relatively benign and non-toxic substances that act as surrogate markers for many other unmeasured uremic toxins.

Azotemia can be subcategorized into prerenal (or volume-responsive), intrinsic renal, and postrenal mechanisms. Azotemia, as traditionally defined by BUN and creatinine concentrations outside their defined reference ranges, does not occur until approximately 75% of kidney function has been impaired. Using this definition, many patients with significant kidney injury will not be diagnosed until late in their disease process once they have developed acute renal failure (ARF). As an example, a patient could have functional loss of an entire kidney and creatinine measurements could still be within the normal reference range. While it is critical for a clinician to recognize the presence of non-azotemic kidney injury, the focus of this chapter will be on azotemic kidney injury.

Acute renal failure is characterized by an abrupt and sustained decrease in GFR and is associated with high treatment costs and high morbidity and mortality. One of the speculated reasons for this high mortality is late recognition of disease and consequently the narrow window of opportunity for therapy. It is therefore critical for

the attending clinician to look at changes outside established reference ranges, but also to evaluate for small changes in the serum concentration of these markers, which may indicate significant injury.

The term AKI has replaced the numerous definitions of ARF that had developed over the years, to allow for uniformity amongst clinicians when evaluating affected patients. AKI represents a spectrum of renal injury and disease severity, ranging from non-azotemic injury that is clinically non-detectable to severe damage resulting in fulminant ARF. ARF is the most severe stage of AKI and is associated with the highest morbidity and mortality. In the emergency setting, patients presenting with azotemia will likely be in the higher grades of kidney injury and this will therefore be the focus of this chapter. Nonetheless, it is crucial for any treating clinician to recognize that critical evaluation of creatinine is essential for identifying the development of kidney injury in patients presenting with other co-morbidities, such as pancreatitis.

An International Renal Interest Society (IRIS) grading system for AKI has been adopted from human medicine for use in veterinary medicine (Table 94.1). The term *grading* was used to confer the idea that grades of AKI are not static, but represent a time point during kidney injury and/or recovery. This grading system categorizes patients into five grades of AKI, ranging from non-azotemic AKI (where creatinine is still in the reference range) to severe AKI and ARF. These categorizations are based on absolute levels of creatinine, as well as changes in azotemia over a specified period of time. Patients can span through the various spectrums of AKI as they either progress or improve. An increase in creatinine by 0.3 mg/dL (even in the non-azotemic range) within a 48-hour period is consistent with an AKI. It is these small changes in creatinine that should be recognized as development of an AKI. Subgrading is also made based on urine output and on need for renal replacement therapy.

Table 94.1 The current International Renal Interest Society (IRIS) acute kidney injury (AKI) grading system. Note that grading is based on absolute creatinine values, and subgrading is based on urinary output, as well as a need for renal replacement therapy. For grade 1 AKI (non-azotemic AKI), grading is based on a ≥ 0.3 mg/dL increase in creatinine from baseline in a 48-hour period (<http://iris-kidney.com/guidelines/grading.html>)

AKI grade	Blood creatinine	Subgrade
Grade I	<1.6 mg/dL ($<140 \mu\text{mol/L}$)	Each grade of AKI is further subgraded as:
Grade II	1.7–2.5 mg/dL (141–220 $\mu\text{mol/L}$)	1. non-oliguric (NO) or oliguric (O)
Grade III	2.6–5.0 mg/dL (221–439 $\mu\text{mol/L}$)	2. requiring renal replacement therapy (RRT)
Grade IV	5.1–10.0 mg/dL (440–880 $\mu\text{mol/L}$)	
Grade V	>10.0 mg/dL ($>880 \mu\text{mol/L}$)	

Prerenal Azotemia

Prerenal or volume-responsive azotemia is defined by a decreased GFR occurring secondary to hypoperfusion in a structurally normal kidney. Correction of hypoperfusion leads to rapid resolution of the azotemia, providing that intrinsic AKI has not developed. Hypovolemia, poor cardiac output secondary to cardiovascular dysfunction and pathological vasodilatory conditions (such as shock) are some of the common causes for prerenal azotemia in veterinary medicine. When prerenal azotemia occurs, the BUN to creatinine ratio is often increased (greater than approximately 20:1) due to the increased reabsorption of BUN in the nephron as physiological mechanisms function to re-establish a euvolemic state. In veterinary medicine, hypoadrenocorticism is commonly associated with prerenal azotemia and can be mistaken for intrinsic renal disease (see Chapter 115).

The assessment of azotemia should include determination of urine specific gravity. Suspicion for prerenal azotemia will increase when a corresponding urine sample is concentrated; however, in conditions where altered urinary concentrating ability is present, prerenal azotemia can occur without the presence of concentrated urine.

Intrinsic Renal Azotemia

Acute renal azotemia or AKI occurs due to intrinsic kidney dysfunction. Common causes for AKI in veterinary medicine include leptospirosis, pyelonephritis, and injury secondary to drugs, toxins, and ischemia (see Table 94.2 for a full list). With renal azotemia, crit-

Table 94.2 Common etiologies responsible for acute kidney injury (AKI) in dogs and cats. In many cases, the underlying etiology may not be definitively known, but each of these causes should be considered and ruled in or out with appropriate diagnostic testing, as indicated. Please note, this is not a comprehensive list of all causes of AKI.

Dog	Dog and cat	Cat
	Pyelonephritis	
	Hemodynamic instability (including hypertension)	
	Acute pancreatitis	
	Drugs, for example amphotericin B, aminoglycosides, non-steroidal anti-inflammatories	
Grape/raisin toxicity	Other nephrotoxins	Lily toxicity
	Ethylene glycol	
	Melamine/cyanuric acid	
Leptospirosis		Ureteral obstruction
Lyme nephritis		Renal lymphoma
		Feline infectious peritonitis

ical evaluation of creatinine is crucial as misdiagnosis of renal disease can occur if the attending clinician simply uses established reference ranges. Significant renal dysfunction occurs before creatinine increases outside established reference ranges and earlier identification may lead to better outcomes. The search for novel biomarkers that are more sensitive than creatinine for early diagnosis of AKI is actively under way [1,2]. In addition, with application of the AKI grading system, patients can be appropriately categorized based on their severity of azotemia and early AKI will not be missed.

Postrenal Azotemia

Postrenal azotemia occurs secondary to obstruction of the urine drainage system (renal pelvis, ureter, bladder or urethra). When relief of obstruction is achieved, complete correction of azotemia often occurs rapidly if there is no concurrent prerenal and/or intrinsic renal disease. As discussed above, unilateral ureteral obstruction may lead to non-azotemic kidney disease, but astute clinicians may note the importance of small but significant increases (i.e. >0.3 mg/dL increase) in creatinine that could lead to early detection. In the emergency setting, the most common causes for postrenal azotemia include

ureteral obstruction(s) and urethral obstruction (see Chapters 97 and 98).

Diagnosis of Acute Azotemia

Physical Examination and History

Every patient with established AKI requires individualized treatment, but there are key aspects of evaluation and management that must be performed for each patient. A complete history should be obtained and can aid in prioritizing differential diagnoses (see Table 94.2) and in establishing the presence of more chronic kidney disease, which can be crucial for prognostication (Table 94.3).

A thorough physical examination should be performed, but the attending clinician should focus on the common abnormalities that can be found in a patient with acute azotemia.

Initial assessment should focus on fluid/hydration, cardiovascular and respiratory status, as well as evaluation for common consequences of uremia. AKI patients with oliguria or anuria readily develop overhydration when overzealous fluids are administered. Manifestations of fluid overload can include refractory hypertension, peripheral edema, pulmonary edema, and pleural effusion, the latter of which can lead to severe respiratory compromise. Life-threatening bradycardias and arrhythmias may be noted in patients with severe

hyperkalemia. Careful evaluation of the urinary bladder must be made so that urine production status can be assessed; this should be done in conjunction with evaluation of hydration status. A dehydrated patient with an empty urinary bladder may simply need restoration of vascular volume so that renal blood flow and urine output can be re-established. On the other hand, a severely overhydrated patient with an empty bladder is more likely to have intrinsic anuric or oliguric renal failure. Neurological status should also be evaluated as severe fluid overload can lead to cerebral edema, as can uremic and hypertensive encephalopathy. Abdominal palpation should be complete to detect possible underlying causes for AKI, but should focus on renal palpation. In cats, one small kidney and one large kidney may suggest an etiology of ureteral obstruction, while painful kidneys may suggest an underlying pyelonephritis or bilateral obstruction; it is important to note that any AKI can be painful due to renal capsular distension. In addition, renal swelling secondary to AKI can cause chronic, fibrotic kidneys to palpate within normal size limits. A careful oral examination should be performed, as severe oral ulceration can occur secondary to severe AKI (Figure 94.1).

Table 94.3 A comparison of some common findings in patients with acute kidney injury (AKI) versus chronic kidney disease (CKD). It is important to note that each individual patient has their own unique presentation and a single patient may have characteristics that fall within both the CKD and AKI categories.

Acute kidney injury	Chronic kidney disease
Shorter history of illness	Longer history of illness
Normal to increased body condition score (BCS)	Normal to decreased BCS
Normal hematocrit	Anemia
Normal to enlarged kidneys on palpation (often painful)	Normal to small, irregular kidneys on palpation
Normokalemia to hyperkalemia	Normokalemia to hypokalemia
Oliguria to anuria	Polyuria
More profound hyperphosphatemia	Moderate hyperphosphatemia
Normal sized to enlarged kidneys with hyperechoic cortices and perirenal fluid on ultrasound	Normal sized to small kidneys with irregular borders, cortical cysts, and previous infarcts on ultrasound



Figure 94.1 Image of a “uremic” oral ulcer (red arrow) in a feline patient with severe acute renal failure secondary to lily intoxication.

As discussed, a thorough examination should be performed to evaluate for underlying etiologies that may have caused AKI.

Initial Diagnostics

Initial diagnostics should be performed to fully assess patients with suspected AKI. Bloodwork, including a complete blood count and serum chemistry screen, is essential in the assessment of these patients. Complete blood counts may demonstrate a neutrophilia, which could suggest an underlying pyelonephritis or pancreatitis. Serum chemistry screens allow for evaluation of the severity of azotemia, and specific changes in the chemistry panel, such as a hepatopathy, can help to define underlying disease, such as leptospirosis or pancreatitis. As the kidney is largely responsible for potassium regulation, AKI can result in altered excretion of potassium and subsequent hyperkalemia that can lead to life-threatening cardiac arrhythmias (see Chapter 109). Other electrolytes that are often abnormal on the chemistry screen include phosphorus, sodium, and magnesium and these should be considered when devising a treatment plan (see Chapter 110). Metabolic acidosis is common in patients with AKI due to decreased bicarbonate production from damaged kidneys, in conjunction with increased concentrations of uremic and lactic acids (if dehydration is present) (see Chapter 107).

Evaluation of urine via urinalysis and urine culture is critical. The urine specific gravity (preferably obtained prior to fluid therapy) may assist in the determination of prerenal or volume-responsive azotemia and renal or postrenal azotemia, and should be monitored closely during AKI therapy. The degree of proteinuria should be evaluated in the context of urine specific gravity, as well as urine sediment. Tubular injury can lead to postglomerular proteinuria; however, in a patient with significant proteinuria (urine protein:creatinine ratio (UPC) > 10), especially in patients with exposure to ticks, testing for tick-borne infections should be submitted. A urine culture (obtained prior to antibiotic therapy) is an extremely important step in determining the pathogenesis of AKI and projected treatment regimen. In some cases of anuric renal failure, it is not possible to obtain a urine sample.

Imaging of patients with AKI may include thoracic and/or abdominal radiographs and abdominal ultrasound. Abdominal radiographs can identify urinary tract calculi and renal size, but are otherwise poorly sensitive in determining the underlying cause of AKI. Thoracic radiographs are important to assess AKI patients for other underlying disease processes, such as cardiac disease, aspiration pneumonia, and metastatic disease, and for secondary fluid overload. Abdominal ultrasound is

the imaging diagnostic of choice for kidney assessment as an evaluation of corticomedullary distinction, kidney, renal pelvic and ureter size can be made. Additionally, ureteral obstructions may be noted, but it is important to recognize that acute obstructions are not always accompanied by significant hydronephrosis or hydroureter (especially if the patient is dehydrated at the time of initial evaluation).

Treatment

Initial therapy for an AKI patient in the emergency room should focus on life-threatening abnormalities. Serum potassium concentration should be evaluated immediately and hyperkalemia treated as appropriate (see Chapter 109).

Patients with AKI can present with a wide array of hydration and fluid volume statuses. Dehydrated or hypovolemic patients should be treated so that they become volume replete. Once euvolemia is achieved, more accurate assessments of urine output can be made. As many patients with AKI have ongoing losses via vomiting and diarrhea, it is crucial to maintain adequate hydration, so that the already damaged kidneys are not further compromised by decreased renal perfusion that can accompany hypovolemia. Careful and continual evaluation of hydration status is critical and this point cannot be overemphasized.

The presence of azotemia does not by definition require aggressive fluid therapy; instead, the goal of fluid therapy is to achieve and maintain hydration without creating overhydration, a condition that can be as life-threatening as the AKI itself. Successful monitoring can be achieved via serial assessments of skin turgor, body weight, respiratory rate and effort, PCV/TP, urinary output, and blood pressure. A urinary catheter is rarely necessary to monitor hydration status if careful attention is paid to the above factors.

In all cases of oliguria/anuria, it is essential to rule out the presence of a lower urinary tract obstruction. Initial treatment of oliguria/anuria is aimed at ensuring adequate hydration and ruling out a prerenal condition. Once this has been done, diuretics such as mannitol and furosemide should be considered. Furosemide may result in an increased urine output, but it is important to recognize that the increased urine output does not necessarily represent improved renal function. Other treatment options for oliguria/anuria include fenoldopam administration, hemodialysis (especially if fluid overload is present), and surgery (if ureteral obstruction is present). Fenoldopam has been shown to be relatively safe when used in dogs and cats, but there are no outcome data to show a definitive improvement with its use [3–5].

If oliguria/anuria is noted secondary to urinary tract obstruction (i.e. calculi, strictures, neoplasia), surgical intervention should be considered. Ureteral obstructions can typically be successfully managed with surgery, stenting or ureteral bypass. If no response is noted with the above therapies and surgery is not indicated, dialysis should be offered, especially in patients with severe hyperkalemia or fluid overload.

Consequences of metabolic acidosis include disrupted cellular metabolism, exacerbation of hyperkalemia, and increased protein and bone turnover (see Chapter 107). Treatment for metabolic acidosis is focused on correcting hypoperfusion to decrease lactic acidosis and the administration of sodium bicarbonate, once it is confirmed that a patient is volume replete. Dialysis can also correct acidemia.

Hypertension is a common sequela of AKI, and severe consequences such as retinal detachment, hypertensive encephalopathy with secondary seizures, progressive renal damage, and cerebral hemorrhage can all occur secondary to hypertension (see Chapter 63). Overhydration can significantly cause and/or exacerbate hypertension. The use of antihypertensive medications to maintain blood pressure within a safe range is imperative. Amlodipine, acepromazine, hydralazine, and nitroprusside can be considered. Angiotensin converting enzyme inhibitors can also be considered, but should be used cautiously in patients with significant azotemia, and are not administered as a first-line antihypertensive therapy to severely azotemic patients at this author's institution.

Pulmonary compromise occurs frequently in AKI patients. Underlying etiologies include iatrogenically induced fluid overload, aspiration pneumonia, and pulmonary hemorrhage secondary to leptospirosis infection. Therapy should be directed at preventing fluid overload, treatment of the underlying cause, if possible, as well as administration of supportive care to maintain patient stability. Given possible evidence for an immune-mediated component for the pulmonary manifestations of leptospirosis infections, plasmapheresis may be indicated in severely affected patients [6].

In any patient suspected to have pyelonephritis or an antibiotic-responsive infection, such as leptospirosis, antibiotic therapy should be instituted pending diagnostic testing (see Chapter 200). While judicious use of antibiotics is critical, so is the immediate treatment

of conditions that are antibiotic responsive; this can improve outcome by allowing for more rapid renal recovery to occur. In addition, the primary underlying cause of disease should be evaluated for and treated accordingly.

Gastrointestinal issues, such as vomiting and GI ulceration, are seen regularly in patients with AKI (see Chapter 74). Vomiting can result from direct effects of uremic toxins on the chemoreceptor trigger zone (CRTZ), gastritis, gastrointestinal edema, and delayed gastric emptying/ileus. Gastrointestinal ulceration can occur secondary to decreased gastrin excretion or increased activity of urease-producing bacteria. Treatment for gastrointestinal-related disease is often focused on antiemetics (maropitant, ondansetron, phenothiazine derivatives, metoclopramide) and gastrointestinal protectants (H2 antagonists, proton pump inhibitors, sucralfate). Severe oral ulceration and stomatitis can also occur due to the conversion of urea by bacterial urease into ammonia, which is caustic to the oral mucosa (see Figure 94.1). Veterinary patients with stomatitis can be treated with oral chlorhexidine; as uremic stomatitis is often very painful, aggressive pain management is also indicated.

Hemodialysis should be considered in patients with severe azotemia with secondary adverse clinical signs, and in those with severe hyperkalemia (not correctable by medical intervention) or fluid overload. If a treatable condition, such as ureteral obstruction, is present, it is the author's recommendation to pursue definitive surgical treatment rather than hemodialysis, whenever possible. Hemodialysis can be a life-saving therapy that has the ability to improve patient well-being, quality of life, and ease of patient management while waiting for renal recovery to occur [7,8].

Acute kidney injury represents a spectrum of disease severity and clinicians should become astute at recognizing damage at an early stage, before it develops into a life-threatening problem. Established ARF is a severe disease process with life-threatening complications. Many affected patients can be managed successfully if careful and appropriate care is provided. The primary insult causing AKI, if identified, needs to be treated aggressively, as do the secondary complications of severe uremia. When medical management cannot maintain patient stability, hemodialysis should be offered, as it can be a life-saving treatment.

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Oliguria

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Pathogenesis of Oligoanuria

Urine output (UOP) is an important aspect of monitoring the hospitalized patient, as it can provide valuable information regarding kidney function and patency of the urinary tract, as well as helping to guide fluid therapy. This is particularly true for the patient with renal disease. Normal urine production has been reported to be 1–2 mL/kg/h in dogs and cats [1–3]. Renal dysfunction, such as acute kidney injury and chronic kidney disease, typically includes impaired tubular solute reabsorption. This results in a solute diuresis and subsequent polyuria (>2 mL/kg/h UOP). Numerous definitions have been used for anuria and oliguria in veterinary patients. Because most patients with renal disease will be polyuric, UOP < 2 mL/kg/h indicates relative oliguria. UOP < 1 mL/kg/h is considered absolute oliguria and anuria is defined as 0–0.5 mL/kg/h UOP.

While urine production is an important observance in monitoring renal function, UOP cannot be used as a surrogate for glomerular filtration rate (GFR). Rather, UOP is a function of GFR, tubular solute reabsorption, and tubular solute secretion. Patients with complete anuria will have a GFR of 0 mL/kg/min, but the restoration of UOP in these patients does not necessarily indicate improvement in GFR.

Oligoanuric acute kidney injury can occur due to several processes (Table 95.1) [4,5]. Dogs and cats with oligoanuric acute kidney injury (AKI) have higher mortality rates and as much as a 20-fold increased risk of death compared to polyuric animals [6,7].

Patient Assessment and Initial Diagnostics

Oligoanuric patients should be evaluated with a thorough physical examination with particular emphasis on detection of subcutaneous edema, cardiopulmonary auscultation, respiratory rate and effort, presence of

Table 95.1 Causes of oligoanuria.

Pathogenesis	Potential causes
Decreased renal blood flow	Hypovolemia or hypotension Decreased cardiac output Renal artery stenosis or thrombosis Sepsis Vasodilatory drugs
Tubular obstruction from casts or cellular debris	Pyelonephritis Acute interstitial nephritis Leptospirosis Acute tubular necrosis Nephrotoxicity
Backflow of glomerular filtrate into renal interstitium	Ureteral, renal pelvis, or urethral obstruction Tubular obstruction from casts and cellular debris
Intrarenal renin-angiotensin system activation	Failure of NaCl reabsorption within proximal tubule High chloride-containing intravenous fluid therapy
Altered permeability of glomerular filtration barrier	Glomerulonephritis Vasculitis

abdominal distension or pain, as well as urinary bladder size. Assessment of patient hydration status and intravascular volume should be made and noted within the patient's medical record. Blood pressure measurement and body weight are also very important to record.

Initial diagnostics should include imaging to document the size or volume of the urinary bladder (often achievable with bedside ultrasound machines), PCV/TS, serum chemistry with electrolytes, and acid–base analysis. Urine should be collected for analysis prior to the initiation of fluid therapy; cystocentesis is preferred to also

provide a sample for urine culture. The urine specific gravity can be helpful to determine if a prerenal cause of oligoanuria is present. Urine may be difficult to obtain in anuric patients. Thoracic radiographs and/or ultrasound should be performed in patients with any concern for pulmonary edema or pleural effusion.

Managing the Oligoanuric Patient

The therapeutic approach to the oligoanuric patient is dependent on their current volume and hydration status (Figure 95.1). Hypovolemic patients should be treated with boluses of isotonic replacement solutions, given rapidly through an intravenous route (see Chapter 167).

Patients with decreased renal perfusion will have an appropriate reduction in UOP secondary to activation of the renin-angiotensin-aldosterone system. Therefore, patients should be adequately hydrated with normal intravascular volume prior to definitively declaring an oliguric or anuric state. Patients that are cardiovascularly stable but dehydrated should have their degree of dehydration estimated from physical examination findings, and this volume calculated and replaced over 6–8 hours (unless cardiopulmonary disease is present that could create an intolerance of such fluid rates) [5]. Once the patient has been rehydrated, an appropriate UOP is 2–5 mL/kg/h depending on the rate of intravenous fluid administration. A UOP less than 2 mL/kg/h would be considered oliguria in a hydrated patient receiving intravenous fluids.

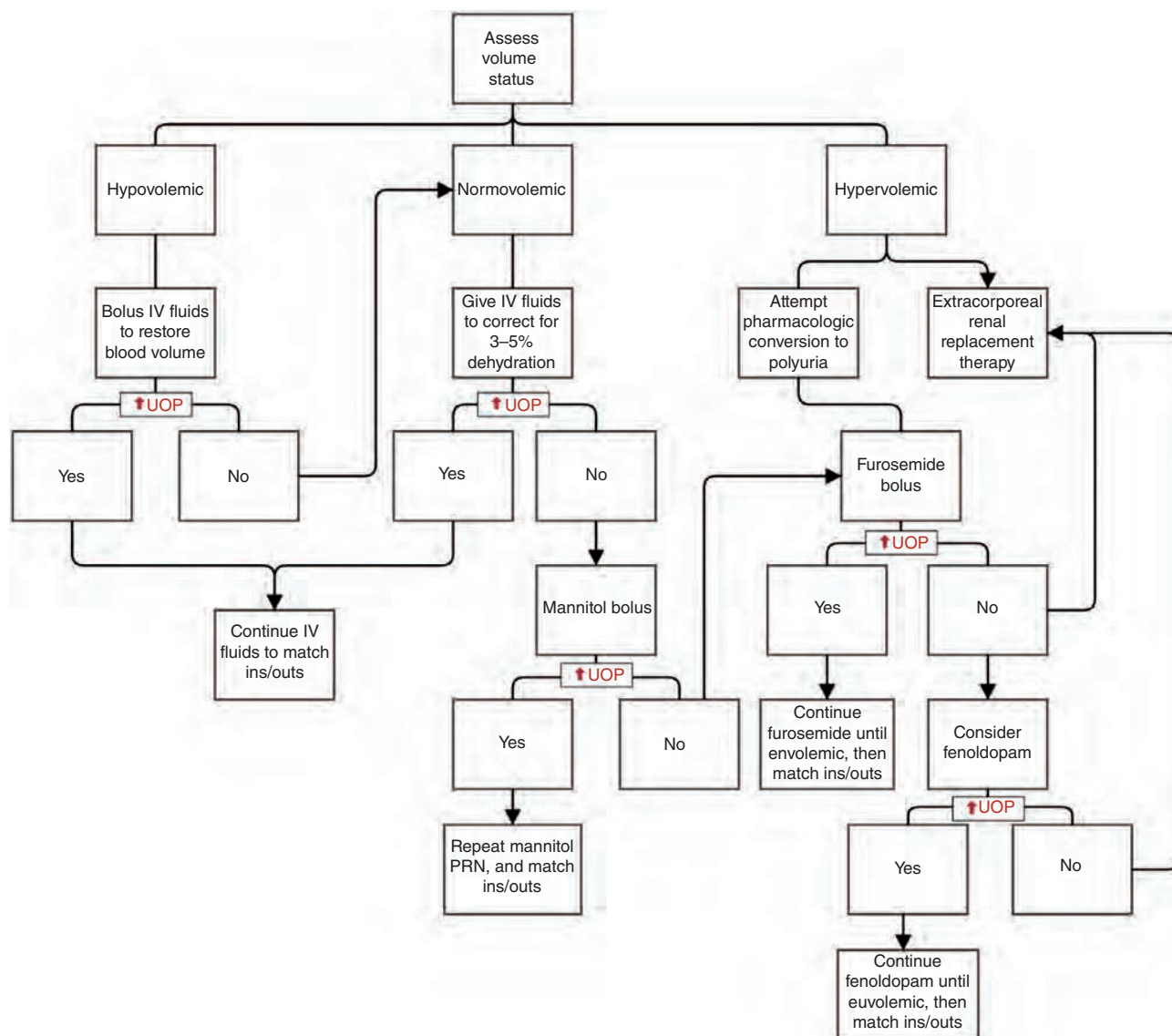


Figure 95.1 Therapeutic intervention for oligoanuria.

For euhydrated patients, an isotonic crystalloid of a volume of fluid equal to 3–5% of body weight should be administered because dehydration of less than 5% cannot be detected clinically. If UOP fails to reach an appropriate magnitude (2–5 mL/kg/h), pharmacological conversion to polyuria may be attempted (see below).

Oligoanuric patients who are hypervolemic often show evidence of serous ocular and nasal discharge, subcutaneous edema, pleural and abdominal effusion, pulmonary edema, and arterial hypertension. Although less commonly seen in veterinary oligoanuric patients, conditions such as systemic inflammatory response syndrome, vasculitis, sepsis, burns, trauma, or pancreatitis can result in intravascular volume depletion with interstitial overhydration in humans (see Chapter 159) [8]. Most patients have normal to increased intravascular and interstitial fluid volumes. Hypervolemic patients with systemic hypotension should be treated with pressors, and intravascular volume expansion should be performed in any patient with a decreased effective circulating volume.

Monitoring UOP in comparison to volume of fluids administered (sum of all IV and PO fluids, often referred to as “ins/outs”) is very helpful in the assessment of oligoanuric patients. Aseptic placement of a urinary catheter and a closed collection system should be considered, as it is more accurate, allows for more frequent assessment of urine output, and protects hospital staff from potential zoonotic agents compared to weighing urine collected in pans and bedding. Hypervolemic patients should be managed so their “outs” exceed their “ins.” GI fluid losses through diarrhea or vomitus should be estimated and included in this assessment. Euvolemic patients should be managed with a neutral or minimally negative total daily fluid balance. It has been documented in people that a positive fluid balance is associated with a worse prognosis in patients with AKI, greater risk of developing AKI, and a poorer chance of return of renal function following AKI [9,10].

The goal of fluid therapy is to maintain renal perfusion. Several studies have shown that supraphysiological rates of intravenous fluids fail to increase GFR in dogs and cats [11,12]. Therefore, patients should have frequent assessments and the fluid plan be adjusted to prevent fluid accumulation.

Converting Oligoanuria to Polyuria

It is now accepted that pharmacological conversion from an oligoanuric to a polyuric state is the mainstay of management in veterinary medicine. Studies in dogs and cats are lacking, but it should be noted that numerous studies in people have demonstrated that successful phar-

macological induction of polyuria has no effect on patient mortality [13]. Hypervolemia in an oligoanuric patient is an indication for extracorporeal renal replacement therapy, and referral for this treatment should be considered early in the course of patient evaluation. In people, an increase in urine output with diuretic use often delays referral for dialysis, potentially at the expense of worse clinical outcomes [14]. Currently, there is scant evidence to show that pharmacological attempts at inducing polyuria are effective, or when it occurs that this carries an improved survival and return of renal function in veterinary patients with AKI.

Mannitol is an osmotic diuretic that decreases cellular swelling and may help to wash out obstructive casts and debris from the tubules. It may also serve as a free radical scavenger. Mannitol is administered as an intravenous bolus of 0.25–1.0 g/kg, administered over 15–20 minutes. If an increase in UOP is achieved, mannitol can be dosed intermittently q4–6 h or administered as a CRI (60–120 mg/kg/h). Mannitol should not be given to patients that are dehydrated because it can further exacerbate intracellular dehydration. Importantly, it is contraindicated if overhydration is present, and may worsen pulmonary edema. Due to lack of evidence showing that mannitol can help prevent AKI and potential risks of hypervolemia secondary to administration, consensus guidelines in people suggest that mannitol not be used in patients with AKI [15]. It is still used in euvolemic veterinary patients, but no publications have reported its efficacy.

Furosemide is a loop diuretic, which inhibits the Na-K-2Cl transporter in the thick ascending loop of Henle. Experimental models have shown potential benefits, including decreased renal oxygen consumption and less ischemic damage. It should be noted that it is the concentration of furosemide within the tubular filtrate and not the blood that determines the observed effect [16]. Furosemide enters the tubular filtrate via active secretion within the proximal tubule as well as filtration of non-protein-bound furosemide across the glomerular filtration barrier. Anuric patients with minimal to no tubular flow are unlikely to have furosemide reach the site of activity, and therefore this drug is often ineffective in increasing UOP in these patients. Human patients who fail to respond to furosemide are more likely to have progression and greater severity of AKI [17]. Furosemide is typically administered as an intravenous bolus or intramuscular dose of 1–4 mg/kg. If an increased UOP is observed, the dose may be repeated every 6–12 hours as needed, or a constant-rate infusion may be administered. The function of the CRI is to maintain serum concentrations sufficient to allow continuous accumulation within the tubular filtrate. Patients who fail to respond to a bolus of furosemide

are unlikely to respond to a CRI, as they likely have adequate serum concentrations for several hours following bolus administration. It should be noted that in people, consensus guidelines suggest that furosemide only be used in early or established AKI for management of fluid balance, hyperkalemia, and hypercalcemia, but any putative role in amelioration of the AKI course is unproven [18].

Renal dose dopamine has been advocated for the management of oliguric AKI for its effects on renal vasodilation. Human studies have shown limited to no improvement in morbidity, mortality, or need for dialysis in established AKI. Additionally, even at low doses, dopamine is potentially toxic in critically ill patients and can induce tachyarrhythmias and myocardial ischemia [19]. Based on these data, dopamine is not currently recommended for treating AKI in humans or animals [20].

Fenoldopam is a selective postsynaptic dopamine receptor (DA-1) agonist that causes more potent renal vasodilation and natriuresis than dopamine. However, it can also promote hypotension by decreasing systemic vascular resistance. Fenoldopam has been shown to increase UOP in healthy cats [21]. Compared to placebo, fenoldopam administration resulted in an increase in GFR and fractional excretion of sodium in healthy dogs [22]. Pharmacokinetic data exist for healthy dogs [23]. A retrospective study of fenoldopam use for both dogs and cats with AKI demonstrated no improvement in survival or length of hospitalization in patients who were administered fenoldopam compared to those who were not [24].

Diltiazem is a calcium channel blocker that may improve renal blood flow through afferent arteriolar vasodilation, which may increase GFR and UOP [25]. It may also be renoprotective by preventing the intracellu-

lar accumulation of calcium, which can trigger cellular necrosis. A retrospective study evaluating the effect of diltiazem in dogs with AKI secondary to leptospirosis did not identify significant improvements in rate of reduction of serum creatinine, recovery of renal function, or survival [26].

Extracorporeal Renal Replacement Therapy

The most significant complications of oligoanuria are hyperkalemia, hypervolemia, and uremia. Extracorporeal renal replacement therapy (ERRT) is extremely effective in correcting all three of these, as well as acid–base and other electrolyte disturbances. Both intermittent hemodialysis and continuous renal replacement therapy can perform ultrafiltration of blood, which removes plasma water to help correct hypervolemia. Referral to a hospital with ERRT capabilities should be discussed with the clients and offered early in the management of the oligoanuric patient, particularly those who are hypervolemic. By helping to normalize the patient's volume status, electrolytes, and uremia, ERRT affords greater opportunity and time to manage the oligoanuric patient. Volume can be controlled so that intravenous medications and nutrition can be administered without causing hypervolemia. Uremia may be improved to allow for initiation of enteral nutrition and fewer antinausea medications.

For clients for whom ERRT is not an option, due to financial restraints or geographic distance to the nearest hospital with ERRT capabilities, pharmacological conversion to polyuria should be attempted. Peritoneal dialysis should also be considered, as ultrafiltration can be achieved by use of hypertonic dialysate [27,28].

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Urinary Tract Infections

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The therapy of uncomplicated urinary tract infections (UTIs) is exclusively antimicrobial, whereas successful treatment of complicated UTIs also includes identification and correction of predisposing conditions. Microscopic examination of appropriately stained urine sediment can be a valuable screening tool to support UTI in symptomatic patients. Fluoroquinolones and third-generation cephalosporins should not be routinely used for initial therapy of UTIs in small animals. Repeated treatment of animals without culture and susceptibility testing may lead to incorrect antimicrobial choices, unnecessary adverse effects of treatment, and possible selection of resistant bacterial populations.

Definition

A urinary tract infection (UTI) occurs when microbes, most commonly bacteria, adhere to, multiply and persist in the urinary tract [1–3]. UTIs are subdivided by anatomic site of involvement into lower UTI (cystitis) and upper UTI (pyelonephritis) [4,5]. Infections at these sites may occur together or independently, and may be subclinical or associated with a wide range of symptoms and clinicopathological findings in dogs and cats. Lower UTIs are generally superficial (or mucosal) infections whereas pyelonephritis and prostatitis signify tissue invasion.

Urinary tract infections can be further classified as simple or complicated infections in order to determine the extent of diagnostic testing, risk of recurrence, duration of treatment, prognosis, and requirements for follow-up evaluations in a given patient [1,3,4,6]. Simple UTIs involve the bladder and are typically initial or sporadic infections of the bladder with no concurrent disease or underlying structural or functional abnormalities (i.e. no compromise of host defense mechanisms). Complicated UTIs are associated with pyelonephritis,

prostatitis, concurrent systemic diseases and either systemic or local alterations in immunity that increase the risk of acquiring infection, or predispose to recurrent infection or treatment failure [3,4]. The majority of UTIs in dogs are simple (uncomplicated) and occur as a single episode [7].

While the stratification into “simple” and “complicated” has proven useful in human medicine, the applicability of this algorithm-based binary classification to UTIs to veterinary patients is less clear. Specifically, this classification scheme does not account for the diversity of “complicated” syndromes in veterinary patients. In companion animals, uncomplicated UTIs are by definition confined to the bladder, and uncomplicated or simple cystitis is a more relevant term. UTIs in intact male dogs are classified as complicated infections, since most have concurrent prostatic involvement. Recurrent UTIs (defined as three or more UTIs during a 12-month period) are classified as complicated infections, and any patient with an identifiable risk factor for UTI is considered to have a complicated infection [8]. Risk factors that predispose to UTI generally do so by compromising immune function, causing obstruction to urine flow, or by providing a nidus of infection that is not readily treated by antimicrobials (Table 96.1) [1,3].

The differentiation between UTI and non-pathogenic bacteriuria is becoming increasingly important because of the emergence of antimicrobial resistance among common uropathogens. Traditionally, the presence of bacteria in urine constituted evidence of infection, and the terms occult or silent UTI were used in veterinary medicine to indicate bacterial infection in the absence of clinical signs. However, bacteriuria does not indicate the presence of disease or potential for future disease. The term UTI implies not only that an organism multiplies in the urinary tract, but that it causes clinical disease [3].

Asymptomatic, or subclinical bacteriuria (SB) is a microbiological diagnosis, defined in the human literature

Table 96.1 Co-morbidities and risk factors that predispose patients to urinary tract infections.

Co-morbidity or risk factor	Examples
Anatomical abnormalities	Abnormal vulvar conformation (dogs) Ectopic ureters Uroepithelial neoplasia Cystic diverticulum
Systemic disorders	Diabetes mellitus Hyperadrenocorticism (dogs) Hyperthyroidism (cats)
Medication causing immunosuppression	Chemotherapeutic agents Corticosteroids, cyclosporine
Urinary tract disorders	Chronic kidney disease Urolithiasis Obstruction (structural, e.g. mass/stones, or functional, e.g. neurogenic urinary retention)
Urinary incontinence	Neurogenic bladder (thoracolumbar myelopathy) Urethral sphincter mechanism incompetency
Miscellaneous	Previous urethrostomy (especially cats) Cystostomy or nephrostomy urinary diversion Urinary instrumentation Urinary catheterization

as the isolation of bacteria in urine from an appropriately collected urine specimen obtained from a person without symptoms or signs referable to the urinary tract. In human medicine, SB is usually transient and does not require antibiotic therapy. SB is increasingly recognized in diverse populations of dogs and cats, although the significance of a positive urine culture in dogs and cats without overt clinical signs of infection remains unclear. Diseases or conditions commonly associated with SB include glucocorticoid excess, diabetes mellitus, obesity (dogs), hyperthyroidism (cats), chronic kidney disease, and presence of indwelling urinary catheters [1,2,6].

Incidence and Pathogenesis

Urinary tract infections are reported to occur commonly in dogs [1]. The true incidence is difficult to determine, largely because criteria for defining UTI differ among sources [9]. Spayed female dogs are more susceptible to UTIs than castrated male dogs and intact female dogs. UTIs are least commonly found in intact males. UTIs can occur in dogs at any age, but are more common in older dogs [1,10].

In contrast to dogs, bacterial UTIs are relatively rare in cats [1,9]. Young healthy cats have an innate resistance and rarely develop UTIs. Most young cats with lower

urinary tract signs have disorders such as idiopathic cystitis or bladder stones, which are generally not associated with bacterial infection [1,11]. UTIs most often occur in older cats (>10 years) and the incidence increases with age [1,2,10,12]. Common metabolic diseases in cats, such as diabetes mellitus, hyperthyroidism and chronic kidney disease (CKD), or other co-morbidities, are often present at the time of diagnosis [2,11–13]. It is likely that cats with DM and CKD have impaired host defense mechanisms that allow colonization of bacteria in the urinary tract, although the exact reasons why cats with these disorders appear predisposed are unclear. As in dogs, the exact prevalence of UTI in cats is difficult to determine, because the inclusion criteria for establishing diagnosis of UTI vary between investigators [11].

The bacteria that most commonly cause UTIs are similar in dogs and cats [5,11]. Although UTIs can comprise mixed bacterial infections, most involve a single bacterial species [1,2,5,7]. *E. coli* infections are most common, accounting for one-third to one-half of all positive urine cultures [1,7]. Other relatively common genera are *Staphylococcus* spp, *Enterococcus* spp, *Proteus* spp, *Streptococcus* spp, and *Klebsiella* spp [1,2]. Cats appear to be infected with a unique staphylococcal strain, *Staphylococcus felis* [1,5]. *S. felis* is a normal commensal organism, but the high prevalence of *S. felis*-positive UTIs suggests that it is a common feline urinary tract pathogen [11].

Commercial phenotypic identification systems may not differentiate *S. felis* from other coagulase-negative *Staphylococcus* spp [5]. Gram-negative rods, including *Enterobacter* spp and *Pseudomonas* spp, assume increasing importance in recurrent and nosocomial UTIs [3,7,8]. Canine infections with *Staphylococcus*, *Proteus*, and *Corynebacterium* spp are often associated with formation of struvite calculi due to alkalization of urine by urea metabolism by these organisms [1].

Primary fungal infections occur uncommonly in dogs and cats. Periodic infection with *Candida* spp is reported in animals that receive chronic antibiotics or are immunocompromised. The causative role of several more unusual pathogens, including *Mycoplasma* spp and *Ureaplasma* spp, remains poorly defined [1,5].

The urinary tract may be viewed as a single anatomic unit that is united by a continuous column of urine extending from the urethra to the kidney. In the vast majority of UTIs, enteric organisms residing in the bowel gain access to the urethra after colonizing the perineum and external genitalia [1,2,14]. The female urethra is particularly prone to colonization owing to its short length and proximity to the anus, and female dogs and cats are at increased risk for UTI. Ascent of bacteria from the bladder may follow and is the most common pathway for most renal infections in both dogs and cats [1,5]. Hematogenous spread is uncommon. Whether bladder infection ensues depends on the interacting effects of the pathogenicity of the strain, the inoculum size, and local and systemic host defenses [2]. Under normal circumstances, bacteria that gain access to the bladder are rapidly cleared, partly due to micturition and dilutional effects of voiding, but also as a result of antibacterial properties of urine and the bladder mucosa [1,2]. Owing mostly to high osmolality and high urea concentration, the urine of dogs and cats inhibits bacterial growth [11]. Mucosal secretions such as immunoglobulin and glycosaminoglycan prevent the adherence of uropathogens to epithelium [1]. In male dogs, prostatic secretions possess antibacterial properties as well.

Escherichia coli is the most common pathogen associated with simple and complicated UTIs in dogs and cats [1]. Not all *E. coli* strains are equally capable of infecting the healthy urinary tract, and many strains that cause uncomplicated UTIs belong to a small number of uropathogenic subgroups that have a selective advantage for colonization and infection [11]. Uropathogenic *E. coli* (UPEC) is a specific subset of pathogenic extraintestinal *E. coli* that has the potential for enhanced virulence. Genes encoding virulence factors, including fimbriae, flagella, adhesins, siderophores, toxins and polysaccharide coatings, have been identified in canine and feline UPEC strains. Bacterial virulence factors enable bacteria to subvert host defenses, facilitate microbial entry into

host tissue, and can markedly influence whether a given strain, once introduced into the bladder, will cause UTI. UPEC virulence determinants are thought to be less significant in the pathogenesis of complicated UTIs [15]. However, complicated UTIs often have a wider range of associated pathogens.

Less is known about the pathogenicity of other bacteria. Several uropathogens, including *Staphylococcus* spp, *Proteus* spp and *Corynebacterium* spp, possess high urease activity. The resultant cleavage of urea to ammonia is not only irritating to the bladder mucosa but increases urine pH and promotes crystalluria (dogs and cats) and struvite stone formation (dogs) [1].

Fungal UTIs are rare in dogs and cats, and generally occur in patients with altered host defense mechanisms [2,16]. Concurrent bacterial infection is common in animals with fungal UTIs and clinical signs are indistinguishable from bacterial UTIs [1]. If fungal elements are identified on urine sediment, fungal culture should be performed to identify the infecting species. Primary fungal UTIs are most commonly caused by *Candida* spp. Other ubiquitous fungi, including *Aspergillus* spp and *Cryptococcus* spp, occasionally cause UTIs in dogs and cats, respectively [2,16].

The organisms and predisposing causes of pyelonephritis are similar to those of lower UTIs [5]. Any impediment to normal flow of urine from the renal pelvis to the bladder, such as obstruction, ureteroliths, or any condition that may promote reflux of urine from the bladder into the ureters may contribute to the development of pyelonephritis [5]. In many instances, however, an underlying cause is not identified. Acute prostatitis is typically due to the same array of pathogens causing other UTIs, with *E. coli* being most common. *Brucella canis* should be considered as a cause of both acute and chronic prostatitis [5].

History and Physical Examination

Patient history and clinical signs of simple cystitis/lower UTI are those of lower urinary tract inflammation or irritative voiding. Clinical history may include varying degrees of pollakiuria, dysuria, and inappropriate urination [5]. Stranguria may persist after the bladder is empty, presumably from inflammation-induced detrusor hyperactivity or urethritis [2]. The bladder and proximal urethra are in close proximity so that inflammation in one is thought to affect the other and passage of urine may elicit discomfort. Primary infectious urethral disorders are rare in both dogs and cats, but when inflammation is confined to the urethra, the pain associated with voiding may cause some animals to retain urine and not fully empty their bladder. Hematuria, "cloudy" urine, or

an offensive ammonia-like odor often prompt owners to seek veterinary attention. If a UTI is associated with an underlying or concurrent disorder (e.g. diabetes mellitus, hyperadrenocorticism), history and clinical signs of that condition may predominate [2].

Patients with lower UTI may exhibit mild sensitivity to bladder palpation but physical examination findings are otherwise unremarkable [2]. When lower UTIs are recurrent or long standing, bladder wall thickening and tenderness may be appreciated. Fever is an uncommon finding in patients with simple UTIs. Rectal examination should be performed in all dogs with signs of lower urinary tract disease to evaluate for urethral stones and irregularities. The urethra may be prominent with severe urethritis, or thickened in cases of urethral neoplasia. Rectal examination in male dogs may disclose pain and prostatomegaly. Inspection of external genitalia should be performed in all patients with suspected or confirmed UTI. Female dogs should be examined for vulvar recession/hypoplasia and regional pyoderma [2]. When possible, digital vaginal examination should be performed to identify vestibulovaginal abnormalities in dogs that may predispose to infection. In male dogs, the prepuce, ostium, glans, and meatus should be examined for discharge, foreign material, or mass lesions. Similar detailed evaluations are seldom possible in cats.

Acute or acute-on-chronic pyelonephritis is commonly associated with non-specific signs of severe systemic illness such as lethargy, anorexia, and vomiting [5]. Polyuria and polydipsia may occur despite minimal nephron damage owing to inhibition of antidiuretic hormone activity in the renal tubules [5]. Hematuria and signs of cystitis may or may not be present. With acute infection, physical examination often reveals dehydration, fever, renomegaly, and dorsal abdominal or lumbar tenderness.

Prostatitis should be suspected in any intact male dog with UTI. Dogs with acute prostatitis often have lower urinary tract signs as well as hemorrhagic or purulent urethral discharge, stiff gait and abdominal pain [5]. Tenesmus may occur if the enlarged prostate compresses the distal colon. Depression, diarrhea, and dehydration occur commonly. Rectal examination may reveal an enlarged, asymmetric painful prostate. Most dogs with prostatitis also have bacterial cystitis. Bacterial prostatitis is rarely identified in domestic cats.

Diagnosis

The diagnostic evaluation of a patient with suspected simple cystitis is the approach for any patient with lower urinary tract signs. The extent of diagnostic work-up varies depending on severity of illness, history of prior

infection, and presence of co-morbidities. Although clinical signs are non-specific, a provisional diagnosis of simple cystitis is often made based on historical information and physical examination findings. Survey abdominal radiographs may reveal concurrent abnormalities that alter urinary tract immunity, including stones, masses or changes in renal size [10]. Simple cystitis does not generally result in changes to routine laboratory studies, and routine bloodwork is seldom helpful [10].

Challenges to evaluating and managing UTIs in the acute care setting often include limited history, lack of longitudinal follow-up, and lack of microbiological information. Urine culture is the gold standard for confirming bacterial infection in patients with clinical signs [3]. Final results are often not available for several days. In-house screening techniques provide timely results and are critical when investigating for the presence of infection [17]. Complete urinalysis is performed in all patients with suspected UTI, and includes measurement of urine specific gravity and microscopic examination of sediment, in addition to routine biochemical evaluation of urine supernatant with a commercially available reagent strip (dipstick) [1,3,10,12]. In human healthcare, the reagent strip (dipstick) is a useful screening test for UTI, where it is routinely used to detect pyuria and bacteriuria. In veterinary patients, the predictive ability of reagent pads is generally poor, and the urine dipstick does not have a prominent role in the diagnosis of UTI in dogs and cats. Leukocyte (WBC) and nitrite (bacteria) test pads are not reliable in dogs and cats [10]. Many dogs and cats with UTIs will have non-specific changes to urine test pads, including qualitative proteinuria and microscopic hematuria [3,10]. Positive results for glucose or bilirubin may indicate the presence of diseases outside the urinary tract.

Alkaline urine in association with UTI suggests infection with a urease-producing agent such as *Proteus* and *Staphylococcus* spp. *E. coli* is the most common agent causing UTIs and urine pH is often acidic with *E. coli* infections. Most healthy dogs and cats have relatively acidic urine, and pH is not always predictive of infection or the causative pathogen, particularly when pH is determined on a reagent strip and not a pH meter. Urine specific gravity is variable in dogs and cats with UTIs. Dilute or minimally concentrated urine may be identified in patients with concurrent diseases predisposing to UTI (e.g. diabetes mellitus, hyperadrenocorticism) or in patients with impaired renal concentrating ability (e.g. CKD).

Microscopic examination of urine from symptomatic patients is often useful as a rapid albeit imperfect screening tool to support a diagnosis of UTI [3,17,18]. Urine for routine sediment examination is prepared by placing a coverslip over a small drop of resuspended sediment on a glass slide, followed by prompt examination. Sediment findings that suggest UTI are white blood cells (WBCs)

(pyuria), red blood cells (RBCs) (hematuria), and bacteriuria [10,16]. Although increased numbers of RBCs are often observed with UTI, hematuria (>5 RBC/high-power field) may also result from non-infectious causes such as interstitial cystitis, neoplasia or urinary calculi. Pyuria (>5 neutrophils/high-power field) is documented in some but not all patients with UTI [1,3,17].

Several non-infectious disorders, including obstruction, calculi and epithelial neoplasia, can cause inflammation and clinical signs of lower urinary tract inflammation [2]. The inflammatory response is often dampened in disorders that impair host defenses, such as diabetes mellitus, hyperadrenocorticism, and feline leukemia virus [1,2,10,16,17]. Thus, the presence of white blood cells in any number should not be used as a criterion for the presence or absence of infection.

In addition to cells, infectious elements are often identified [17,18]. Results of sediment findings have limitations and can yield discordant results [1,17–19]. False-positive results (i.e. bacteria observed in a sample with a negative urine culture) occur as a result of misidentification of amorphous debris as pathogens, or the presence of non-viable organisms. False negatives (i.e. no bacteria observed but positive urine culture) are common, particularly when bacteria are present in low numbers [17]. Examination of air-dried urine sediment stained with modified Wright stain (e.g. Diff Quik) is more sensitive and specific for detection of bacteria compared to routine wet-mount sediment evaluation [1,16]. The procedure is simple, and should be a component of routine microscopic evaluations. Gram staining of air-dried sediment further improves accuracy for identifying bacteria [1,2,10,18]. An additional advantage of gram staining is its ability to identify bacteria as gram negative or gram positive, since gram-staining characteristics may help narrow differentials and allow for improved empirical antibiotic selection [18]. The observation of bacteria and pyuria in patients with clinical signs of lower urinary tract disease is indicative of active inflammation associated with infection.

Not all bacteria are pathogenic, and the significance of bacteriuria in dogs and cats without clinical history and signs of infection remains unclear [3,10,20]. Identification of fungal elements in sediment is diagnostic for fungal UTI [10]. *Candida* spp are responsible for most fungal UTIs [2]. Most pathogenic yeasts grow on blood agar plates that support bacterial growth. Thus, separate submission of urine for fungal culture is not always indicated. Selective fungal media is more useful for rare instances in which there is a high probability that a UTI is caused by a more fastidious yeast or mold.

Urine is most often collected from dogs and cats by cystocentesis, since any observed cytological abnormalities or infectious agents likely originate in the bladder

(or kidneys), and not the urethra or periurethral tissues [3]. Catheterized samples using aseptic technique are acceptable for interpretation of urinalysis and urine microscopy. However, infectious elements from the urethra may be introduced as the catheter advances. The examination of voided samples is generally discouraged, but it is not a pointless endeavor. While not ideal, mid-stream voided urine is often satisfactory for the initial evaluation of urinary disorders, and for screening purposes. Bacterial contamination from the urethra in voided samples usually does not result in enough organisms to be visualized microscopically. Nothing is gained by collecting urine by a more invasive method if microscopic findings of a voided sample are normal. Manual bladder expression should be avoided, as it can cause unnecessary bladder trauma, and increased hydrostatic pressure in the bladder may propel infectious elements into the ureters and kidneys.

A quantitative bacterial urine culture, from urine obtained by cystocentesis, confirms the presence of infection in dogs and cats with signs of lower urinary tract disease, and to identify resistant bacteria that may not respond to initial therapy [3,7]. Cystocentesis is considered the gold standard against which results using either voided or catheterized samples are compared. A quantitative urine culture includes identification of the organism and determination of the number of organisms.

The concept of relevant or significant bacteriuria was introduced to differentiate between bacterial contamination and infection, and quantitation of the number of bacteria in colony forming units/volume (cfu/mL) is standard when reporting urine culture results. It is recognized that low but variable numbers of commensal flora are occasionally identified by culture, and significant bacteriuria is the number inferred to define clinically relevant infection [2,6,21]. General guidelines based on quantitative bacterial counts and method of collection (cystocentesis, voided, catheter) are published for small animals, but there is limited evidence to support proposed veterinary “cut-off” values [3,22]. Whether colony counts are relevant in animals is unclear, and accurate interpretation of culture results must also rely on clinical information [3]. While the recovery of a single organism at $>10^4$ cfu/mL is proposed as a cut-off for significant bacteriuria, it is possible that lower counts may represent “significant” infection in patients with appropriate clinical signs. Conversely, the presence of $>10^4$ cfu/mL bacteria in a urine sample obtained by cystocentesis from an asymptomatic patient may signify transient colonization or subclinical bacteriuria, and skepticism is warranted before concluding that UTI is present [10]. Any amount of bacterial growth is significant in urine obtained by cystocentesis, particularly when signs of lower urinary

tract disease are present. Midstream voided urine is least desirable for purposes of sampling urine for culture in dogs and cats [3,10,21].

Urine should be submitted in sterile tubes that do not contain additives [10]. To avoid false-positive and false-negative results, immediate culture after collection of a urine specimen is recommended [10]. Longer delays are often unavoidable, and samples should be refrigerated within 1 hour of collection and processed as soon as possible. Commercially available urine culture collection tubes containing preservative may be used to preserve refrigerated specimens for up to 72 hours. Culture swabs allow drying of liquid specimens and loss of viability and are not intended for submitting urine cultures. Further, culture swabs do not permit bacterial enumeration and are thus not suitable for submission of urine for quantitative culture.

Most veterinary diagnostic laboratories classify an organism as susceptible, intermediate, or resistant according to Clinical and Laboratory Standards Institutes (CLSI) recommendations for serum breakpoints. Most antimicrobials are eliminated through the kidneys, and attain higher concentrations in the urine than serum as long as renal function is normal. Therefore, a higher rate of susceptibility among isolates could be predicted if traditional (urinary) breakpoints are applied. Some investigators propose using urinary breakpoints for simple UTIs, whereas serum breakpoints are preferred for complicated UTIs and pyelonephritis [8]. Using urinary breakpoints for simple UTIs may be problematic if a pathogen invades the bladder wall, in which case tissue (i.e. serum) and not urine drug concentration is relevant. Microbiology results could lead to ineffective or inappropriate therapy, and possible recurrent infection, in this example. Veterinary-specific urinary breakpoints have been developed for only a small number of currently available drugs, and the Antimicrobial Guidelines Working Group of the International Society of Companion Animal Infectious Diseases (ISCAID) recommends using serum interpretive criteria for UTIs [3].

In-clinic urine cultures allow immediate processing of urine and may decrease cost to owners by allowing veterinarians to select only positive samples for species identification by external laboratories. However, bacterial isolation should only be attempted in clinics with appropriate facilities, proper biosafety containment and waste management, and trained staff [3].

Point-of-care testing can reduce both turnaround time and costs, and may serve as a bridge between urinalysis and urine culture. The Uricult Veterinary System™ is an in-house diagnostic test that identifies clinically relevant bacterial growth in canine and feline urine samples [13]. Although suitable as a screening test for UTIs, this test is not widely utilized in private practices. More recently, a point-of-care test that allows for the semi-quantitative

enumeration of bacteria in urine, presumptive identification of pathogens, and prediction of antimicrobial susceptibility after overnight incubation has been optimized for use in veterinary patients. The Flexicult Vet™ was found to be sensitive and specific for detection of bacteriuria in dogs and cats, and may have a role as a timely and cost-effective point-of-care test to guide antimicrobial therapy [9].

The role of in-house methods for the timely detection of bacteriuria and antimicrobial susceptibilities remains to be defined in veterinary medicine. If cost-effectiveness and diagnostic utility are corroborated by further studies, such tests could also represent a valuable approach to overcoming problems related to storage and transport of urine samples for culture.

While limited diagnostics are generally performed in patients with simple cystitis, patients with complicated infections and those with suspected prostatitis or pyelonephritis require more extensive evaluations, including urinalysis, urine culture, complete blood count, serum biochemical profile, and diagnostic imaging to evaluate for the presence of systemic inflammation, azotemia, concurrent illness and predisposing structural or systemic conditions that impair host immune defenses. Leukocytosis is a common finding with pyelonephritis. Azotemia may be present if both kidneys are affected, or if unilateral pyelonephritis occurs in a patient with pre-existing renal disease. If survey radiographs are unremarkable and a predisposing cause for infection is suspected, abdominal sonography is indicated. Contrast studies may be indicated to investigate for anatomic defects. Evaluation of endocrine function is indicated if suggested by presentation, such as measurement of serum thyroid hormone in an older cat with weight loss and polyphagia. There are no reliable methods to clinically distinguish renal parenchymal infections from lower UTIs.

The diagnosis of pyelonephritis is generally based on clinical signs, laboratory studies (e.g. leukocytosis, azotemia), radiographic (e.g. renomegaly) and/or sonographic (e.g. pyelectasia) abnormalities. A positive culture of urine sampled from the renal pelvis confirms renal involvement, but pyelocentesis is seldom indicated. Similarly, sampling of prostatic fluid for culture is not usually warranted, or performed for acute infections. It is generally assumed that the causative pathogen will be identified in urine appropriately sampled from the urinary bladder [16].

Therapy

Successful antimicrobial therapy consists of avoidance of antimicrobials when appropriate, and when antimicrobials are indicated for UTI, optimizing the selection,

dosing, route of administration, and duration of therapy [3,23]. Antibiotics are indicated to limit the spread of infection and alleviate pain. While selecting an antibiotic based on susceptibility information is ideal, therapy is often initiated on the basis of history, clinical signs, and urine sediment findings, and not withheld until culture results are available, particularly for patients in obvious discomfort. Important considerations for treating all UTIs include location of infection, history of antibiotic use, presence of complicating factors or concurrent illness, risk of adverse effects, and cost [10]. Most first-time UTIs are due to one of a limited number of common uropathogens with predictable antimicrobial susceptibilities. While susceptibility patterns can vary over time and regionally, local prevalence data are rarely available to most clinicians.

In addition to other patient variables, the decision to initiate therapy and select initial empirical antimicrobial(s) can often be guided by microscopic examination of urine sediment. When present in sufficient numbers, recognition of bacteria is often possible on standard wet-mount preparations of urine sediment, and modified Wright staining of dried sediment increases the likelihood of identifying bacteria. Recognition of bacterial morphology, particularly if gram staining is performed, affords clinicians an opportunity to make an educated guess about the type of organism present and a reasonable first-choice antibiotic [2]. Microscopic observations are often most useful when interpreted along with urinalysis and in the context of history and clinical findings. For instance, *E. coli*, the most prevalent uropathogen in dogs and cats, is a gram-negative rod often associated with aciduria [2]. The identification of gram-positive cocci forming doublets or clusters suggests infection with enterococci or staphylococci. Occasionally, streptococci are observed lining up and forming long chains. Alkaline urine suggests possible infection with a urease-producing organism, with staphylococci (cocci) and *Proteus* spp (rods) being the most prevalent urease-producing bacteria causing UTIs in dogs and cats [2].

The most comprehensive source of information for management of UTIs in dogs and cats was developed by the Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infections Diseases (ISCAID) and published in 2011 [3]. These guidelines, based on literature reviews, microbiological data and expert opinion, provide a detailed series of recommendations for the diagnosis and management of UTIs in dogs and cats, and most suggestions for therapy in this chapter are in line with them.

While the spectrum of micro-organisms causing UTIs is largely unchanged, patterns of resistance can change over time, and relevant companion animal-specific clinical reports and research studies have been published

since 2011. Further, it was recognized that present algorithms for subdividing UTIs in veterinary medicine, based on classification of UTIs in humans, could not easily be applied to define naturally occurring syndromes in both dogs and cats, and the process of revising the 2011 guidelines was initiated in 2015. Revised guidelines are not yet published, but will expand on information in current guidelines in both scope and depth. Treatment recommendations and definitions will likely supplant those in the 2011 version. Importantly, guidelines are intended to educate veterinarians about appropriate management of UTIs in dogs and cats, and recommendations for therapy should not be inferred to represent a standard of care, or to replace clinical judgment.

The microbiology of simple cystitis is generally limited to a relatively small number of bacteria, and guidelines for empiric therapy are based on the limited predictable spectrum of the most common etiological organisms [2,3]. Susceptibility patterns may exhibit regional differences, and can change over time. Updated regional antimicrobial surveillance data in dogs and cats would be useful to supplement therapeutic guidelines, but this information is generally not available [1,3,8]. Although urine culture is the reference standard for confirming the diagnosis of UTI, it provides no immediate diagnostic utility in the acute care setting. Urine microscopy is often sufficient, and many patients with simple cystitis are successfully managed without the benefit of pretreatment culture results. For example, if an otherwise healthy adult female dog develops acute clinical signs, and there is microscopic evidence to support infection, urine culture may be omitted and treatment initiated with an empirically selected antimicrobial. If there is no improvement after 48 hours of therapy, additional investigations, including urine culture, are required to determine the etiological agent and to exclude non-infectious causes [1,3]. Urine culture should always be performed in patients with recurrent clinical signs, history of recent antimicrobial use, and known or suspected risk factors for infection [2,3,8,24].

Clinical practice guidelines support the use of targeted, narrow-spectrum “first-line” antimicrobials for initial empiric therapy of simple cystitis [3]. However, practitioners commonly prescribe more familiar, typically broad-spectrum “second-line” drugs for simple infections even though narrower-spectrum and more cost-effective options are available. While many of these drugs (fluoroquinolones, third-generation cephalosporins) have a proven track record in treating infections, their spectrum and potency are not required for initial therapy of most first-time or sporadic UTIs [14,16].

Appropriate antimicrobial therapy optimizes clinical and microbiological cure and limits the possibility of acquiring infection with a resistant pathogen. ISCAID guidelines emphasize the importance of considering

ecological adverse effects of antimicrobial agents (i.e. development of resistance to other antibiotics – so-called “collateral damage”) along with drug effectiveness when selecting therapy. Initial use of a first-line agent minimizes the selection for antimicrobial-resistant organisms colonizing or infecting the urinary tract of the individual patient, whereas overuse of broader spectrum antimicrobials promotes antimicrobial resistance in the general population [8]. Particularly concerning in veterinary medicine is the increasing resistance to amoxicillin-clavulanic acid, fluoroquinolones, and third-generation cephalosporins, and the parallel development of co-resistance to other antibiotics [8,23,24].

Suggested first-line agents for simple cystitis in dogs include amoxicillin, cephalexin, and TMP/S (trimethoprim-sulfamethoxazole or trimethoprim-sulfadiazine) (Table 96.2) [2,3,7,16]. Amoxicillin is bactericidal and relatively non-toxic, with a spectrum of antibacterial activity greater than that of natural penicillins. Amoxicillin retains activity against streptococci, enterococci, and *Proteus*, and often achieves urinary concentrations high enough to be effective against staphylococci, and wild-type strains of *E. coli* and *Klebsiella*. Amoxicillin is a weak acid with a low volume of distribution, so therapeutic concentrations in renal and prostatic tissues are not often achieved. Amoxicillin, like most antimicrobials,

Table 96.2 Recommended antimicrobials for treating urinary tract infections.

Drug	Dose	Comments
Amoxicillin	11–15 mg/kg PO q12h	Suggested first-line therapy in dogs and cats
Amoxicillin-clavulanic acid	Dogs: 12.5–20 mg/kg PO q12h Cats: 62.5 mg/cat PO q12h	
Cephalexin	15–30 mg/kg PO q8–12h	Enterococci are resistant
Cefovecin	Dogs: 8 mg/kg SC q14 days	Appropriate for resistant infections and/or when oral treatment is problematic. Pharmacokinetic data support use in cats q21 days
Cefpodoxime	Dogs: 5–10 mg/kg PO q24h Cats: No dose established	Enterococci are resistant
Ceftiofur	Dogs: 2.2–4.4 mg/kg SC injection q24h Cats: No dose established	Enterococci are resistant
Ciprofloxacin	Dogs: 30 mg/kg PO q24h	Lower and more variable oral bioavailability than veterinary-approved fluoroquinolones. Difficult to justify use over approved fluoroquinolones. Dosing recommendations are empirical
Enrofloxacin	Dogs: 5–20 mg/kg PO/IM/IV q24h Cats: 5 mg/kg PO/IM/IV q24h	Reserved for documented resistant UTIs. Associated with retinopathy in cats at higher doses
Marbofloxacin	2.7–5.5 mg/kg PO q24h	Reserved for infections resistant to first-line antimicrobials. Not recommended for enterococci
Orbifloxacin	Tablets: 2.5–7.5 mg/kg PO q24h Oral suspension (cats): 7.5 mg/kg PO q24h	Reserved for documented resistant infections
Trimethoprim/sulfadiazine	15 mg/kg PO/IV/SC q12h	Idiosyncratic and immune-mediated reactions reported in dogs. Initial and periodic monitoring of tear production recommended. Avoid in dogs of Doberman pinscher lineage. Hypersalivation and nausea common in cats. Not effective for enterococci
Trimethoprim/sulfamethoxazole		
Pradofloxacin	Dogs: 3–5 mg/kg PO q24h Cats: 3–5 mg/kg PO q24h (tablets) Cats: 5–7.5 mg/kg PO q24h (suspension)	Reserved for documented resistant infections. Greater activity against some pathogens than other fluoroquinolones
Chloramphenicol	Dogs: 30–40 mg/kg PO/IV q8h Cats: 10–15 mg/kg PO/IV q12h (50 mg/cat q12h)	Reserved for multidrug-resistant infections. Avoid contact by humans (idiosyncratic bone marrow aplasia)

IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

achieves very high urine concentrations, such that urinary tract sterility is often possible when it appears that the drug would fail to do so based on concentrations achieved in plasma. For example, the majority of urinary *Staphylococcus pseudintermedius* produce beta-lactamase, and isolates are often reported to be resistant to amoxicillin yet lower UTIs due to these organisms are often successfully treated with amoxicillin, as a result of high concentration of active drug in urine. This is not inferred to mean that amoxicillin is appropriate therapy for such infections. Urinary staphylococci are becoming increasingly resistant to aminopenicillins, and initial therapy with a beta-lactamase stable antimicrobial (e.g. cephalexin, amoxicillin-clavulanic acid) should be chosen when staphylococci are suspected or preliminarily identified [7].

Amoxicillin-clavulanic acid is familiar to most veterinarians and approved for the treatment of UTIs. It has a spectrum of activity against gram-negative bacteria, often including *Proteus* and *Klebsiella* spp that are generally resistant to amoxicillin, and it is usually effective against beta-lactamase-producing staphylococci. It is a reasonable choice for initial therapy of simple cystitis, particularly when staphylococci are suspected. However, current ISCAID guidelines suggest that amoxicillin-clavulanic acid should not be included among first-line agents, because the need for clavulanic acid has not been demonstrated, and to encourage use of more narrow-spectrum agents when possible [3]. Clavulanic acid undergoes some hepatic metabolism and excretion, and the antimicrobial activity of amoxicillin-clavulanic acid against bladder pathogens is due in part to the high concentrations of amoxicillin achieved in urine.

Potentiated sulfonamides (TMP/S) are active against most urinary *E. coli* isolates in dogs and cats, and their spectrum often encompasses other gram-negative enteric pathogens and many veterinary staphylococci. All enterococci are resistant to TMP/S, despite information indicating otherwise in culture reports. While initial therapy with TMP/S is “microbiologically sound,” the potential for infrequent but well-described adverse drug reactions has reduced the attractiveness of TMP/S for routine empirical use [23]. The routine clinical use of potentiated sulfonamides is limited by the potential for hypersensitivity reactions that include blood dyscrasias, hepatotoxicity, polyarthropathy and skin eruptions, as well as idiosyncratic events, such as keratoconjunctivitis sicca (KCS). TMP/S is most often prescribed to dogs without incident [1] but clients should be appropriately educated about potential toxicities. Normal hepatic function as assessed by routine liver chemistries and adequate tear production should be documented prior to initiating therapy in all dogs. Tear production should be monitored during therapy with TMP/S, especially in

small dog breeds [1]. TMP/S should not be used in dogs of Doberman pinscher lineage, due to increased incidence of adverse reactions in these breeds. Sulfonamide hypersensitivity reactions occur > 5 days after beginning therapy, and short courses of TMP/S may be effective and safe in some dogs with simple cystitis [23].

TMP/S is also suggested for initial therapy of UTIs in cats. However, hypersalivation and anorexia are frequently observed following oral administration, making it difficult to support recommendations for routine use in cats. If TMP/S therapy is indicated based on culture information or clinical judgment, oral administration in capsule (but not liquid) formulation or by subcutaneous injection may obviate objectionable acute events. Injectable trimethoprim/sulfadiazine (Tribrissen 24%™) is available outside the USA and approved for use in companion animals.

Cephalexin, a first-generation cephalosporin, is generally active against gram-positive and some gram-negative bacteria in the urinary tract. Some but not all sources support the use of cephalexin for initial empiric therapy of UTIs (see Table 96.2) [1]. Cephalexin is often effective for simple cystitis due to streptococci and beta-lactamase-producing staphylococci. Activity against Enterobacteriaceae, including *E. coli*, is less predictable compared with other first-line antimicrobials, and (as with all cephalosporins) enterococci are resistant to cephalexin [1]. Cephalexin is not effective for renal or prostatic infections.

The use of potentiated beta-lactams (amoxicillin-clavulanic acid), oral (cefpodoxime) and extended-release injectable (cefovacin) third-generation cephalosporins for initial therapy is generally discouraged. While these drugs exhibit activity against most aerobic pathogens associated with UTIs in dogs and cats, their use should be reserved for complicated and/or recurrent infections, and optimally, as indicated by culture and susceptibility data [2]. Fluoroquinolones also cover most expected pathogens and achieve high levels in urine. Resistance is increasing in dogs and cats at a rapid pace and has limited the usefulness of this class of drugs in veterinary medicine [2,16]. The use of fluoroquinolones for empiric therapy of simple cystitis is discouraged. Their use should be reserved for complicated UTIs and systemic infections.

While simple cystitis is by far the most common UTI in dogs, simple or “primary” UTIs are uncommon in cats [9,12]. Most young cats with lower urinary tract disease have idiopathic cystitis, which is generally not infectious, and the reflex action to associate irritative voiding and hematuria with a treatable infection and prescribe antimicrobial therapy without further evaluation in young cats is thus inappropriate. In older cats, UTIs (based on positive urine culture alone) are frequently documented

in cats with one or more common endocrine diseases, yet only a small percentage of bacteriuric cats have histories or clinical signs supportive of lower urinary tract disease. For cats especially, the need for antibiotic therapy must be assessed before selecting or prescribing any agent.

While ISCAID guidelines recommend the same antimicrobials for initial empiric therapy of UTIs in dogs and cats (including amoxicillin and TMP/S), there is comparatively less information available to guide empiric therapy of UTI in cats. Amoxicillin is appropriate initial therapy for feline cystitis, especially when caused by gram-positive organisms [3,12]. Because the susceptibility of *E. coli* to aminopenicillins in cats is increasingly unpredictable, amoxicillin-clavulanic acid has been suggested for initial therapy of gram-negative infections, such as when rods are observed in urine sediment [9,10]. Currently, amoxicillin retains activity against many wild-type strains of common gram-negative uropathogens. It is still a suitable first-line agent in cats, considering its lower cost, narrow (targeted) spectrum, and reduced tendency to cause adverse gastrointestinal effects when compared to amoxicillin-clavulanic acid [11,19].

Simple cystitis in dogs is typically treated for 7–14 days, although the optimal duration of antimicrobial therapy has not been systematically studied [3]. Short-duration antimicrobial therapy is standard treatment for cystitis in women, and it is likely that both microbiological and clinical cures can be achieved with shorter courses of therapy in some dogs [5]. A multicenter clinical trial showed that a 3-day course of oral enrofloxacin dosed at 20 mg/kg/day showed comparable efficacy to conventional therapy with 2 weeks of amoxicillin-clavulanic acid in dogs with simple cystitis [25]. A more recent study compared 3 days of therapy with TMP/S to 10 days of cephalexin for treating simple cystitis in female dogs [23]. Both regimens were effective, with similar eradication rates following therapy. Advantages of short-term therapy include fewer adverse events, lower cost, decreased antimicrobial resistance, and better owner compliance. Appropriate duration of therapy for first-time UTIs is not well studied in cats, and recommendations vary. Since many cats with lower UTIs have concurrent systemic disease or other predisposing factors for “complicated” infection, it is recommended that all UTIs in cats, including initial occurrence of cystitis, be treated for at least 21 days. Further research is required to determine the optimal duration of antimicrobial therapy for initial UTIs in both dogs and cats.

Resolution of clinical signs is usually used as a marker for successful treatment of simple cystitis, particularly in female dogs. Clinical signs usually resolve within 48 hours after initiating therapy. Urinalysis results generally improve over a similar time frame, although posttreatment urinalysis and culture are generally not performed

in the absence of clinical signs [3]. When patients with simple cystitis do not improve after 48 hours with an initially chosen antimicrobial, additional investigations are needed to determine the etiological agent or exclude non-infectious causes. Other diverse disease processes, including neoplasia and urolithiasis, result in inflammatory lesions of the urinary tract characterized by proteinuria, hematuria, and pyuria. In addition to initiating therapy with a broader spectrum agent, urinalysis, urine culture, survey abdominal radiographs and routine bloodwork should be performed to evaluate for important potential causes of apparent treatment failure.

In contrast to simple cystitis, complicated UTIs encompass an extraordinarily broad range of infections that often warrant a more extensive diagnostic evaluation. The variety of underlying conditions, and diverse bacterial agents with unpredictable susceptibilities make generalizations about antimicrobial therapy difficult. It is imperative that aerobic culture is performed for all complicated UTIs [7].

In antibiotic-naïve patients, initial antibiotic recommendations for complicated cystitis are no different from first-line agents for managing simple cystitis. However, patients with complicated cystitis more often have UTIs that are recurrent or fail to respond to appropriate initial treatment. Ideally, antibiotic selection would be postponed until susceptibility information is available. However, when signs of lower urinary tract disease are present, a drug belonging to an antibiotic class different from that used to treat the most recent infection should be prescribed while awaiting culture results. Although the presence of a resistant strain on its own does not define a UTI as complicated, the prevalence of resistance among bacteria causing complicated UTIs is increasing and antibacterial susceptibilities are less predictable [8,15]. While isolates may remain susceptible to one commonly prescribed oral antimicrobial drug, it becomes increasingly less likely that first-line antimicrobials will be effective for complicated UTIs, highlighting the importance of urine culture in all cases [1,8].

Second-line antimicrobials include amoxicillin-clavulanic acid, third-generation cephalosporins, and fluoroquinolones (see Table 96.2) [16,23]. While empiric use is often indicated, none of these antimicrobials should be prescribed without culture and susceptibility information. Amoxicillin-clavulanic acid (or similar beta-lactam/beta-lactamase inhibitor) may be prescribed for complicated cystitis [16]. Amoxicillin-clavulanic acid often retains effectiveness against beta-lactamase-producing staphylococci and gram-negative pathogens resistant to amoxicillin, cephalexin, and TMP/S. Amoxicillin-clavulanic acid is an appropriate selection for dogs and cats with lower UTIs that have not been on repeated courses of antimicrobials.

Third-generation cephalosporins are also suitable second-line agents for managing complicated UTIs. Both oral (cefpodoxime) and extended-release injectable (cefovacin) products are effective against most major bacterial pathogens associated with UTIs in dogs and cats, although enterococci are universally resistant to all cephalosporins. Neither drug is approved for the treatment of UTIs in the United States. However, off-label use is reported, and treatment is often successful, particularly when culture information is used to guide therapy. Cefpodoxime is more active than cephalixin against Enterobacteriaceae. It is not registered for use in cats, but safe use in felines is reported. Cefovacin is given by subcutaneous injection every 14 days, eliminating problems with client compliance and ensuring that drug levels are consistently maintained above the MIC of common uropathogens. Cefovacin appears to be particularly effective against urinary isolates of *Staphylococcus pseudintermedius* and *Proteus* spp.

Ceftiofur, a third-generation cephalosporin used extensively in cattle, is approved for treatment of UTI in dogs due to susceptible strains of *E. coli* or *Proteus* spp. It is given by daily subcutaneous injection. It is economical, relative to the cost of therapy with other veterinary-approved third-generation antimicrobials. Beyond cost, specific indications for use are unclear. Indications may include treatment of UTI caused by a pathogen uniquely susceptible to ceftiofur, or when subcutaneous injection is preferable to oral treatment of UTI (i.e. dogs that experience unacceptable gastrointestinal side-effects with oral medication, or when a pet's disposition makes oral administration difficult). At the manufacturer's recommended dose, ceftiofur is not effective for infections outside the bladder. While a dose has not been established for cats, dose recommendations for dogs have been extrapolated for feline use.

Fluoroquinolones have a broad spectrum of activity against many uropathogens and are appropriate second-line agents as directed by susceptibility information. Fluoroquinolones are rapidly bactericidal, well tolerated and can be administered by a variety of routes. They are frequently useful against a broad range of gram-positive and gram-negative organisms, including *Staphylococcus pseudintermedius*, *E. coli*, *Klebsiella* and *Proteus* spp. Fluoroquinolones are often, though not uniformly, effective for infections caused by *Pseudomonas aeruginosa* and *Enterobacter* spp. They are generally ineffective for streptococcal and enterococcal infections, despite *in vitro* reporting of susceptibility.

Among fluoroquinolones, enrofloxacin is the most extensively studied. It is available in oral and injectable formulations. Enrofloxacin is registered for intramuscular injection only, but slow dilute intravenous injection has been used by veterinarians for many years. Fluoro-

quinolones penetrate tissues well and enrofloxacin is considered the drug of choice for pyelonephritis and prostatitis in dogs. Enrofloxacin is not recommended for use in cats because of the risk of treatment failure with low doses and retinopathy at high doses.

Enrofloxacin is converted *in vivo* to ciprofloxacin. Ciprofloxacin is effective for susceptible pathogens in urine, including some isolates of *Pseudomonas aeruginosa*, but penetration into prostate and renal tissue is relatively poor. It is relatively inexpensive compared with fluoroquinolones approved for veterinary use. Beyond cost containment, it is difficult to support the use of ciprofloxacin over approved veterinary fluoroquinolones. There are no interpretive criteria for testing isolates from animals, and human breakpoints do not apply to veterinary patients.

Enrofloxacin (dogs) and marbofloxacin (dogs and cats) are generally most effective for *E. coli* UTIs. Difloxacin undergoes less renal excretion than other fluoroquinolones and is less likely to be effective against urinary pathogens. Studies have documented cross-resistance among fluoroquinolones [16]. More specifically, if an organism is reported as resistant to one fluoroquinolone, resistance to all other available fluoroquinolones (except pradofloxacin) should be assumed, regardless of susceptibility results [1]. Pradofloxacin is a third-generation fluoroquinolone developed to treat infections in dogs and cats. It is highly active against a wide range of canine and feline urinary pathogens, including strains of *E. coli* and *Staphylococcus* spp, and generally outperforms other fluoroquinolones in regard to both potency and efficacy. In the USA, pradofloxacin is only approved for treating skin infections in cats, but it is licensed in Europe for a wide variety of infections, including UTIs in dogs and cats. It may be a particularly attractive choice for pathogens with reduced susceptibility to other fluoroquinolones.

Fluoroquinolones have the potential to cause retinal degeneration and irreversible blindness in cats. Retinal damage is reported when enrofloxacin is administered to cats at higher doses (>5 mg/kg/day). Retinal damage is not reported with either pradofloxacin or marbofloxacin. Fluoroquinolones can cause damage to cartilage in weight-bearing joints of young growing dogs. Neurological signs including seizures are infrequently reported, particularly with intravenous or high-dose administration.

Fluconazole is recommended for initial treatment of fungal UTIs, given its favorable safety profile and efficacy against *Candida* spp. Some isolates may respond to intravesicular administration of 1% clotrimazole [2]. Secondary fungal UTIs occur when organisms are shed into the urine in patients with systemic fungal infections.

A uniform recommendation for treatment duration for complicated UTIs is likely not appropriate because of

variation of types and severity of infections. Most veterinarians suggest treating complicated UTIs for 4–6 weeks. There is no supporting evidence for this recommendation and it is suspected that shorter courses of therapy might be effective in some patients. As with simple cystitis, clinical improvement should occur within 48 hours. However, resolution of clinical signs, hematuria and bacteriuria may be misleading, as these may resolve transiently because of reduced activity of infection, without eradication of the pathogen.

If the patient has not responded, the choice of antibiotic should be reviewed in light of culture and susceptibility results. Successful treatment is defined as sterile urine during and after antimicrobial administration. A urine culture should be obtained 7 days after antimicrobial therapy is initiated, and approximately 7 days after completing the full course of therapy [3]. Bacterial growth at either time point indicates treatment failure. With recurrent infections, urine culture should be performed 1 week before cessation of antimicrobial therapy, and repeated at 8, 12, and 24 weeks after therapy is discontinued.

Although appropriate antimicrobial therapy is critically important, it is often impossible to cure or prevent recurrence of complicated cystitis without identifying and correcting underlying functional, anatomic or metabolic defects [1,2]. When underlying conditions and predisposing factors cannot be determined, repeat courses of antibiotics typically prove ineffective at achieving bladder sterility. Instillation of antimicrobials into the urinary bladder is ineffective for treatment of bacterial UTIs.

Cystitis is not associated with signs of illness, and is generally managed on an outpatient basis with oral antibiotics. Dehydration, fever, nausea, unremitting discomfort or other signs of severe systemic disease are not present with lower urinary tract infections. Intravenous fluid support and parenteral antimicrobial therapy are indicated while further diagnostics, including bloodwork (CBC, serum chemistries/electrolytes), and imaging studies are performed to evaluate for prostatitis, pyelonephritis, and extraurinary sources of infection.

Management of Particular Conditions

Subclinical Bacteriuria

Circumstances in which bacterial growth should be classified as asymptomatic colonization, or SB, are currently undefined in the veterinary literature [3]. However, infection implies the presence of clinical and not just clinico-pathological abnormalities. UTIs in small animals with underlying disease are frequently asymptomatic, or clinically silent, and there is no apparent correlation between occurrence of signs of lower urinary tract disease and the

presence of a positive urine culture [11,14]. Since bacteria are not always harmful or pathological and therapy not always warranted, using the terms “silent” or “occult” UTI to characterize a non-pathological condition not requiring antimicrobials or other intervention may be misleading [3].

Veterinarians have justified therapy given reports that failure to do so is a risk factor for pyelonephritis, prostatitis, or urosepsis. Results of studies to prospectively determine the impact of treating SB on clinical outcome or on the frequency of antimicrobial resistance in companion animals have not been published. In general, antimicrobials are not routinely prescribed for animals with indwelling urinary catheters, or otherwise healthy dogs and cats with a positive urine culture and no clinical signs of infection. The risk of SB leading to cystitis or ascending infection or other possible complications in dogs and cats with underlying chronic disease, including hyperthyroidism, hyperadrenocorticism and diabetes mellitus, as well as dogs receiving chemotherapy and immunosuppressive drugs remains to be studied. The decision to screen for and treat SB in dogs and cats should be made on an individual basis. However, similar to recommendations in humans, treatment of SB is not recommended for most dogs and cats.

Some veterinary patients at high risk of complications may warrant a more aggressive approach to treatment, including those with anatomic abnormalities and patients undergoing urological surgery. It is likely that by treating SB with antimicrobials, patients stand little chance of benefit and are exposed to greater risk for antimicrobial resistance, and evidence-based guidelines are needed [1].

Urinary Tract Infections Associated with Urinary Catheters

Urinary catheters are a risk for UTI in dogs and cats [5,26]. However, judicious patient selection and vigilant management can decrease the morbidity associated with their use.

Subclinical bacterial colonization is common in catheterized patients and bacteriuria should not raise concern. If, however, there is an abrupt change in the gross appearance of urine (hematuria or turbidity) or urine changes supporting infection (pyuria) or clinical signs of illness (fever), urine culture and treatment are likely warranted. For patients that develop a catheter-associated UTI, treatment is more likely to be successful if the catheter can be removed. Urine for culture should be obtained by cystocentesis, and never sampled from the collection bag or catheter [3]. Concurrent use of antimicrobials in a patient with an indwelling urinary catheter is discouraged, and promotes infection or colonization with multi-drug-resistant organisms.

To reduce catheter-associated infections:

- place a urinary catheter only when needed [5]
- educate personnel regarding aseptic placement, hand-washing, and wearing gloves when manipulating the catheter
- use collection bags with a distal drainage port, and periodically clean the port with a dilute chlorhexidine solution
- consider replacing the catheter every 48 hours, or sooner if gross contamination is evident
- avoid antibiotics while patient has a catheter in place [5]
- clean the outside of the penis/vulva and external catheter line several times daily with dilute chlorhexidine solution
- do NOT culture the urinary catheter tip, as this is not predictive of UTI or UTI risk [3].

Placement of urinary catheters is common in cats but few studies have examined the incidence of infection that may develop as a result. One study showed that 33% of catheterized cats developed significant bacteriuria during catheterization [26]. In another study, 26.9% of cats with multidrug-resistant *E. coli* infection had a history of urinary obstruction managed with catheterization [24].

Acute Prostatitis

Dogs with acute prostatitis are often severely ill, frequently requiring hospitalization, intravenous fluids, and analgesics, in addition to antimicrobial therapy. Initial outpatient management is often unsuccessful. Physical exam findings and associated clinical signs in conjunction with results of CBC, radiography, urinalysis, and urine culture are generally sufficient to establish a presumptive diagnosis. *E. coli* is the most common causative organism. Culture of prostatic fluid is generally not necessary for acute infections, and antimicrobial therapy can be guided based on urine culture results.

Parenteral therapy with a fluoroquinolone is initially selected while susceptibility data are pending. With the availability, predictable efficacy, and safety profile of fluoroquinolones, therapy with other drug classes is only pursued if clinical signs do not resolve and susceptibility to another drug is documented. Other lipid-soluble drugs, such as TMP/S and chloramphenicol, are also described for treating prostatic infections. Both achieve high concentrations in the prostate, and are available in intravenous and oral formulations. Chloramphenicol is not used for initial therapy but is occasionally prescribed for prostatic infections caused by methicillin-resistant staphylococci. Gastrointestinal upset, reversible bone marrow suppression, and peripheral neuropathy affecting predominantly pelvic limbs are the most commonly reported

adverse events reported with chloramphenicol in dogs. Antibiotics are continued for no less than 4 weeks. Urine culture should be performed 5–7 days after treatment is concluded to document microbiological cure.

Acute prostatitis generally responds favorably to treatment. Abscess formation occurs, and should be suspected if signs do not improve, caudal abdominal pain worsens, or signs of sepsis develop. Culture of prostatic fluid is recommended for dogs with chronic prostatitis, and non-ionic lipid-soluble drugs such as chloramphenicol, fluoroquinolones, and TMP/S are sporadically required for therapy of chronic infection. However, the challenges of treating chronic prostatitis (selecting lipid-soluble drugs such as CHPC and TMP/S that cross the blood–prostate barrier) are less of a concern for acute infections in which the blood–prostate barrier is typically disrupted by inflammation. For some dogs, long-term microbiological cure and durable control of clinical signs may not be possible without castration.

Acute Pyelonephritis

Empirical antibiotic therapy should be initiated immediately in all patients with suspected pyelonephritis. Initial treatment should include an antibiotic with proven efficacy against gram-negative enteric organisms, due to the frequency of their involvement in pyelonephritis. Antibiotics diffuse into renal parenchyma from plasma so achieving high drug levels in plasma may be more important than urine. Urine culture and susceptibility testing should be performed, and initial therapy can be tailored to the individual pathogen, if appropriate, when results become available. Fluoroquinolones penetrate renal parenchyma and are recommended for initial therapy. Dogs with acute pyelonephritis are usually systemically ill and require monitoring and intravenous fluid support. Indications to hospitalize patients with acute pyelonephritis include pain, hemodynamic instability, azotemia, nausea or inability to tolerate oral medications. Opioids given by intermittent intravenous injection, or as a constant rate infusion, are often effective for pain management. Parenteral therapy is continued until patients eat and drink voluntarily.

There are no published systematic reviews of pyelonephritis in dogs or cats. Scientific evidence for appropriate duration of antimicrobial therapy is lacking. Treatment is generally continued for 6–8 weeks, with regular monitoring for recurrence of infection. Urine culture should be performed 5–7 days after antimicrobial therapy is discontinued. Progressive, sometimes irreversible renal damage is a possible consequence of infection, but uremic symptomatology and long-term renal functional impairment are not commonly reported when acute pyelonephritis is recognized and treatment initiated promptly [1].

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Urolithiasis

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Introduction

Formation of uroliths is not a disease, but rather a complication of several disorders. A common denominator of these disorders is that they can occasionally create oversaturation of urine with one or more crystal precursors, resulting in formation of crystals. If these crystals are retained and the urine remains oversaturated with the crystal precursors, the microscopic crystals may aggregate to form macroscopic uroliths.

Patients with uroliths may present with urinary tract obstruction (urethroliths or ureteroliths), lower urinary tract signs without urinary obstruction, or with no clinical signs and an inadvertent diagnosis of urolithiasis. In an emergency situation, patients will present usually with clinical signs associated or unassociated with urinary obstruction. Clinical signs may include vomiting, anorexia, and abdominal pain. If urethral obstruction is present, a large urinary bladder or uroabdomen may be present. With ureteral obstruction, renal pain may be found. Initial management is aimed at relieving the obstruction, correcting any metabolic abnormalities that result from obstruction, if present, and/or minimizing clinical signs until more definitive treatment is undertaken.

A detailed discussion of urolith formation and medical preventive therapy is beyond the scope of this chapter and the reader is referred to other sources for this information [1–3]. This chapter will focus on management of the emergent patient.

Diagnosis of Uroliths

Imaging is the most definitive diagnostic tool for detection of uroliths. Abdominal radiography is generally the first diagnostic imaging modality (Figure 97.1). Ultrasonography or contrast radiography (e.g. contrast and

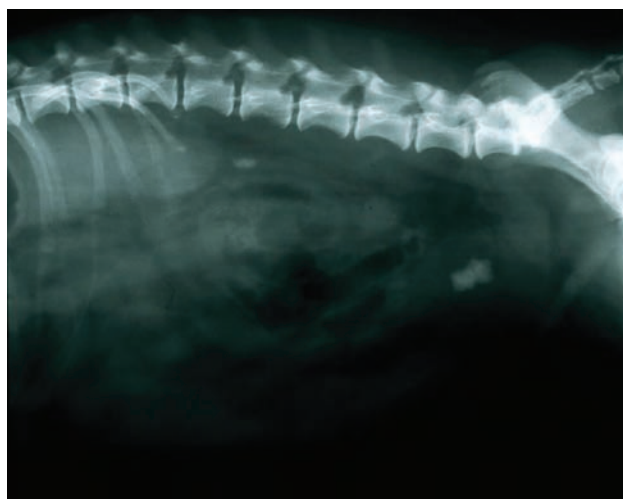


Figure 97.1 Lateral abdominal radiograph of an 8-year-old miniature schnauzer showing a ureterolith and two urocystoliths composed of calcium oxalate.

double contrast urocystography or excretory urography) can be used to detect uroliths, including those that are radiolucent [4]. These abdominal imaging techniques are used to verify the presence, location, number, size, shape, and density of the uroliths.

Urinalysis is an important part of the diagnostic evaluation. Crystalluria does not confirm the presence of uroliths but it does suggest risk, and some patients may have active urocystoliths but not have crystalluria [6]. Urine specific gravity and urine pH can help assess the chemical environment of urine. A high urine specific gravity suggests an increase in concentration of urolithic precursors [6]. Calcium oxalate, purines, and cystine uroliths form typically in urine with a pH less than 7.0, whereas struvite calculi form typically in urine with a pH greater than 7.0 [7]. Urine culture and susceptibility testing are indicated because urinary tract infections may occur secondary to uroliths or may induce urolith formation

in the case of infection-induced struvite uroliths [2,8,9]. Factors contributing to this condition include mucosal damage induced by the stones, incomplete urine voiding, or micro-organism entrapment in the stone.

When uroliths are found, particularly when associated with urinary tract obstruction, it is important to obtain a blood biochemical profile; this may suggest presence of underlying diseases, such as hypercalcemia, that can predispose patients to urolith formation [10–13]. Because uroliths occasionally cause urinary tract obstruction, electrolyte, calcium, phosphorus, creatinine, and blood urea nitrogen concentrations should be closely monitored. Urate calculi may be caused by underlying liver disease, particularly congenital vascular anomalies, so hepatic function should be determined in patients with suspected or confirmed urate uroliths [14,15].

Management of Uroliths Associated with Urinary Obstruction

Urinary obstruction may be associated with azotemia, hyperkalemia, metabolic acidosis, and dehydration if there is urethral obstruction, uroabdomen, or bilateral ureteral obstruction, or if unilateral ureteral obstruction occurs in a patient with chronic kidney disease [16,17]. Treatment for urethral obstruction involves relieving the obstruction and correcting the metabolic imbalances. Performing perineal urethrostomy in cats, or urethrotomy or scrotal urethrostomy in dogs, on an emergency basis is unnecessary and not recommended. Relief of urethral obstruction by retrograde hydropropulsion allows time for additional diagnostic testing and stabilization of the patient. If urethroliths cannot be retropulsed into the urinary bladder, then passage of a small-diameter urethral catheter around the urethroliths or repeated cystocenteses may be done (see Chapter 106).

When ureteral obstruction is present, medical expulsion therapy utilizing intravenous fluids, amitriptyline, and prazosin may be attempted; however, often a urinary diversion technique, such as a nephrostomy tube, ureteral stent, or subcutaneous bypass device, must be employed to preserve remaining renal function in the obstructed kidney.

Management of Uroliths Unassociated with Urinary Obstruction

Medical Treatment

Certain types of uroliths are amenable to medical dissolution therapy.

Struvite

Struvite is another name for magnesium ammonium phosphate hexahydrate. Struvite uroliths may occur as a consequence of a urinary tract infection with a urease-producing microbe (infection-induced struvite) or without the presence of a urinary tract infection (sterile struvite) [18]. Infection-induced struvite uroliths occur most commonly in dogs [19] and pediatric dogs and cats; sterile struvite uroliths occur most commonly in cats. Any animal that develops a bacterial urinary tract infection with a urease-producing micro-organism can develop infection-induced struvite uroliths (see Chapter 96). Sterile struvite uroliths have been documented to occur in dogs [20] but they are very rare.

Infection-induced struvite uroliths can be dissolved by feeding a “struvite dissolution” diet and administering an appropriate antimicrobial agent based on bacteriological culture and susceptibility testing, although there is a case report of dissolution with administration of an antimicrobial agent only [21] (see Chapter 200). Average dissolution time for infection-induced struvite uroliths is approximately 8–12 weeks [18]. An alternative dissolution protocol utilizing a urinary acidifier, d,l-methionine, administered at a dosage of 75–100 mg/kg PO q12h in combination with an appropriate antibiotic, induced medical dissolution in 1–4 months [22]. It is important that the patient receive an appropriate antimicrobial agent during the entire time of medical dissolution.

Sterile struvite uroliths can be dissolved by feeding a diet that is magnesium, phosphorus, and protein restricted, and that induces aciduria [18,23]. Average dissolution time of feline sterile struvite uroliths was 36.2 ± 26.6 days (range 14–141 days) [18,24]. In a more recent study of 32 cats with presumed struvite urocystoliths comparing two low-magnesium acidifying diets, one a “struvite dissolution” diet and the other a “struvite prevention” diet, the mean ($\pm$ SD) times for a 50% reduction in urolith size (0.69 ± 0.1 weeks) and complete urolith dissolution (13.0 ± 2.6 days) were significantly shorter for cats fed the struvite dissolution diet compared with those (1.75 ± 0.27 weeks and 27.0 ± 2.6 days, respectively) for cats fed the struvite prevention diet [25]. Therefore, sterile struvite urocystoliths often dissolve in 2–4 weeks.

Calcium Oxalate

Currently, it is impossible to dissolve calcium oxalate uroliths in dogs and cats so the only management strategy is removal by minimally invasive methods or surgery.

Purines

Urates

Most information concerning urate uroliths is derived from dogs, with very little information available for cats. Uric acid is one of several biodegradation products of

purine nucleotide metabolism [26]. In most dogs and cats, allantoin is the major metabolic endproduct; it is the most soluble of the purine metabolic products excreted in urine. Ammonium urate (also known as ammonium acid urate and ammonium biurate) is the most common form of naturally occurring purine uroliths observed in dogs and cats. Urate is the third most common mineral found in uroliths in dogs and cats, accounting for 5–8% of uroliths, and the second most common urolith occurring in dogs and cats < 1 year of age (infection-induced struvite is the most common urolith in these patients). Urate uroliths form because of liver disease (usually a portosystemic vascular shunt) [14,15] or because of an inborn error of metabolism resulting in hyperuricosuria (e.g. Dalmatians and English bulldogs) [27,28]. They are more common in dogs and cats less than 7 years of age [27–29].

Dissolution is not possible in dogs and cats with uncorrected liver disease (e.g. non-surgical portovascular anomalies or microvascular dysplasia). Surgical removal, voiding urohydropulsion, or cystoscopy ± laser lithotripsy remain the treatments of choice for animals with symptomatic urate stones that cannot be dissolved.

In dogs without underlying liver disease, dissolution may be attempted. Dissolution of urate uroliths in dogs is accomplished by feeding a purine-restricted, alkalinizing diet that induces a diuresis and administering the xanthine oxidase inhibitor allopurinol (15 mg/kg PO q12h) [26,30–34]; allopurinol has not been evaluated in cats and should not be used in this species. While “renal failure” diets are protein restricted and thus lower in purines, there are two commercially available diets formulated to be low in purines: Prescription Diet u/d (Hill’s Pet Products) and UC Low Purine (Royal Canin). Canned diets may be better than dry diets. In one study, medical dissolution was effective in approximately 40% of Dalmatians, partial dissolution occurred in approximately 30%, and no dissolution or growth of uroliths due to xanthine formation occurred in approximately 30% [26].

Until further studies are performed to confirm the safety and efficacy of medical dissolution, surgical removal or minimally invasive procedures remain the treatment of choice for urate uroliths in cats.

Xanthine

Xanthine urolithiasis may occur with allopurinol administration to dogs, especially when dietary purines are not restricted. Management involves adjusting dosage of allopurinol and changing diet. Spontaneously occurring xanthine uroliths have been reported rarely in cats (0.14% of uroliths analyzed at the Minnesota Urolith Center). They are composed typically of pure xanthine and have been reported in cats less than 5 years of age with an average age of approximately 3 years; they occur with approximately even distribution between males and females.

Xanthine uroliths have also been found in a few Cavalier King Charles spaniels [35–37]. No medical dissolution protocol for naturally occurring xanthine uroliths exists.

Cystine

Cystinuria occurs when there is a proximal renal tubular defect in reabsorption and is often present with other amino acids (notably ornithine, lysine, and arginine) [38–43]. Affected animals also demonstrate altered intestinal transport of cystine [44–46]. Several genetic mutations that are associated with cystinuria have been identified in dogs and cats [47–50]. Cystinuria is only associated with urolith formation and is not associated with protein malnutrition or amino acid deficiency, although it can be associated with hypercarnitinuria and/or hypertaurinuria and associated dilated cardiomyopathy [51]. Cystinuria by itself does not result in urolithiasis, however, and many cystinuric dogs and human beings do not form uroliths [52].

Canine cystine uroliths can be dissolved medically by feeding a diet that is low in protein, alkalinizing, and induces a diuresis. While “renal failure” diets are protein restricted and thus lower in amino acids, there are two commercially available diets formulated to be low in sulfur-containing amino acids: Prescription Diet u/d (Hill’s Pet Products) and UC Low Purine (Royal Canin). Canned diets may be better than dry diets.

Administration of 2-mercaptopyrionylglycine (2-MPG, Tiopronin, Thiola) is recommended [38,39,53]. This drug is similar to D-penicillamine in that it binds to the individual cysteine molecules, preventing formation of the disulfide bond of cystine; however, it is associated with fewer side-effects and complications. Dosage is 15 mg/kg PO q12h for dissolution. There are studies showing that administration of 2-MPG without modifying diet may result in dissolution of cystine uroliths. Cats do not tolerate 2-MPG well and it is associated with GI signs, liver disease, and anemia; therefore, it should not be used in cats and dissolution of cystine uroliths has not been successful.

Compound and Mixed Uroliths

Between 5% and 15% of uroliths may be mixed or compound stones. This refers to a situation where more than one mineral is present within the stone, either mixed within layers or different parts of the stone are composed of various minerals (nidus versus major volume of the stone versus the outer layer or shell).

As mentioned previously, ammonium urate and calcium carbonate (or calcium apatite) may be mixed with struvite as part of infection-induced struvite stone formation. In this situation, the struvite caused by the infection is the primary focus for prevention. Some stones may be composed of both struvite and calcium oxalate. In this situation, usually calcium oxalate is the nidus (inner part of the stone) and struvite is layered around it.

This compound stone forms because the patient first formed a calcium oxalate stone and then developed a urinary tract infection and layered infection-induced struvite around the calcium oxalate nidus. Ammonium urate uroliths may contain xanthine in patients that receive allopurinol for dissolution or prevention. This may be due to (a) too high a dose of allopurinol, (b) lack of restriction of dietary protein/purine, or (c) individual patient metabolism of allopurinol despite appropriate allopurinol dosage and dietary management. Prevention is directed to (a) decreasing or discontinuing allopurinol, (b) changing the diet to a more protein/purine-restricted diet, or (c) both.

Minimally Invasive Techniques

There are several minimally invasive treatment options for retrieval of bladder and urethral stones. These include voiding urohydropropulsion, transurethral cystoscopic stone removal (with or without use of laser lithotripsy), and mini-laparotomy-assisted cystoscopic stone removal, also called percutaneous cystolithotomy (PCCL).

In catheter-assisted retrieval or voiding urohydropropulsion of calculi, the patient is sedated or anesthetized, a catheter is passed into the urinary bladder transurethrally, and the bladder is filled with sterile crystalloid solution [54]. In cats, a 3.5 Fr or 5 Fr catheter is used and in dogs a 5, 8, or 10 Fr catheter is used, depending on patient size. During catheter retrieval, the contents of the bladder are aspirated while the bladder is agitated by palpating and manipulating it or rotating the patient's body. This is difficult in most male cats and in small male dogs due to the limiting size of the urethra and the small size of the catheter.

With voiding urohydropropulsion, the patient is anesthetized and held vertically while the distended bladder is manually expressed [54]. Sizes of uroliths that may be retrieved with this technique are approximately 1 mm in male cats, up to 5 mm in female cats, 1–3 mm in male dogs, and up to 10 mm in female dogs.

These methods are used to eliminate small calculi and collect them for analysis to plan further treatment. These techniques will not be successful, however, if a patient presents with urethral obstruction as this situation indicates that there is at least one urolith that is too large to pass through the urethra.

Percutaneous cystolithotomy is a procedure where the bladder is approached through a small abdominal wall incision and is temporarily fastened to the incised linea, thus allowing for cystoscopic stone removal through a stab incision or a laparoscopic port placed in the urinary bladder [55,56]. This method is an effective, safe, and efficient means for managing urocystoliths.

Cystoscopy produces magnified images of the fluid-distended urinary bladder, allowing identification of abnormalities such as strictures, masses, and calculi [57,58]. This is the minimally invasive procedure of choice for male dogs and cats because the diameter of the male urethra limits insertion of a cystoscope with operating channel. Cystoscopic techniques are more efficient than surgical procedures, decreasing the risk of trauma and abdominal contamination [57,58]. When performing transurethral cystoscopy, a cystoscope is inserted into the urethra and passed into the urinary bladder. This procedure is preferred for use in females but has been described in male dogs because it is less invasive than other diagnostic and treatment methods. If calculi are small enough, they can be removed using stone retrieval devices such as stone baskets and graspers.

For larger calculi, lithotripsy may be used, if available [58]. Lithotripsy uses a laser fiber that is passed through the operating channel on the cystoscope. The fiber emits light at an infrared wavelength to fragment calculi [59–64], and the resulting fragments are removed transurethrally. This procedure is possible in female dogs and cats and male dogs, but not male cats due to the limiting size of the male cat urethra and inability to insert a large enough scope with an operating channel.

In patients with ureteral obstruction, minimally invasive techniques are primarily used to either bypass the obstruction or divert urine flow from the obstructed kidney to the urinary bladder. These techniques include placement of a nephrostomy tube, ureteral stent, or subcutaneous urinary bypass device. Nephrostomy tubes provide temporary relief of pressure within the obstructed kidney until more definitive therapy can be undertaken [65]. A ureteral stent may be placed fluoroscopically with or without cystoscopic guidance, depending on the patient, or using a surgical approach (Figure 97.2) [65]. Subcutaneous ureteral bypass devices are placed surgically, diverting urine flow down the path of least resistance, which is through the renal catheter, subcutaneous port, and urinary bladder catheter into the urinary bladder (Figure 97.3) [65].

Surgical Treatment

Detection of uroliths does not necessarily warrant surgical intervention; however, obstruction of urine outflow, an increase in size and/or number of calculi, persistent clinical signs, and a lack of response to therapy are indications for calculi removal [2]. Surgery is required in patients with non-dissolvable calculi and clinical signs. Traditional open surgical options are available for treatment of urolithiasis, including cystotomy, urethrotomy, and urethrostomy, and for ureteroliths, ureteral resection with neoureterocystostomy.

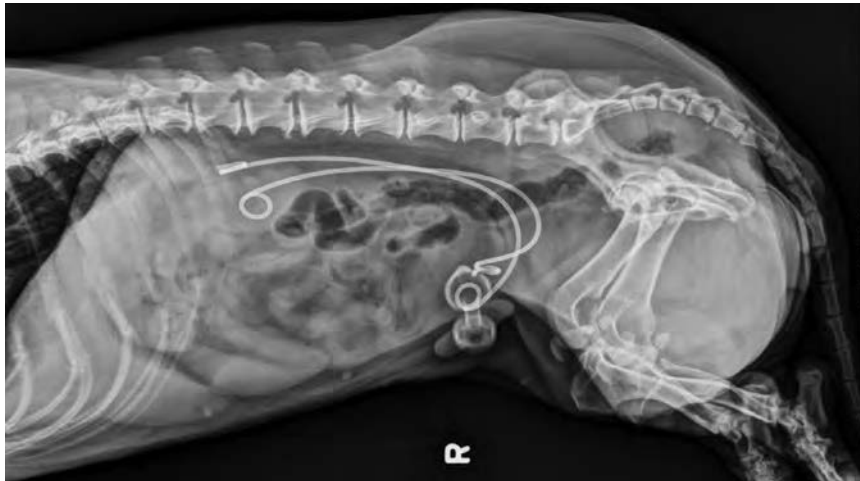


Figure 97.2 Lateral abdominal radiograph of a 10-year-old spayed female mixed breed dog with bilateral ureteral stents and a cystostomy tube due to urethral and ureteral obstruction by transitional cell carcinoma.



Figure 97.3 Lateral abdominal radiograph of a 14-year-old castrated male, domestic short-haired cat with bilateral subcutaneous ureteral bypass devices due to bilateral ureteral obstruction from uroliths.

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Feline Ureteral Obstruction: Diagnosis and Management

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Introduction

An increasing incidence of problematic ureteroliths, ureteral strictures, obstructive pyonephrosis, and obstructive neoplasia has been seen in veterinary practice over the past decade, particularly for feline patients. The traditional invasiveness and morbidity associated with traditional surgical techniques [1–3], which are often even more complicated for non-stone-related obstructions, make the investigation of minimally invasive alternatives appealing. Interventional radiological (IR) and interventional endoscopic (IE) techniques, like ureteral stenting and the use of a subcutaneous ureteral bypass (SUB) device, have aided tremendously in the ability to treat difficult ureteral obstructions in a more minimally invasive manner, with long-term ureteral protection from future obstruction, while concurrently lowering the perioperative morbidity and mortality when compared to traditional surgical techniques (ureterotomy, neoureterocystostomy, ureteronephrectomy or renal transplantation) [4–12]. The treatment of ureteral obstructions in human medicine is routinely done using more minimally invasive endourological techniques, and this has recently been a similar trend in veterinary medicine.

This chapter will focus on the diagnosis, management, and treatment of cats with ureteral obstructions from various causes and will review data from what has been reported in the past, and some of the more recent data pertaining to more novel approaches and not to their management. Data from over 325 interventionally treated consecutive cases in the author's practice will be expanded upon.

Etiology

Greater than 90% of feline upper tract stones are reported to have a composition of calcium oxalate, meaning that they will not dissolve medically. They either need to pass

spontaneously or be removed, or the urine needs to be diverted when an obstruction is present. Additionally, obstructions can occur for other reasons beyond stone disease, such as dried solidified blood clots (~8% cats) [6], strictures (25–30% or more of cats) [6,9,12], tumors (<5% of cats), accidental ureteral ligation during surgery, ureteral trauma, ureteral edema following ureteral surgery, and secondary to purulent material associated with pyelonephritis/pyonephrosis [6]. Obstruction can result in life-threatening azotemia, particularly when presenting bilaterally (~15–20%) in cats with concurrent pre-existing renal insufficiency/failure (>75–90%) [1,6]. For each of these conditions, different options exist and should be considered.

Regardless of the cause of the obstruction, treatment needs to be considered in an expedited manner and should not be delayed. The physiological response to a ureteral obstruction is very complex [13–17]. In dog models, it is shown that after a complete ureteral obstruction, an immediate increase in renal pelvic pressure occurs and the renal blood flow diminishes by 60% over the first 24 hours, and 80% within 2 weeks. This excessive pressure decreases the glomerular filtration rate (GFR). The contralateral kidney will increase its GFR in response, as long as that kidney is normal and has the potential for hypertrophic compensation [13–17]. It has been shown that the longer the ureter remains obstructed, the more progressive the damage (after 7 days the GFR is permanently diminished by 35%, and after 2 weeks by 54%).

Since this research model was performed in normal dogs with a complete ureteral obstruction, without pre-existing azotemia, chronic interstitial nephritis, fibrosis, or chronic obstruction, an extrapolation of a worse outcome might be expected in a clinical patient once the hypertrophy mechanisms are exhausted. Additionally, since over 30% of cats will develop renal azotemia as an adult, leaving less than 25% of renal function, and over 95% of cats diagnosed with a unilateral ureteral

obstruction are azotemic at the time of diagnosis, suggesting compromised renal function of the contralateral kidney [6], any preventable loss in GFR should be avoided. This encourages aggressive and timely intervention whenever possible.

Interestingly, in contrast to the irreversibility of a complete obstruction, partial obstructions have been shown to result in less severe and slower nephron destruction, giving more time for intervention when needed [18]. It is estimated in the author's practice that over 85% of feline ureteral obstructions are considered partial, based on ureteropyelography. In a dog model, it was found that after decompression, the GFR returned to normal after 4 weeks from a partial obstruction. Knowing that many patients are partially obstructed, with concurrent renal compromise, aggressive diagnosis, management, and obstruction relief are recommended whenever possible, regardless of the chronicity.

It is now clear that partial obstructions do result in permanent renal damage, just at a slower pace than a complete obstruction, so they should always be treated whenever possible, regardless of the degree of pelvic dilation noted on ultrasound or the suspected chronicity of the condition [6,8]. Knowing the cause of the obstruction is very important when deciding on traditional surgical fixation methods, as different therapeutic methods will be considered for a tumor, stricture, or stone-induced obstruction. For the newer interventional treatment options (double pigtail ureteral stents or a subcutaneous ureteral bypass device), these details are slightly less important, as all can safely be used to treat most causes of a ureteral obstruction effectively, regardless of obstruction cause, location, stone number, or presence of concurrent nephrolithiasis.

Treatment of Feline Ureteral Obstructions

Medical management should always be considered to stabilize a patient prior to any potential anesthetic event. Successful stone passage after medical management has been reported in approximately 8–13% of cases [2], with stones often moving into different positions to allow urine to pass, but the stone itself not actually moving out of the ureter. When this occurs, there is a high risk of reobstruction. The author's recommended approach is to consider fluid diuresis, a ureteral muscle relaxer (alpha-adrenergic blockade), and mannitol (0.25 g/kg bolus IV then 1 mg/kg/min CRI for 24 hours), as long as the patient is not overhydrated, hyperkalemic, oliguric, or showing evidence of progressive renal pelvic dilation on daily imaging. If no stone is seen and there is clear pyuria/bacteriuria (~10–30% of cats with a ureteral obstruction have a positive urine culture) [6,10] then

antibiotics should be started. Purulent plugs can cause a ureteral obstruction in the proximal ureter and medical management can be successful in decompression (Brent, unpublished data). If medical management fails to encourage stone passage after 24–48 hours, then immediate resolution of the obstruction should be considered.

The main interventional options considered in veterinary medicine include nephrostomy tube placement, ureteral stenting, and the placement of a subcutaneous ureteral bypass (SUB) device [4]. Decompression of the renal pelvis will decrease the hydrostatic pressure and stop the permanent damage that is occurring to the renal parenchyma, allowing for immediate renal recovery. When a patient is not stable then intermittent hemodialysis should be considered.

Traditional Surgery

Traditional intervention for *ureterolithiasis* has been accomplished surgically via ureterotomy, neoureterocystostomy, ureteronephrectomy, and renal transplantation [1–3]. In 2005, Kyles et al. reported two retrospective studies in a large number of cats [1,2]. There were high procedure-associated complications (over 30%) and perioperative mortality rates (21%). This study was from two universities that have extensive expertise with ureteral surgery. The morbidity and mortality may be higher in environments where operating microscopes and microsurgical experience are not as readily available. Nearly 10 years later, another study from a different university found the same perioperative mortality rate of 21% [3].

Many of the complications associated with surgery are due to site edema, recurrence of obstruction from stones that pass from the renal pelvis to the surgery site, stricture formation, and ureterotomy-associated or nephrostomy tube-associated urine leakage. In one study [2], over 10% of cats that survived their complications required a second surgical procedure during the same visit and 30% of those cats were then subsequently euthanized or died from serial complications associated with their ureteral stones/surgeries. Of the cats that had long-term imaging follow-up, 40% had evidence of ureteral stone recurrence, 85% percent of which had evidence of ipsilateral nephrolithiasis at the time of the first ureteral surgery [2]. The number of animals that did not have stone recurrence with prior nephrolithiasis was not evident in that study. Chronic kidney disease was found to be common at the time of diagnosis (>75% were azotemic with a unilateral obstruction), and persistent azotemia was commonly seen after a successful surgery (over 50–80% of cats). Even with all of the surgical concerns, survival rates were dramatically higher for cats that had surgical intervention compared to those treated with medical

management alone (33% mortality prior to discharge; 87% failure to see any renal functional improvement).

Additionally, over the past 8 years, the number of stones found in the ureter and kidney have been much greater (median of four stones per ureter in our recent study of 79 ureters) [6], with over 60% of patients in that study not being considered good traditional surgical candidates due to the number of stones, location of stones, presence of a proximal stricture, etc. In this same study, over 86% of cats had evidence of ipsilateral nephrolithiasis, making the risk of ureteral reobstruction higher than that reported in previous studies.

Feline *ureteral strictures* were reported in 10 cats in 2011 by Zaid et al. [12], and have since been reported in a larger series of 79 feline ureteral obstruction [6] and a series of 22 cats with circumcaval ureters [9]. Ureteral strictures can occur for various reasons, and are most commonly seen secondary to a previous surgery of the ureter for stone disease, from a stone becoming embedded in the ureteral mucosa, as a congenital abnormality, associated with idiopathic renal hematuria, as an idiopathic process, and possibly associated with a circumcaval (retrocaval) ureter. Most ureteral strictures were found to occur in the very proximal ureter (<2.5 cm from the renal pelvis), in which traditional surgical approaches were difficult, requiring reimplantation with renal descensus and psoas cystopexy or a ureteral resection and anastomosis. With a cat ureter being <0.4 mm in luminal diameter, this can be a very challenging situation, particularly in a potentially unstable patient.

The ideal procedure would result in immediate decompression and stabilization of the kidney, while concurrently allowing patency to be established quickly and effectively, for any cause of ureteral obstruction (stone, numerous stones, stricture, debris, blood clots, purulent debris, blood stones, tumors, etc.), while decreasing postoperative complications, mortality and long-term reobstruction.

The use of interventional radiological (IR) techniques has aided in circumventing the complications of tradi-

tional ureteral surgery (perioperative leakage, stricture, reobstruction, long anesthesia times, worsening renal function, etc.), particularly in cases that are not considered good surgical candidates. IR techniques have allowed successful and efficient stabilization of the patient regardless of the cause of ureteral obstruction, while decreasing renal pelvic pressure and stopping the cycle of pressure-induced nephron damage and loss [6–10]. It is important to realize when interpreting the current literature that most of what is reported is by groups that have expertise in a certain type of fixation approach. In the hands of an average operator who is not an expert in that particular modality, the outcomes would be expected to be worse, which is the case for traditional surgery and interventional treatment. Additionally, it is important to realize that making a decision between traditional surgery or interventional treatment is not always clear cut. Many, if not most, of the cases reported in the early stages of IR development were those that were considered poor surgical candidates and had failed a previous surgery or were not amenable to traditional surgery. This encouraged an interventional approach to be undertaken. Additionally, most of these early reported cases were in the learning stages of each interventional procedures. It would be unrealistic to try and compare the literature on traditional surgery versus IR techniques due to these reasons. The IR cases were commonly far more complicated, and not amenable to traditional surgery. Instead, the ideal procedure for each patient should be that which would provide the best ultimate outcome in the hands of a particular operator for a particular situation.

Interventional Options

Percutaneous Nephrostomy Tube Placement (Figure 98.1)

Fixation procedures can be relatively prolonged and complicated in highly debilitated patients, especially in facilities where expertise in treating feline ureteral obstruction is not extensive. One possibility is to place



Figure 98.1 Nephrostomy tube placement in a cat with a ureteral obstruction using the modified Seldinger technique. (a) Renal puncture into the kidney of a cat for pyelocentesis and antegrade pyelogram. A guidewire is passed through the catheter and coiled inside the dilated renal pelvis. (b) The catheter is removed over the guidewire and the locking loop pigtail catheter is advanced over the guidewire and coiled inside the renal pelvis. (c) The guidewire is removed and the renal pelvis is drained.

a nephrostomy tube to quickly relieve the obstruction and determine whether adequate renal function remains before prolonged anesthesia for ureteral surgery, ureteral stent or SUB device placement can be performed. A locking loop pigtail catheter is recommended (5 or 6 Fr) to decrease the risk of inadvertent tube removal or urine leakage.

Historically, nephrostomy tubes have met with much resistance due to the high risk of postplacement complications (over 50%). These complications were usually due to premature removal or dislodgment, urine leakage, or poor drainage. With the advent of sturdy, multifenestrated tubes, that form a loop that will lock the catheter in the renal pelvis, these complications seem to have declined dramatically. We reported on the use of the locking loop pigtail catheter in 20 patients [19]. One patient developed leakage into the subcutaneous space and the remaining catheters worked without complication. These locking loop pigtail catheters were deemed to be safe, effective, and well tolerated in both dogs and cats. Placement is typically undertaken percutaneously in dogs using ultrasound and fluoroscopic guidance, and surgically assisted with fluoroscopy and a nephropexy in cats.

Subcutaneous Ureteral Bypass Device

The subcutaneous ureteral bypass device (Norfolk Vet Products) was initially created for feline patients as an alternative to ureteral stents when either a stricture was present (higher rate of stent occlusion, > 50%) or a stent could not be successfully placed due to excessive stones, very narrow lumen, or patient stability. The long-term outcomes documented with the SUB device, the long-term complications, and patient comfort were all found to be superior to those of stents and traditional surgery [8–11]. Due to these findings, the trend in the author's

practice has moved toward using the SUB device as a primary treatment option for all-cause ureteral obstruction in cats. It is very important to understand the risks and benefits of traditional surgery, ureteral stenting, and SUB device placement prior to deciding the best treatment option for your patient, all of which should be carefully discussed with the pet owner.

The placement of nephrostomy catheters in veterinary medicine has demonstrated excellent success when the appropriate device is used [19], but the limitation is the externalized drainage, which is not a long-term fixation, requiring an additional surgery to create something more definitive. The development of an indwelling SUB device using a combination locking loop nephrostomy catheter and cystostomy catheter connected to a subcutaneous shunting port has been highly successful for the treatment of all causes of ureteral obstructions (stones, stricture, tumors, and obstructive pyelonephritis) (Figure 98.2). This device reduces the complications associated with externalized nephrostomy tubes and ureteral stents (see below), and has been shown to be associated with lower mortality and long-term complications than both traditional surgery and ureteral stents in cats [2,3,6,9].

We recently evaluated 174 SUBs in 137 cats, of which 33% were bilaterally obstructed. Twenty percent had bilateral SUBs placed, and 13% had the contralateral side treated with alternative options (a ureteral stent, traditional ureteral surgery, or successful medical management prior to SUB placement). The cause of the ureteral obstruction was stone related in 67%, a stricture in 13%, and a stricture with stones in 20%, documenting the high rate of concurrent strictures (33%) associated with ureteral obstructions in cats. The median preoperative creatinine was 6.6 mg/dL (mean 8) and the creatinine at discharge, 3 months, 6 months, 1 year, 2 year, 3 year,

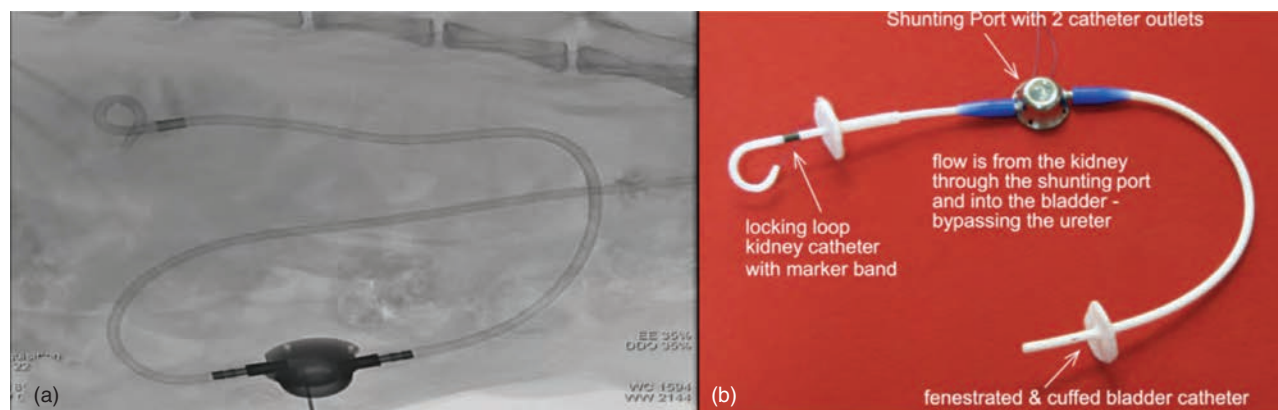


Figure 98.2 Subcutaneous ureteral bypass (SUB) device in a cat. (a) Lateral fluoroscopic projection of a cat after SUB placement for a unilateral ureteral obstruction. Note the nephrostomy tube in the renal pelvis, the cystostomy tube in the urinary bladder and the connection to the subcutaneous metallic shunting port. (b) Catheter hooked up outside the patient.

4 year, and 5 years postoperatively was 2.7, 2.6, 3.1, 2.5, 2.6, 2.2, 2.6 and 4.2 mg/dL, respectively. The perioperative mortality after surgery was 6.6%, with one death associated with an anesthetic-related complication, and none associated with the procedure. The remaining causes of death prior to discharge included failure of improvement of the CKD (2%), pancreatitis (0.7%), neurological signs (0.7%), cardiac causes (0.7%), and other unrelated causes (1.4%). This compares well to traditional surgery (21% perioperative mortality) and ureteral stenting (7.5%). The median survival time was 827 days (range 1 day to 6.6 years), with 51% of patients still alive at the time of data collection. At the time of death, 65% of cases that died were determined to have a renal cause of death as the primary diagnosis. Postoperative complications include leakage of urine (3.4%), kinking of the catheter (5%), and blockage of the system with blood clots or purulent debris (7.5%), or with stone deposition (25%). The need for device exchange from stone deposition in the long term, even in the face of device occlusion, was only apparent in 13% of cases due to the development of ureteral patency at some point after device placement. SUB occlusion was documented in four of 23 of cases with a primary stricture and 35 of 150 (23%) of cases with stones +/- a stricture, compared to 54% of stents in cases with primary strictures.

Dysuria was seen in 23% of cats pre-SUB placement and was uncommonly seen in cats post-SUB placement (8.2%), compared to those with ureteral stents (38%). Of the 8% that had evidence of postprocedural dysuria, 55% had reported dysuria prior to SUB placement, suggesting the possible presence of feline lower urinary tract disease rather than SUB-associated dysuria.

Urinary tract infections were carefully evaluated in this large series of cats after SUB placement, as device implantation and chronic infections had been of concern. Interestingly, chronic urinary tract infections were uncommonly seen after SUB placement in this study (12%) compared to cats after ureteral stenting (30%), with 60% being associated with *Enterococcus* infections, and those cases were nearly always asymptomatic and did not require therapy. Twenty-five percent of cats had a positive culture prior to SUB placement, 10.5% had one infection at any time after SUB placement, and 12% had more than one infection after SUB placement. Only 2.4% of cats had evidence of more than one UTI that did not have a UTI prior to SUB placement, suggesting the SUB device was likely not solely responsible for inducing new infections. Only 8.9% of cats with more than one UTI after SUB placement were considered symptomatic, only one of which (0.8%) was associated with a positive *Enterococcus* infection. Those cats that had urinary tract infections were commonly associated with cats that had externalized urinary catheters (32% of cats with one or

more UTIs and 40% of cats with > 1 UTI) during or after SUB placement.

The SUB device is considered a functional option and is the author's treatment of choice in cats with ureteral obstructions. As with all interventional procedures, the learning curve is steep and the procedure should not be performed until the operator is properly trained and is comfortable with the associated risks.

Ureteral Stenting (Figure 98.3)

Ureteral stenting has been performed for a variety of disorders in both dogs and cats (over 400 cases to date). The goal of using a feline double pigtail ureteral stent (Infiniti Medical, LLC) is to divert urine from the renal pelvis into the urinary bladder during a ureteral obstruction (ureterolithiasis, obstructive neoplasia, ureteral stricture/stenosis, dried solidified blood clots or severe obstructive pyelonephritis or pyonephrosis). Stents also encourage passive ureteral dilation (for ureteral stenosis/strictures or future ureteroscopy, extracorporeal shockwave lithotripsy, etc.), which has recently been documented in normal dogs [20]. The double pigtail stent, which is recommended in cats, is completely intracorporeal, and can remain in place long term, maintaining ureteral patency and passive ureteral dilation (a 0.4 mm ureter was documented to dilate to 1.5–2.0 mm within 3–7 days in over 90% of cats in the author's experience). Each loop of the pigtail is curled (one in the bladder and one in the renal pelvis), allowing for direct urinary diversion from the kidney to the urinary bladder, around the stones, or through the stricture.

In most cats (male and female), the procedure is done using fluoroscopy and surgical assistance using nephrostomy needle access in an antegrade manner, although it can be attempted endoscopically in female cats with a reported 20% success rate (compared to over 95% success with antegrade surgical assistance). Endoscopic



Figure 98.3 Lateral radiograph in a cat after ureteral stent placement for nephroureterolithiasis. Note one pigtail is in the renal pelvis and the other is in the urinary bladder. The shaft of the stent is within the lumen of the ureter.

approaches are not typically performed due to the technical complexity in most practices. This procedure requires special training and experience using wires, catheters and stents, and is not recommended in all patients with a ureteral obstruction. If the operator is not comfortable placing a locking loop pigtail catheter for a nephrostomy tube then this procedure should not be attempted because if stent placement is not successful, the ureter will experience severe edema and spasm and will be acutely obstructed, requiring another mechanism of drainage. Those that are using ureteral stents should be well trained in SUB device placement, nephrostomy tube placement and traditional ureteral surgery so that all options are available for each patient.

A recent study evaluating 69 feline patients (79 ureters) with ureteral obstructions treated with a ureteral stent had a 96% placement success, 14% were bilaterally obstructed, 28% were associated with strictures (+/- concurrent ureteroliths), and 85% of cases had concurrent nephroliths [6]. The median number of stones in the obstructed ureter was four. Approximately one-third of cats had documentation of a urinary tract infection prior to stent placement, and 30% of cats had at least one positive culture in their lifetime after stent placement. The median preoperative creatinine was 5.3 mg/dL and 2.1 mg/dL after stent placement. The perioperative mortality after surgery was 7.5%, with no death associated with a ureteral obstruction or the procedure. This compares to 6.6% mortality with the SUB device [6,9] and 21% with traditional surgery [2,3]. The most common long-term (>1 month) complications after ureteral stent placement were dysuria (38%, but only persistent in 2% after medical management), chronic hematuria (18%), stent occlusion (19%), stent migration (6%), and ureteritis/mucosal proliferation (4%). The dysuria typically resolved with short-term steroid therapy. A ureteral stent exchange with either a bigger stent or a SUB device was needed in 27% of cats for either occlusion or migration. This complication was most commonly associated with ureteral strictures (over 50% of strictured ureters experienced reocclusion) or an occlusion at a previous ureterotomy site. Ureters remained patent long term in most cats, with the longest stent in place and functional for over 5 years. The median survival time was 498 days in this study. The median survival time with a renal cause of death was over 1250 days, with only 21% of cats dying of suspected CKD. With evaluation of cases being treated with all the different options, the author finds that the SUB device is the safest and most expeditious procedure for most causes feline ureteral obstruction, especially in when performed by trained operators.

Another study evaluating preoperative prognostic factors for short- and long-term survivals and renal recovery did not identify any clinical, biochemical or imaging findings to suggest overall survival in patients. It is

important to note that in this study, as well as the SUB device study, there was no association or prediction of renal pelvis size, or kidney size, on preoperative ultrasound and long-term survival. Making an assumption of chronicity and treatment success based on any preoperative information was not shown to be predictive of survival and the ultimate prognosis for renal recovery was considered good to great.

Extracorporeal Shockwave Lithotripsy for Ureterolithiasis

Extracorporeal shockwave lithotripsy (ESWL) is another minimally invasive alternative for the removal of ureteral calculi. ESWL delivers external shockwaves through a water medium directed under fluoroscopic guidance in two planes. The stone is shocked at different energy levels to allow for implosion and powdering. This procedure has been effective in only a small number of feline cases and is possible for very distal ureteroliths or small stones <3 mm in diameter, but is not commonly done in cats. It is important to remember that the feline ureter is normally only 0.3–0.4 mm in diameter and the ESWL unit will break stones to approximately 1 mm in diameter. Without ureteral dilation (concurrent ureteral stent), most of these stones will therefore not pass, and if they do pass, it can take weeks to see that benefit, which promotes renal function deterioration. In addition, feline stones are typically embedded into the ureteral mucosa, so even if the stones fragment well with ESWL, they may not pass as effectively as seen in dogs.

Postoperative Management

Feline patients can have a substantial postobstructive diuresis after relieving a ureteral obstruction, necessitating a large quantity of fluids to maintain hydration. This should be carefully monitored and managed. The leading postoperative complication found in the ureteral stent series was the development of congestive heart failure associated with fluid overload [6]. Most of these patients had a normal echocardiogram prior to their procedure, but the volume of fluids required to maintain their hydration was overloading to their heart. Because of this finding, the author has advocated using a combination of a maintenance rate of enteral hydration (unflavored electrolyte solution – Pedialyte) through the use of an esophagostomy tube (placed at the time of ureteral decompression); a maintenance rate of a low sodium maintenance fluid (0.45% NaCl + 2.5% dextrose); and the remainder of fluids necessary as a replacement fluid. This has been found to lower the sodium load and decrease the risk of fluid overload in the author's experience. Body weights are monitored extremely carefully with fluid rate adjustments occurring throughout each weight assessment.

In the SUB patients, there was no one cause of death due to fluid overload, and all patients were managed similarly with the above protocol. Due to this improved fluid balance in these critically ill patients, the author advocates this approach. Once the creatinine level reaches a plateau, the patient can be weaned off IV fluids, discharged and monitored at 1 and 4 weeks postoperatively (with bloodwork and a urinary tract ultrasound), and a 4-week SUB flush. After this evaluation, they are evaluated every 3 months with bloodwork, a focal urinary tract ultrasound with a SUB flush, and a urinalysis and urine culture is obtained during this flush. Currently the SUB device is being regularly flushed with an antiseptic and anti-mineralization material called tetra-EDTA. Since starting this protocol less than 2% of patients have had any signs of SUB device mineralization or chronic infections.

Conclusion

The feline ureter is a frustrating area to gain access to for both diagnosis and treatment of disease. With recent advances in veterinary interventional endourological techniques, diagnosis and treatment have become less invasive, more effective, and safer. Proper training and the availability of specialized equipment are needed to help these procedures become more available in the future. With these new devices in veterinary medicine, we are hoping to find better alternatives for these problematic conditions, as we have seen in our human counterparts. These techniques offer an alternative option to traditional surgery, and as the data are published, the veterinary community can decide if, and when, interventional techniques will replace traditional surgery, as is the case in human medicine.

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Feline Lower Urinary Tract Obstruction

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Pathogenesis of Obstruction

Urethral obstruction (UO) is a potentially life-threatening manifestation of feline lower urinary tract disease. It has long been held that a physical obstruction, such as a calculus or urethral plug (or, much less commonly, stricture or neoplasia), is responsible for occluding the lumen of the urethra in these cases. However, there is evidence to suggest that functional (or “idiopathic”) obstruction secondary to urethral spasm and edema may play an equally important role in up to 50% [1,2].

These conditions in the urethra are thought to be brought about by underlying feline idiopathic cystitis (FIC). The pathogenesis of FIC is still unclear but it appears to be a sterile inflammatory process as attempts to isolate a bacterial or viral cause have been unsuccessful [3,4]. Instead, documented neurohumoral alterations in cats with FIC suggest the disease may be related to a sympathetic and hypothalamic-pituitary-adrenal imbalance brought about by stressful situations [5]. This imbalance is thought to result in impaired blood flow and release of inflammatory mediators which cause edema, smooth muscle spasm, and pain within the lower urinary tract. These conditions, either independently or in conjunction with a physical obstruction such as a plug or stone, are ultimately what lead to urethral obstruction in cats.

Predisposing Factors

Given their long and narrow urethra (compared to females), it is generally thought that male cats are much more likely to develop obstruction. Further, the likely association with FIC suggests there is also potential cross-over with regard to predisposing factors for UO. In one study examining patients with FIC, it was determined that male, pedigree and long-hair cats were at increased risk, as well as multi-cat households and

known with a housemate [6]. No association was found with age, diet, and indoor–outdoor status. Another FIC study similarly found weight and number of household cats to be risk factors, but did not find an association with breed, long hair, or neuter status [7]. This study also found use of a litter pan, decreased water intake and predominant indoor status were risk factors, but number of litter boxes, conflict with a housemate, and feeding wet versus dry food were not.

In the only available study specifically investigating predisposing factors in cats with UO, it was determined that indoor–outdoor cats in the control population had a decreased likelihood of obstruction [8]. Obstructed cats were older, weighed more and were more likely to be fed dry food only [8]. This study did not reveal any association with breed, neuter or vaccination status, or number of pets in the household.

Pathophysiology of Obstruction

Regardless of underlying cause, complete obstruction of the urethra leads to the accumulation of urine and pressure within the urethra and urinary bladder. Once the tissue can no longer distend, pressure necrosis and mucosal injury will occur. Pressure within the urinary bladder is then transmitted up the ureters to the kidney, with subsequent reduction of glomerular filtration. Within 24–48 hours of obstruction, the kidney's excretory ability ceases, resulting in an accumulation of blood urea nitrogen, creatinine, phosphorus, potassium, and hydrogen ion in the blood which largely contributes to the clinical signs associated with UO.

Uremia can cause depression, nausea, vomiting, and anorexia. The combination of decreased intake of food and water, along with potential gastrointestinal losses (vomiting and diarrhea), can result in dehydration and potential for hypovolemia. Development of profound

metabolic acidosis can lead to denaturing of proteins, enzymatic dysfunction, and catecholamine hyposensitivity. Severe hyperkalemia is considered to be the most life-threatening aspect of UO because of its effects on the cardiovascular system. Elevations in serum potassium affect electrical conduction by raising resting membrane potential and causing diminished sodium conductance. As a result, the rate of depolarization is significantly diminished, resulting in bradycardia. If the serum potassium level gets high enough (typically greater than 10–12 mEq/L), electrical activity in the heart can cease altogether. Without intervention, these changes will ultimately progress to cardiovascular collapse and death, typically within 3–5 days.

History and Clinical Signs

The classic history associated with UO involves a male cat which has been vocalizing and straining unproductively in the litter box. However, these signs might be difficult to distinguish from a cat with FIC. In addition, FIC cats will often urinate very small amounts frequently, and sometimes outside the litter box, making it difficult to know for sure if urine is produced. Multicat households can also present challenges for owners to keep track of whether or not the cat has been urinating. One distinguishing feature of UO (versus FIC) is the development of systemic signs as the obstruction progresses. This could include vomiting, lethargy, anorexia, and abdominal pain which can eventually progress to changes in mentation and lateral recumbency. These signs are fairly non-specific if UO is not suspected, so obstruction should be considered as a differential for any sick male cat.

Clinical signs can vary considerably, depending on severity at the time of presentation. Patients that present early may not have any striking physical exam findings aside from a firm, moderate to large urinary bladder. In the “healthy” blocked cat, this is the most definitive way to help distinguish between obstruction and cystitis (as cystitis cats should have a small, barely palpable bladder). If the obstruction has been present for greater than 24 hours, the patient may be showing signs of systemic illness such as dehydration, bradycardia, and/or hypothermia. The presence of bradycardia in male cats should always raise concern for hyperkalemia as the normal stress response to hospital presentation should result in tachycardia (though cats in septic or cardiogenic shock can also demonstrate bradycardia). In fact, the combination of bradycardia (HR < 140) and hypothermia (T < 96.6°F) has been found to be strongly predictive of severe hyperkalemia (serum level greater than 8 mEq/L) in cats with urethral obstruction [9].

Initial Stabilization

Presentation of the “sick” blocked cat warrants immediate medical attention. An IV catheter should be placed and initial blood samples obtained (PCV/TP, stat electrolyte/acid–base/renal values). Fluid therapy should be started immediately to support vascular volume and help dilute serum potassium concentration, even if bladder decompression cannot be performed immediately. While there are theoretical arguments for use of 0.9% NaCl versus a balanced electrolyte solution (potassium content and acid–base effects), two studies have shown no difference in outcome (survival, length of stay) or in reduction of serum potassium levels [10,11]. And while the acid–base abnormalities corrected more rapidly with a balanced electrolyte solution, overall it does not appear that fluid type has a significant clinical impact. Volume and rate of fluid administration should be dictated by cardiovascular stability, as well as hydration status and/or any concern for underlying cardiac disease.

An ECG is beneficial, even if the patient is not bradycardic, to determine any effects hyperkalemia might be having on cardiac electrical conduction. Classic ECG changes associated with hyperkalemia include prolonged P-R interval, diminished to absent P-waves, widened QRS and tall tented T-waves. As hyperkalemia worsens, ECG changes can progress to atrial standstill, ventricular fibrillation or asystole. While deobstruction and IV fluids will ultimately be the primary means of eliminating potassium and reversing the adverse affects of hyperkalemia, this process takes time. If the patient has significant bradycardia (HR < 140) then immediate intervention to protect the heart (calcium gluconate) and promote intracellular shift of potassium (regular insulin, dextrose, terbutaline, and/or sodium bicarbonate) should be employed (see Table 99.1 for dosing recommendations). Given that calcium gluconate does not serve to decrease potassium levels, if administration is needed to stabilize electrical conduction, the patient should also receive dextrose, or insulin and dextrose (note: dextrose should always be given with insulin to prevent the development of hypoglycemia).

Although controversial, cystocentesis can also be a part of initial stabilization by allowing immediate relief of pressure within the urinary tract and more rapid resumption of glomerular filtration. This could be especially important when busy emergency receiving does not afford the time which might be necessary to relieve the obstruction by passing a urinary catheter (particularly for a novice clinician). In addition, only moderate sedation is usually necessary to perform cystocentesis and a “pure” urine sample can be obtained for urinalysis or urine culture. Finally, relieving the backpressure against the obstruction (whether stone, plug or spasm) may make for easier passage of a urinary catheter, although this has not been substantiated.

Table 99.1 Emergency dosing for severe hyperkalemia. All medications given intravenously.

Medication	Dose	Rate of administration	When to administer
Calcium gluconate	50–150 mg/kg	3–5 minutes	Bradycardia, major ECG changes
Regular insulin	1 unit	IV bolus	If Ca gluconate given
			Potassium > 8 mEq/L
Dextrose	0.5 g/kg	3–5 minutes	If Ca gluconate given
			Potassium > 8 mEq/L
Terbutaline	0.01 mg/kg	IV bolus	If Ca gluconate given
			Potassium > 8 mEq/L
Sodium bicarbonate	1 mEq/kg	5 minutes	Potassium > 10 mEq/L
			pH < 7.0

The major concern raised against performing cystocentesis in UO cats is the potential for tearing or rupture of a distended and friable bladder with resultant uroabdomen. However, a recent retrospective study of 47 UO cats undergoing decompressive cystocentesis did not reveal any significant complications [12]. A prospective study of 45 blocked cats has also demonstrated that development of clinically significant abdominal effusion, as evidenced by abdominal ultrasound performed before and after cystocentesis, occurs very uncommonly and further suggests that this procedure can be safely performed [13].

To help limit the risk of complications, it is important to ensure adequate patient compliance and/or provide sedation so there is minimal patient movement during the procedure. A flexible collection system (syringe, three-way stopcock, extension tubing and 22–20 G needle) may also be beneficial (Figure 99.1).



Figure 99.1 Set-up for performing cystocentesis including syringe, three-way stopcock, extension tubing, and 22 G needle.

Urethral Catheterization

Passage of a urinary catheter to relieve a physical obstruction is generally considered to be essential in the management of UO (see Chapter 187). In addition to successful catheter placement, every effort should be made to minimize urethral trauma as tearing or stricture formation can add significantly to morbidity, cost, and even mortality (from euthanasia) [14].

In order to optimize the likelihood of successful catheterization and minimize damage to the urethra, heavy sedation/analgesia or anesthesia is recommended (Box 99.1). Vocalizing or movement during catheterization attempts, reflecting insufficient sedation, is likely to be associated with significant urethral spasm and an increased risk of urethral trauma. In addition, creating a mixture of saline and sterile lubricant (10:1) as the flush solution can serve to deposit lubricant along the

Box 99.1 Suggested anesthesia protocols for urethral deobstruction.

Stable patient

Premedication/sedation

Ketamine (5–10 mg/kg) + diazepam/midazolam (0.25–0.5 mg/kg)
Buprenorphine (0.01–0.02 mg/kg) and
Acepromazine (0.01–0.05 mg/kg) or diazepam/
Midazolam (0.25–0.5 mg/kg)

Induction

Propofol (1–4 mg/kg, to effect)

Maintenance

Inhalant anesthesia (isoflurane, sevoflurane)

Unstable patient

Buprenorphine (0.01–0.02 mg/kg) + diazepam/
Midazolam (0.25–0.5 mg/kg)
Methadone (0.2–0.25 mg/kg) + diazepam/
Midazolam (0.25–0.5 mg/kg)

Figure 99.2 Catheter flushing apparatus including two syringes, three-way stopcock, extension tubing, sterile saline, and sterile lubricant.

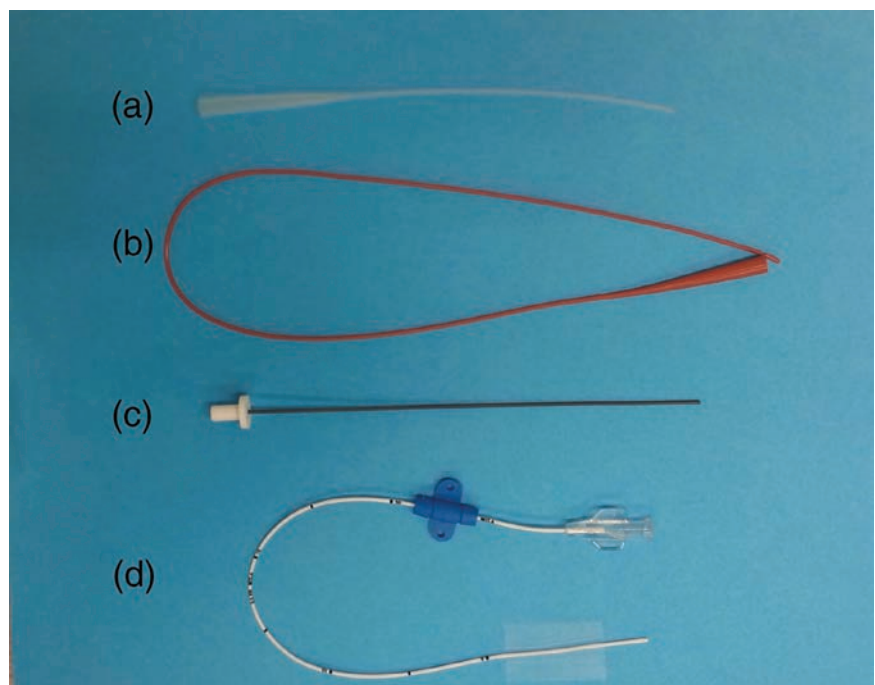


entire length of the urethra and potentially decrease urethral damage (Figure 99.2). Another helpful technique is to pull the prepuce caudally once the catheter is seeded in the penile urethra. This will straighten out the urethra, thus making passage of the catheter easier and less traumatic.

An open-ended catheter (polypropylene, polytetrafluoroethylene or polyurethane) is typically used to

initially relieve the obstruction (Figure 99.3). Given that a polypropylene catheter is rigid and can cause significant urethral irritation [15], it should be withdrawn and replaced by a softer indwelling catheter. Both polytetrafluoroethylene and polyurethane catheters carry the benefit of being firmer at room temperature to facilitate initial unblocking efforts, but then soften when warmed to body temperature (meaning they can be left in place).

Figure 99.3 Common types of catheter used for urethral deobstruction and/or indwelling management – polypropylene (a), polyvinyl (b), polytetrafluoroethylene (c), polyurethane (d).



Findings of a recent study suggest that use of a 3.5 Fr urinary catheter may be associated with less risk of immediate reobstruction when compared to 5 Fr [16]. Given the retrospective nature of this study, care should be taken in interpreting the result, especially given that another similar study failed to find this association [17]. With the catheter securely in place, the urinary bladder can be emptied and flushed, and a closed sterile collection system placed to help decrease the risk of ascending infection.

Diagnostic Evaluation

Careful selection of additional diagnostics to be performed can be very important in UO, especially in cases with limited financial resources. A complete blood count will not often yield significant information beyond that provided by PCV/TP. Urinalysis may reveal crystalluria, along with hematuria and pyuria. Urinary culture at the time of presentation is unlikely to be useful as UO appears to be uncommonly associated with bacterial cystitis [12,18,19]. As there is potential to introduce a UTI, it is recommended that urine culture and sensitivity be performed at the time of catheter removal, although the overall incidence of catheter-associated UTI in UO is currently unknown (see Chapter 96). Given the significant potential for contamination during catheter removal, the practice of submitting the catheter tip for culture should be avoided. It is also prudent to perform abdominal radiographs to assess for cystic/urethral calculi, being certain to include the entire lower urinary tract.

Postobstructive Care

Fluid therapy and monitoring urine output are important aspects of postobstructive care. Patients which have had prolonged obstruction are at risk of a postobstructive diuresis (POD), resulting in massive urine production. This diuresis is thought to occur secondary to the accumulation of osmotically active substances in the blood, pressure necrosis, medullary washout and/or antidiuretic hormone resistance brought about during the obstructive process. It has been demonstrated that POD (defined as urine output > 2 mL/kg/h) may occur in 46% and 88% of postobstructive cats [20,21]. However, in the latter study, the proposed incidence decreased to 37% when corrected for rate of fluid administration. Regardless, it is very important to keep up with urinary losses in these patients as they can quickly become severely dehydrated and hypovolemic.

Another potential concern is for inadequate urine production (< 1 mL/kg/h) after obstruction is relieved.

This could occur as a result of obstruction in the collection system or dehydration. True oliguria could occur as a result of progression to acute renal failure but this appears to be very uncommon in urethral obstruction (see Chapter 95).

Another important aspect of postobstructive care is analgesia and sedation (see Section 7; Chapters 190–193). Cystitis and obstruction, in addition to urethral catheterization, are painful and could be associated with risk of reobstruction. An opioid (such as buprenorphine or methadone) generally provides sufficient pain control. In addition to analgesia, acepromazine can provide adequate sedation to decrease stress and agitation (provided the patient is cardiovascularly stable). The alpha-antagonist effects of acepromazine might promote urethral relaxation [22]. Prazosin, an alpha-1-antagonist, could also be used for this purpose.

A frequent consideration in the postobstructive period is whether the patient should be placed on antibiotics, either to address existing UTI or prevent development of UTI from having a catheter in place. As previously stated, the incidence of UTI at presentation appears to be very low [12,18,19]. Further, it has been well documented that antibiotics do not prevent development of catheter-associated UTI [23,24] and in two studies investigating incidence of acquired UTI, rates of 13–33% were reported [18,19]. Given the low incidence, performing a urine culture and sensitivity after catheter removal is recommended to determine if a UTI has been introduced (see Chapter 96).

Electrolytes and renal values are serially monitored, with frequency dictated by initial severity of abnormalities. Significant reduction in renal values is expected within 24 hours, otherwise complications may have occurred (renal failure, uroabdomen, etc.). Hypokalemia can develop (especially in patients with POD) and potassium should be supplemented accordingly. The urinary catheter is typically left in place until the cat is clinically improved, bloodwork has normalized, POD has resolved, and urine is free of major debris, clots or plugs. Once the catheter has been removed, a 12–24-hour period of observation is recommended to ensure effective spontaneous urination is possible prior to discharge.

Alternative Management Protocols

Owner financial constraints may significantly affect the ability to provide optimal care for cats with UO. For severely affected cats (hypothermia, bradycardia, lateral recumbency, etc.), euthanasia may be the only option. As an alternative to euthanasia in stable UO cats, it has been demonstrated that an in-hospital protocol of

pharmacological manipulation (analgesia and sedation), a low-stress environment, and intermittent cystocentesis can result in spontaneous urination without the need for catheterization [25]. Alternatively, patients that must be seen on an outpatient basis may be managed with bladder decompression through one-time passage of a urinary catheter to clear any physical obstruction. The patient is then discharged with recommendations as outlined below in the hope that continued analgesia and sedation will allow for spontaneous urination to occur.

At-Home Care

Given the potential for recurrence, at-home care may be extremely important to help decrease the likelihood of reobstruction either immediately or in the future. Continued analgesia and sedation after discharge may be helpful, with administration of acepromazine and buprenorphine or gabapentin for 5–7 days. For patients demonstrating significant straining/urethral spasm after catheter removal, it may be of benefit to also administer prazosin as an alpha-1 antagonist and urethral relaxant. Antibiotics should only be dispensed based on results of urine culture taken at the time of catheter removal (see

Chapter 96). Other recommendations which have been made to help decrease the risk of reobstruction include increasing water intake by switching to wet food, flavoring the water, or using a running-water bowl. Given the questionable role that urinary crystals play in the pathogenesis of obstruction, it is unclear whether dietary manipulation of urinary pH to address crystalluria is beneficial. Given the potential role that stress may play in the pathogenesis of this disease, environmental enrichment may also help [26].

Prognosis

The potential recurrence of UO has been reported as anywhere from 15% to 40% [2,16,17,27]. With a second obstructive episode, it becomes more likely that there will be subsequent occurrences, at which point it may be necessary to consider perineal urethrostomy (PU). This surgical procedure can significantly decrease the likelihood of UO, although it does not serve to resolve signs of underlying FIC. In addition, these patients may be at an increased risk for UTI. However, a study of 86 cats undergoing PU showed good long-term quality of life with minimal risk of recurrence [28].

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Urethral Trauma

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Incidence

The reported incidence of traumatic urethral rupture ranges from 0.003% to 5% [1,2] in dogs; however, the incidences in cats and of iatrogenic urethral injury are unknown. Males are more frequently affected in both dogs (85%) [3] and cats (88.9%) [4]. The ischiocavernosus and ischiourethralis muscles anchor the urethra to the ischium in the male [5,6], which may make it less tolerant to traumatic traction and shearing forces [7]. The male urethra also has a smaller diameter, predisposing it to obstruction [7]. This may increase the risk of iatrogenic injury through increased likelihood of urethral catheterization being performed. Differences in temperament with increasing roaming in males may also lead to a greater risk of vehicular trauma [8].

The most common cause of urethral injury in both dogs and cats is trauma, accounting for 70% of cases in dogs [4] and 55.6% of cases in cats [7]. In dogs, urethral injury is associated with pelvic fractures in 85.7% of cases [4]. However, in cats, pelvic fractures account for only 37.1% of cases [7], indicating that blunt trauma without pelvic fracture can lead to significant urethral injury in cats.

Patient Evaluation

Clinical signs are variable and include dysuria, stranguria, anuria, hematuria, abdominal distension and discomfort, anorexia, depression and hind limb, inguinal, and perineal swelling or bruising [4–9]. It is important to ascertain whether the animal has suffered any trauma or has a history of urolithiasis, urethral catheterization or previous surgery in the vicinity of the urethra.

During physical examination, particular attention should be paid to abdominal palpation for bladder assessment and for signs of pain. The hindlimbs, inguinal, and

perineal area must be evaluated for swelling or discomfort, which may indicate subcutaneous urine extravasation. Assessment of hemodynamic status and correction of any metabolic abnormalities is important. Affected animals may be azotemic, hyperkalemic or develop metabolic acidosis. Further information regarding the pathophysiology and correction of electrolyte and acid–base disorders is given elsewhere in this text (see Chapters 107–110).

An emergency minimum database should be collected and ideally includes blood pressure measurement, biochemistry (urea, creatinine, lactate, electrolytes, total solids), packed cell volume, acid–base status, electrocardiogram and abdominal ultrasound to assess for free abdominal fluid (see Chapter 182). If an effusion is identified, fluid should be collected for analysis (see Chapter 186). If the creatinine and potassium levels of the peritoneal fluid exceed those of the serum by >2:1 and >1.4:1 respectively, then a diagnosis of uroabdomen is confirmed [10]. If an initial minimum database is not suggestive of urine leakage and the patient's status does not improve, the authors recommend re-evaluating the minimum database every 6–12 hours as low-volume urine leakage may take 24–48 hours to become apparent. Please see Chapter 103 for further information on uroabdomen.

Diagnosis

Contrast radiography, such as retrograde urethrography, is the diagnostic test of choice for urethral rupture. The presence of urethral disruption is confirmed by extravasation of contrast along the course of the urethra (Figure 100.1). With complete disruption of the urethra, no contrast should flow beyond the urethral defect. However, with partial rupture contrast may reach the bladder.

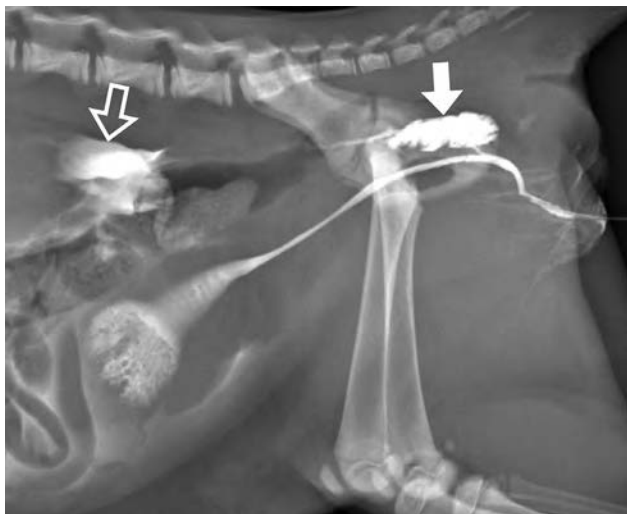


Figure 100.1 Retrograde urethrogram performed in an 8-week-old kitten with a history of urethral obstruction and catheterization. Notice the extravasation of contrast medium dorsally in the intrapelvic portion of the urethra (*closed arrow*), with contrast medium extending into the retroperitoneal space (*open arrow*). The cranial extension of contrast medium past the urethral disruption and into the bladder is consistent with a partial rupture.

It is not always possible to assess the severity of rupture from contrast radiography. Diagnostic urethral catheterization is an alternative but is controversial as it may cause further tearing. With partial rupture, it should be possible to pass the catheter into the bladder. However, with complete urethral rupture, displacement of the urethral ends prevents catheterization of the bladder [9]. Cystourethroscopy can also be considered but is rarely recommended. It can be difficult to perform in patients with urethral injury as leakage prevents fluid distension of the urethra that normally aids visualization [11]. There is also a risk of introducing bacteria into the abdominal cavity or perineal soft tissues [11].

Treatment

Urethral trauma can be managed conservatively through second intention healing, by surgical repair or by permanent urinary diversion (e.g. urethrostomy). Treatment planning should take into account the nature and extent of injury, and consider the requirement for temporary urinary diversion.

The two most important factors in promoting urethral healing are good mucosal continuity and prevention of urine extravasation. The urethral mucosa heals rapidly in as little as 7 days but regeneration of the corpus spongiosum can take 3–5 weeks [12]. The degree of urethral injury influences healing. Experimental resection of up

to two-thirds of the canine urethral circumference for a length of 1–5 cm still leads to good regeneration of the mucosa when a urethral catheter is placed during the healing phase, as long as a strip of urothelium connects the proximal and distal urethral ends [12]. However, with complete transection of the urethra, the urothelium contracts intraluminally due to spastic contraction of the muscle layer and this prevents healing. Periurethral tissue then covers the urethral ends and results in fibrous tissue proliferation [13]. In cases with partial rupture, conservative management with second intention healing can be attempted. However, in cases with complete rupture, surgery is indicated. Traumatic injury is more likely to lead to complete rupture [7] and so appropriate patient selection is important.

Urine is toxic to local tissues and leads to necrosis [7]. It also increases periurethral fibrosis, which in turn can increase stricture formation [13]. Temporary urinary diversion away from the site of injury to prevent extravasation should be utilized in all cases to promote healing.

Conservative Management

This is achieved by temporary urinary diversion whilst the urethral mucosa heals by second intention healing. Urinary diversion may be provided using a cystostomy tube, urethral catheter, or both. The authors' preference is to place a urethral catheter because it will act as a stent to aid alignment and healing [9]. Reported disadvantages of catheterization include mechanical irritation and the risk of ascending infection, both of which may promote stricture formation [13]. It is very important that the catheter is appropriately sized to prevent damage to the urethra during catheterization [13]. Most cases can be catheterized in a retrograde manner but some require normograde catheterization via a cystostomy incision [9]. See Chapters 97 and 189 for further information on how to perform urethral catheterization. In cases that have had urethral anastomosis, both methods of urinary diversion are as effective in promoting urethral healing [14] but the effect of cystostomy versus catheterization on healing in cases managed conservatively has not been established. In some patients, the use of both types of diversion simultaneously may be advantageous, particularly if the patient is fractious or difficult to manage.

The optimal duration of urinary diversion is unknown and has ranged from 3 to 37 days [7,15]. However, as the urethral mucosa takes 7 days to regenerate [12], a minimum period of 7 days urinary diversion is recommended in patients with significant trauma. Shorter periods are likely to only be suitable for cases with minor lacerations to the urethra.

Prior to cessation of urinary diversion, a retrograde urethrogram should be performed to assess for ongoing

leakage. If further leakage is identified, the authors advise to continue urinary diversion for another 3–5 days prior to repeating the contrast study. If persistent leakage is still identified, surgical treatment is indicated. Once urinary diversion is stopped, urination should be monitored for a further 24–48 hours. Urethritis caused by catheterization [13] may lead to transient hematuria or incontinence.

Urinary tract infection occurs in up to 80% of cases even when closed urine collection systems are used [9]. The risk of infection increases with the duration of catheterization [16]. Antibiotics administered while indwelling urinary catheters are in place will not prevent the development of infection [9] (see Chapter 96) but may increase the risk of antibiotic-resistant bacteria. Antibiotics should not be prescribed prophylactically to cases with indwelling urinary catheters unless they are at risk of sepsis or there is a separate infectious process elsewhere. Regular urinalysis to screen for infection is recommended and urine culture should be performed if infection is suspected. Broad-spectrum antimicrobials should be initiated if infection is confirmed and altered dependent on culture results (see Chapter 96). Submission of the catheter tip for culture at the end of catheterization is not recommended. It is unreliable for identifying urinary tract infection in people because presence of bacteria on the catheter does not correlate with urinary tract infection [17]. In addition, some bacteria may be cleared after catheter removal [17]. The authors recommend urinalysis 24 hours after catheter removal even if normal urination is documented.

Success rates of up to 80% have been reported in patients managed conservatively with urethral catheterization [9]. Cats with iatrogenic injury following catheterization for lower urinary tract disease may require long-term ongoing medical management of their underlying disease. See Chapter 99 for further information on feline lower urinary tract obstruction and Chapter 97 on urolithiasis.

Surgical Management

Surgery is indicated for complete transections of the urethra or if conservative management with temporary urinary diversion fails.

Urethral Anastomosis

The surgical approach depends on the location of the defect but involves a caudal celiotomy and/or a pubic placed to identify and orientate the urethral ends. This is usually performed retrograde but a second catheter may need to be placed normograde if identification of the proximal end is difficult. The blood supply to the torn edges of the urethra is often compromised and the edges must be sharply debrided to promote healing.

After apposition of the urethral ends, the urethra is sutured using 4-0 or 5-0 absorbable monofilament suture in an interrupted pattern including mucosa and submucosa in each bite. The mucosa typically retracts into the lumen and must be identified for suturing to ensure correct apposition. Previous experimental work has found that the degree of stricture formation is reduced when suturing of the urethra occurs over a urethral catheter [18]. It is critical that there is no tension at the anastomosis site or dehiscence is likely [18,19]. Ischial osteotomy, ischial osteotomy, and crural release are reported to help decrease tension [19,20]. Once the anastomosis is completed, the authors' preference is to omentalize the surgical site.

Permanent Urethrostomy

Urethrostomy provides permanent urinary diversion by creating a stoma to bypass the area of injury. The location of the stoma depends on the position of the defect. There are higher complication rates associated with urethrostomies performed at more proximal locations so the most distal urethrostomy possible should be performed [7,21].

In male dogs, scrotal urethrostomy is preferred as the urethra in this region is superficial and relatively wide. The urethra is surrounded by less cavernous tissue at this site, which leads to a reduction in the amount of hemorrhage [22]. One of the main complications of this technique is postoperative hemorrhage but this is reduced when a simple continuous pattern and three-needle bite sequence (urethral mucosa first, then tunica albuginea, then skin) is used [23]. This is suggested to improve tissue apposition and uses fewer suture knots to reduce tissue irritation. However, a retrospective study reported postoperative hemorrhage in all cases, regardless of whether a continuous or interrupted suture pattern was used [22].

In male cats, perineal urethrostomy is most frequently performed by amputating the penis and prepuce and generating a urethrostomy at the level of the ischium using the pelvic urethra (Wilson and Harrison technique) [24]. The authors prefer a modified technique that retains the prepuce and anastomoses preputial and urethral mucosa to provide preputial cover to the site [25,26]. This reduces the opportunity for self-trauma and may decrease the incidence of postoperative stricture and urinary tract infection. Adequate dissection of the intrapelvic portion of the urethra from fibrous attachments to the pelvis and release of the ischiocavernosus muscle attachments are very important with both techniques to reduce tension at the stoma site and give access to the wide pelvic urethra.

For more proximal urethral defects, transpelvic urethrostomy and prepubic urethrostomy can be considered, of which the transpelvic urethrostomy may have a lower complication rate [27].

Complications

Complications affect up to 57.1% of cases in the first 10 weeks following treatment and 27% in the long term [7]. They include urinary tract infections, strictures, stenosis of urethrostomy stoma, dehiscence, incontinence, urine scalding, urine extravasation with either peristomal skin necrosis or uroabdomen, and the development of lower urinary tract disease. The most common complication is urinary tract infection, which involves multidrug-resistant organisms in up to 28.6% of cases [7]. Patients requiring permanent urethrostomies have higher complication rates when the urethrostomy is performed at more proximal sites [7,21].

Stricture Management

Stricture development is a severe complication, which can lead to dysuria or complete urethral obstruction, typically seen when reduction of luminal diameter exceeds 60% [18]. Historically, these have been managed with urethral resection and anastomosis, permanent urinary diversion with cystostomy tube placement or, in mild cases, medical management to promote urethral relaxation [7,27,28]. Long-term management of permanent cystostomy tubes in animals can be problematic and bacterial cystitis is reported [29]. Dependent on the length and location of the stricture, repeat surgery with resection and anastomosis or permanent urethrostomy may not be possible.

Minimally invasive alternatives include repeated balloon dilation or urethral stent placement (Figure 100.2), with and without antifibrotic treatment. Disadvantages of balloon dilation include the requirement for multiple dilations in some cases [28]. Advantages of urethral stent placement include immediate relief of obstruction in a single procedure, which may decrease morbidity and save costs [28]. Complications of stent placement in dogs include incontinence (seen in 12.5% of cases with benign obstructions), inadvertent compression of the stent, tissue ingrowth through the stent or incomplete patency

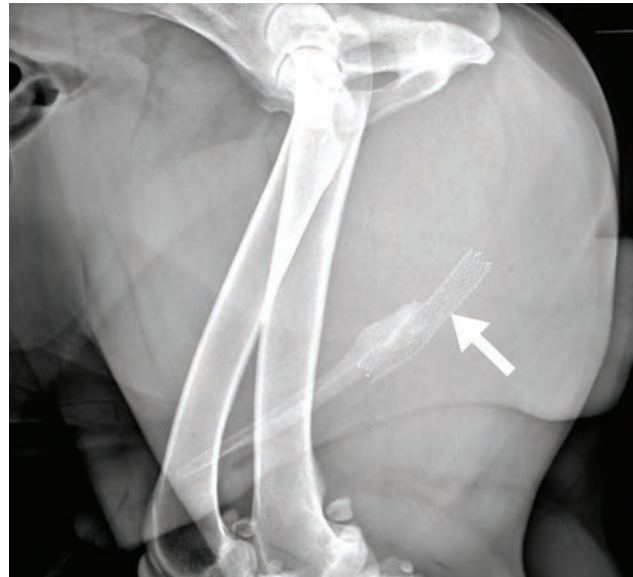


Figure 100.2 Urethral self-expanding metallic stent (arrow) placed in a 3-year-old male entire rottweiler with a urethral stricture secondary to chronic urethrolithiasis and a urethral tear.

after the first procedure [28]. For the latter three complications, a second stent can be placed to improve the outcome. Urethral stents have also been successfully placed in cats for management of urethral strictures [29,30] and incontinence rates appear to be similar to dogs. The proximity of the ureterovesicular junction to the proximal urethra in the cat means that ureteral obstruction is a concern when attempting to address strictures in this area [30].

Outcome

Outcome for patients that have iatrogenic injury is generally better than for those which have had traumatic rupture. A good outcome (survival to discharge and without long-term complications) is seen in 83.3–91.3% of cases after iatrogenic injury and 50–57.1% after trauma [4,7].

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Lyme Nephritis

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Introduction

When dogs present emergently with serious and sudden complications of protein-losing nephropathy (PLN) (e.g. thromboembolism (TE), hypertension, effusions/edema, and/or renal failure), criticalists are called upon to stabilize and support them, submit or save appropriate samples before starting antimicrobial therapy, and discuss estimates for diagnostic tests (to stage disease and rule out differentials), treatments, future monitoring, and overall prognosis, so that owners can make educated decisions concerning their options.

Lyme nephritis [1–4] is suspected in Lyme-seropositive PLN cases (Lyme+ PLN), but in endemic regions, being seropositive for antibodies against the agent (“Lyme+” status) is common in many healthy dogs and possibly coincidental in sick dogs, so other causes of illness need to be considered. Lyme+ status is a marker for tick and wildlife exposure; an important differential diagnosis that may mimic Lyme nephritis is leptospirosis and precautions (isolation) may be necessary due to its infectious and zoonotic potential [5].

Transmission, Prevalence, and an Experimental Model of Canine Lyme Disease

Exposure to the spirochete *Borrelia burgdorferi* is very common in Lyme-endemic areas (New England, Mid-Atlantic, Upper Midwest states, and adjacent Canada). In people, 95% of Lyme disease cases were reported in just 14 states (CT, DE, ME, MD, MA, MN, NH, NJ, NY, PA, RI, VT, VA, WI) [6]. Data concerning exposure rates among dogs are similar [7]. In some areas 70–90% of healthy dogs are Lyme+, but less than 5% showed Lyme arthritis (similar to seronegative dogs) over 20 months of observation [2]. Lyme arthritis is often overdiagnosed; 40% of dogs so diagnosed were later found to have another

cause for their signs [8]. Roughly less than 1–2% of Lyme+ dogs show PLN, often attributed to Lyme nephritis but possibly due to other causes [1–4,9,10]. Proteinuria is rarely associated with Lyme+ status, even among Lyme+ retrievers, which are the predisposed breeds [11].

Transmission of the agent occurs via the bite of the three-host field deer tick or black-legged tick (*Ixodes scapularis* in the East/MidWest, *I. pacificus* in the West, and *I. ricinus* in Europe). Transstadial but not transovarial transmission occurs within the tick. The 2-year life cycle of an *I. scapularis* tick begins with six-legged larvae acquiring the agent during summer feeding on the first hosts, usually mice, small rodents, or migratory birds; after feeding for several days, the ticks fall off, molt to eight-legged nymphs, emerge and feed the following spring on small mammals, birds, and also larger species such as dogs, deer, and people, and transmit the agent to them after roughly 2 days of feeding. After feeding for several days, nymphs molt and emerge as adult ticks in the autumn, again able to transmit the agent to larger animals as the adult ticks quest on higher vegetation. Migratory birds spread infected ticks to new areas. Deer ticks in Lyme endemic areas may also carry *Anaplasma phagocytophilum*, *Babesia microti*, *Borrelia miyamotoi*, *Ehrlichia muris*-like agent, tick-borne encephalitis (Powassan) virus, and possibly *Bartonella* and *Mycoplasma* spp.

A natural tick exposure experimental model of Lyme disease in dogs demonstrated that adult beagles remained seropositive carriers, but showed no illness when observed for more than a year after tick exposure [12]. Exposed beagle puppies (6–12 weeks old) showed no acute signs; 2–5 months after tick exposure and well after seroconversion, they showed only 4 days of self-limiting anorexia, fever, and lameness in the leg closest to the tick bites, sometimes with several similar episodes every few weeks, associated with the agent’s ability to hide from the immune system near collagen and fibroblasts, with antigenic variation during carrier status. Exposed

puppies aged 13–26 weeks showed milder signs (1–2 days) and fewer episodes [1].

Some experimental dogs were inadvertently co-infected with *A. phagocytophilum* and *B. microti*. Carrier dogs maintained high Lyme antibody titers; cultures of skin biopsies of the tick bite sites showed viable spirochetes even a year later while the dogs showed no further illness. When treated with antibiotics for 1 month, about 10–15% of dogs were not cleared of spirochetes in the skin [13]. There is no experimental model for Lyme nephritis; perhaps multiple exposures, different strains of the agent, co-infections, or predisposed breeds are necessary to induce the disease. Since retrievers appear to be at highest risk, a genetic predisposition may involve immunodysregulation or innately abnormal glomeruli that are unable to clear immune complexes normally (e.g. a podocytopathy) [14].

Presentation of Field Cases with Presumptive Lyme Nephritis [1–4,15]

A typical case of Lyme nephritis is a middle-aged Labrador or golden retriever (although any breed may be affected) living in a Lyme-endemic region, presenting with several days' to weeks' history of lethargy, anorexia, acute vomiting and/or diarrhea, mild-to-moderate systemic hypertension, Lyme+ status, hypoalbuminemia, hypercholesterolemia, mild-to-moderate azotemia, possible hyperphosphatemia and/or hyperkalemia, consumptive thrombocytopenia, urine specific gravity 1.020–1.030 (isosthenuria is a late sign), proteinuria/cylindruria, possibly glucosuria, mildly active sediment, and negative urine culture. Polyuria/polydipsia are relatively late signs due to tubular involvement. Oliguria/anuria may be due to acute kidney injury (AKI), therefore other causes should also be considered (e.g. leptospirosis, Rocky Mountain spotted fever) (see Chapter 94). Fever, pallor/anemia, icterus, liver enzyme elevation, petechiation/ecchymoses, lymphadenopathy, or hepatosplenomegaly are not commonly seen with Lyme disease and if present, may be due to co-infection or co-morbidity.

Other presentations may involve thromboembolic events due to vasculitis, hypertension, and hypercoagulability from the PLN and subsequent loss of antithrombin (e.g. dyspnea due to pulmonary TE; weakness/lameness due to a saddle or limb TE; collapse, seizure, or sudden death due to cardiac or neurovascular TE) (see Chapter 62), effusions/edema due to hypoalbuminemia (e.g. dyspnea due to pleural effusion, ascites, incipient edema with crystalloid therapy), hypertensive damage (e.g. blindness due to retinal hemorrhage/detachment, epistaxis, neurological signs) (see Chapter 63), and/or lameness (due to Lyme or other tick-borne arthritis or neurovascular

events). One study reported previous or concurrent lameness in less than 30% of cases and past Lyme vaccination in almost 30% [15]. Still other presentations may be occult (early/mild), so any Lyme+ dog, whether healthy or sick, should be screened for proteinuria. Early/mild cases may have hypoalbuminemia but with only mild (or no) azotemia, and these dogs have the best prognosis.

Recent tick exposure is not a prerequisite. In the experimental model of Lyme disease in young puppies, classic signs of illness (anorexia/fever/lameness) were not seen until 2–5 months after tick exposure, well after seroconversion [12]. The initiation and progression of Lyme nephritis is unknown (the experimental model did not develop PLN), but is assumed to be a later occurrence due to chronic immune stimulation by this stealth pathogen which manifests antigenic variation during the carrier state. A history of previous treatment for Lyme disease for 1 month does not ensure clearance, as 10–15% of experimental dogs so treated still showed cultivable organisms in biopsies taken from tick bite sites [13].

Physical examination is often unrewarding. Dogs with gastrointestinal signs secondary to azotemia may be dehydrated. Cavitary effusions or dependent edema may be evident in dogs with nephrotic syndrome. Dyspnea may be due to pleural effusion, aspiration pneumonia or pulmonary TE. Retinal changes (hemorrhage/detachment/intraocular exudation) and a soft cardiac murmur may be target organ damage from hypertension. Lameness may be due to oligo/polyarthropathy from Lyme or co-morbid tick-borne arthritis, saddle or limb TE (evaluate pulses carefully) or neurological events.

Diagnostic Work-Up to Stage Disease and Rule Out Other Differentials [1–4,9,10]

The diagnosis of Lyme nephritis is often presumed in Lyme+ dogs with PLN until proven otherwise. Diagnostic tests (Table 101.1) are helpful to localize proteinuria, rule out other causes of PLN, stage renal disease, and identify complications requiring special tests or management. Other causes for proteinuria need to be considered, including lower urinary tract disease, pyelonephritis, leptospirosis, tick-borne and other infectious diseases, vasculitis, inflammatory and immune-mediated diseases, neoplasia, amyloidosis, non-amyloid fibrillary deposition, genetic glomerular/renal diseases, systemic hypertension, hyperadrenocorticism, toxins (e.g. shiga-toxin from ingestion of raw meat or wildlife, nephrotoxins), and other renal diseases.

Since seropositivity is a marker for tick and wildlife exposure, a search for co-infections that may cause proteinuria is warranted, especially leptospirosis, dirofilariasis, anaplasmosis, ehrlichiosis, babesiosis, bartonellosis,

Table 101.1 Diagnostic work-up for dogs with suspected Lyme nephritis [1–4,9,10].

Data	Additional detail
History	Travel? Exposure to ticks/wildlife/raw meat? Lameness? Other?
Physical examination	Complete, including retinal examination
Blood pressure measurements (BPM)	One reliable very high BPM vs persistently high BPM
CBC (including platelets)	Cytopenias may indicate co-infection or immune-mediated illness;
Chemistry profile	thrombocytopenia may be due to consumption (TE)
IRIS staging of renal disease [16]	
Possible D-dimers, TEG, AT testing	Hypercoagulopathy
DNA sample for inherited PLN	Where tests are available or for future research
Urinalysis	Sample USG before starting fluid therapy
Urine culture*	Sample urine culture before starting antimicrobials
Urine protein:creatinine ratio (UPC)	Check trend; monitor with mixture of 3 days' equal aliquots
Possible SDS-PAGE to differentiate glomerular and tubular proteinuria	Submit to IVRPS, contact Dr Mary B. Nabity, mnabity@cvm.tamu.edu
SNAP®4Dx®Plus (IDEXX):Heartworm antigen	
Natural exposure antibodies to:	The AccuPlex®4 (Antech) test had lower specificity/sensitivity for antibodies to <i>B. burgdorferi</i> and <i>A. phagocytophilum</i> [17]; may give false-positive results for natural infection in dogs vaccinated with bacterins that produce Lyme ospC antibodies; and may not pick up cross-reacting antibodies against <i>A. platys</i> , <i>E. chaffeensis</i> or <i>E. ewingii</i>
<i>B. burgdorferi</i> (qualitative C ₆ test)	
<i>A. phagocytophilum</i> / <i>A. platys</i> **	
<i>E. canis</i> / <i>E. chaffeensis</i> / <i>E. ewingii</i> **	
Lyme Quant C ₆ * (IDEXX), before and after (3–6 months) treatment	Lyme nephritis cases generally have high titers but so do many healthy dogs (titer height is not predictive). Posttreatment value of <50% of prevale may represent successful clearance and is useful as a new baseline for future comparisons (qualitative testing may be positive for many years)
Leptospirosis: PCR*, antibody titers**	*PCR testing of blood (first week of illness), urine thereafter
Other infectious diseases [9,10]:	See Chapter 200 regarding regional infectious diseases and PLN
Babesiosis	<i>Babesia</i> spp PCR* and titers for <i>B. canis</i> / <i>B. gibsoni</i>
Bartonellosis	<i>Bartonella</i> spp PCR*, titers, culture, and/or Western blot
Rocky Mountain spotted fever (RMSF)**	Consider RMSF only if history is acute
Hepatozoonosis	If exposure (south-eastern states) or raw meat/wildlife ingestion
Leishmaniasis	If exposure or American foxhound, spinone, cane corso, etc.
Brucellosis	For dogs at risk
Imaging	Check for neoplasia, effusion, cardiomegaly
Chest radiographs	Check for neoplasia, lower urinary tract disease, adrenal size; kidney
Abdominal ultrasound	ultrasonogram is often non-remarkable in PLN cases
Possible echocardiogram	Check for hypertensive changes (hypertrophic cardiomyopathy, left ventricular hypertrophy), pericardial effusion, other
Possible search for other causes of hypertension	Consider hyperadrenocorticism, hyperaldosteronism, pheochromocytoma, primary hypertension, etc.
Possible work-up for hyperadrenocorticism	May cause proteinuria and hypertension but usually is not associated with hypoalbuminemia
Renal biopsy [18,19]	TEM and IF are important to document immune-complex glomerulonephritis and rule out other causes of PLN; see text

*Save samples before starting antimicrobials.

**Paired (acute/convalescent) titers may be needed.

AT, antithrombin; BPM, blood pressure measurement; IF, immunofluorescence; PCR, polymerase chain reaction; PLN, protein-losing nephropathy; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; TE, thromboembolism; TEG, thromboelastography; TEM, transmission electron microscopy; USG, urine specific gravity.

and, if the history is acute, Rocky Mountain spotted fever. An extended search may include rarer infections related to travel, breed predisposition, or other exposures. Response to therapy does not prove Lyme nephritis. Most dogs with Lyme arthritis respond to doxycycline quickly, but doxycycline treats many other tick-borne diseases that may cause similar signs, and has antiarthritic and anti-inflammatory properties. The in-house SNAP®4Dx®Plus (IDEXX) test offers quick confirmation of seropositive (natural exposure) status, but the clinician needs to keep an open mind and obtain the appropriate samples to rule out other causes (e.g. save whole blood in refrigerated EDTA (lavender top) tubes for PCR analysis for other agents and urine for PCR and bacterial culture before starting antimicrobials; see Table 101.1). Additional diagnostic investigations may be warranted depending on extrarenal abnormalities found, such as joint tap cytology/culture, lymph node and/or bone marrow aspirates, etc.

Renal Biopsy

Lyme nephritis is associated with immune-complex glomerulonephritis (ICGN), tubular necrosis/regeneration, and interstitial nephritis [15]. Without an experimental model, the progression is unknown, and perhaps early/mild cases have only glomerular disease without secondary tubular or interstitial involvement. Renal damage is due to deposition of Lyme-specific immune complexes in glomeruli and not spirochetal invasion of the kidney. Light microscopy can differentiate amyloidosis as a cause of PLN, but detailed examination by trained personnel with transmission electron microscopy, immunofluorescence, and thin section (3 μ) light microscopy with special stains is best to differentiate ICGN from glomerulosclerosis, hereditary nephritis, or other renal changes [18,19]. A candidate for renal biopsy is not in end-stage disease, has hypertension controlled, sufficient platelets, and has not received antithrombotics in at least 5 days.

Trained personnel should procure the samples and specimens which are then saved in glutaraldehyde, Michel's fixative, and formalin. The samples should be sent overnight with ice packs inside a styrofoam box to veterinary nephropathologists of the International Veterinary Renal Pathology Service (IVRPS) which are prepared to receive the shipments [9,10,18]. Kits for sample submission are obtained from the IVRPS (in the USA: Department of Veterinary Biosciences, Ohio State University, Columbus, OH 43210, contact Dr Rachel Cianciolo, rachel.cianciolo@cvm.osu.edu; in Europe: Utrecht Veterinary Nephropathology Service, Utrecht University, Utrecht, The Netherlands, contact Dr Astrid M. van Dongen, a.m.vandongen@uu.nl).

The finding of ICGN suggests immunosuppressive protocols may be useful in cases that are not responding to antimicrobials and standard therapy for PLN [10]. Although ICGN may be documented by biopsy, there are no validated stains to confirm that such complexes are Lyme specific, that is, they may be due to another tick-borne disease such as babesiosis [20], other infections, or neoplasia, etc. which hopefully will be recognized by the other diagnostic tests (PCR/titers, imaging, etc.) recommended (see Table 101.1) so that appropriate therapy will be given.

Treatment (Table 101.2)

Emergent care may include respiratory and intravascular volume support for dogs with hypovolemia/dehydration, thromboembolic events, hypertension, effusions/edema, and/or AKI or chronic renal disease as reviewed elsewhere (see Chapters 45, 62, 63, 94, 153). Judicious use of crystalloid therapy is warranted (if indicated at all), and colloids, diuretics, and even hemodialysis may be necessary since aggressive fluid therapy in hypoalbuminemic dogs often leads to edema/effusions, especially dogs with renal compromise (see Chapters 167, 168, 169).

Standard treatments for Lyme+PLN dogs (see Table 101.2) include long-term antimicrobials (1–3 months, or until Lyme Quant C₆® (IDEXX) wanes), angiotensin converting enzyme (ACE) inhibitors and/or other inhibitors of the renin-angiotensin-aldosterone system (RAAS), antithrombotics, antihypertensives, renal diet, omega-3 fatty acid supplement, and treatments as necessary for signs of renal failure (antiemetics, gastrointestinal protectants, antacids, phosphate binders, appetite stimulants, etc.) [16,21–23]. Immunosuppressant medication is not generally given without renal biopsy confirmation that ICGN exists, unless the case is deteriorating quickly despite standard therapy. The best protocol is unknown since there is no experimental model of Lyme nephritis and there are no validated stains to prove that immune complexes found in biopsies are Lyme specific. Thus inclusion/exclusion criteria are undefined for documented versus control cases to be studied in therapeutic trials. The current anecdotal favorite immunosuppressive is mycophenolate. Pulse steroids may be used in fulminant cases, but should be weaned as soon as possible to avoid side-effects (increased risk for thromboembolic events, hypertension, and gastric ulceration, for which these animals are already predisposed).

The prognosis for dogs admitted for intravenous fluids due to dehydration, vomiting, and moderately severe azotemia has historically been poor, but may be improving with the addition of treatments in Table 101.2; however, when dogs do well (unexpectedly), it is always

Table 101.2 Treatments for Lyme nephritis [16,21–23].

Treatment	Dose or detail (all drug doses are per os)
<i>Antimicrobial</i> Longer than 1 month, until Lyme Quant C ₆ [*] (IDEXX) shows at least a 50% decline	Doxycycline is first choice, 5–10 mg/kg q12h Other: amoxicillin, azithromycin, or cefovecin Duration to clear carrier status is unknown
<i>ACE inhibitor and/or other RAAS inhibitor*</i> ACE inhibitor Angiotensin-receptor blocker (ARB) Aldosterone-receptor blocker	Goal for UPC < 0.5 or at least < 50% initial value Enalapril or benazepril 0.25–1.0 mg/kg q12h Telmisartan 1–2 mg/kg q24h or Losartan 0.5–1 mg/kg q24h (1/4 this dose if azotemic) Spironolactone (diuretic) 1–2 mg/kg q12h
<i>Antithrombotic</i> (see Chapter 71) Prevention (if renal biopsy is not planned) Treatment for existing TE events	Low-dose aspirin 1–5 mg/kg q24h or clopidogrel 1.1 mg/kg q24h
<i>Antihypertensive</i> (goal: < 150/95 mmHg) If hypertensive even on an ACE/RAAS inhibitor Calcium channel blocker (first choice) Beta-blocker Alpha-blocker Direct vasodilator See Chapter 63	Amlodipine 0.1–0.75 mg/kg q24h Atenolol 0.25–1.0 mg/kg q12h Prazosin, 0.5–2 mg/kg q8–12h Hydralazine 0.5–2 mg/kg q12h Acepromazine 0.5–2 mg/kg q8h
Renal diet Omega-3 fatty acid supplement	Lower in protein, phosphorus, and sodium N-3 polyunsaturated fatty acids 0.25–0.50 g/kg q24h See also Chapter 102
Fluids – colloids/crystalloids	See Chapters 94, 95, 167–169
<i>Diuretic</i> if necessary Aldosterone-receptor blocker Thiazide diuretic Loop diuretic	Spironolactone 1–2 mg/kg q12h Hydrochlorothiazide 2–4 mg/kg q12–24h Furosemide 1–4 mg/kg q8–24h
Antiemetics, antacids, protectants	See Chapter 102
Phosphate binders	See Chapter 102
Immunosuppressives [22] (if renal biopsy shows ICGN and case is not responding to antimicrobials and standard PLN therapy, or in cases without renal biopsy, if deteriorating quickly) [10,23]	Mycophenolate 10 mg/kg q12h Cyclophosphamide, pulse 200–250 mg/m ² q3 weeks Chlorambucil 0.2 mg/kg q24–48h Azathioprine 2 mg/kg/day × 1–2 weeks; 1–2 mg/kg q48h Cyclosporine 5–20 mg/kg q12h (wax upward) Prednisone for fulminant cases: short-term pulse, 1 mg/kg q12h, wean as soon as possible
±Plasmapheresis?	Theoretically may be helpful to decrease circulating immune complexes

*An ACE inhibitor and/or ARB is standard therapy for PLN to decrease proteinuria by dilating both the afferent and efferent arterioles at the glomerulus, and should be used whether or not the dog is hypertensive.

difficult to know whether the diagnosis of Lyme nephritis was really accurate.

Monitoring

After discharge, dogs often require monitoring of arterial blood pressure, urine protein:creatinine ratio

(UPC), albumin, azotemia, and other abnormalities, usually every 1–2 weeks until more stable. Since UPC values have daily variation and tend to be higher from samples obtained in the clinic [24], it is recommended that the owner collect urine samples at home each morning for 3 days; equal aliquots of the samples are then mixed and submitted to the laboratory for one UPC determination [25].

Prevention, Tick Control and Lyme Vaccination

Antimicrobial treatment of non-clinical, non-proteinuric Lyme+ dogs is controversial and reviewed elsewhere [26,27]. Whether or not a Lyme+ dog is treated, it needs continued monitoring for development of proteinuria since not all dogs are cleared of their carrier status with 1 month of antimicrobial treatment.

To avoid (re)exposure to Lyme and other vector-borne diseases, control of fleas and ticks is recommended year

round, preferably including a product that prevents tick attachment (topical or collar containing permethrins or amitraz) or that kills ticks very early during feeding (oral or topical isoxanzolines) in order to prevent acquiring agents that are transmitted much faster than *B. burgdorferi* [3,28]. Vaccination for Lyme disease is still controversial for both healthy and sick dogs [3,29]. There is no evidence of benefit for dogs with Lyme nephritis and vaccination may even be contraindicated lest potential deposition of circulating vaccinal antigen-antibody complexes occur in glomeruli in predisposed dogs.

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Chronic Kidney Disease

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Introduction

Chronic kidney disease (CKD) is a commonly recognized cause of illness in dogs and cats. The prevalence varies with the population examined, but has been estimated between 0.5% and 7% in dogs and between 1.6% and 20% in cats [1]. Given this high prevalence, it is not surprising that many cats and dogs presenting on an emergency basis suffer from CKD. One of the challenges of emergency identification of CKD is differentiating it from presentations of acute kidney injury (AKI) or concurrent CKD and AKI (acute on chronic kidney disease).

For this reason, CKD is defined as kidney damage that has persisted for greater than 3 months. This time period has been proposed because healing and resolution of azotemia may continue for several months after AKI [1]. Identification of chronicity of disease may be based on medical history, physical exam changes, historical laboratory findings, and renal structural changes, as described in Table 102.1. However, it is difficult to rule

out a component of acute on chronic kidney disease, so many of these patients should also be treated as potential AKI cases (see Chapter 94).

Pathophysiology

Most cases of CKD in cats and dogs do not have a well-defined underlying cause. Studies of the underlying histopathology have shown that inflammatory infiltrates and fibrosis are key markers of the disease [2]. A variety of insults and predisposing factors can contribute to the development of CKD. Congenital causes such as renal dysplasia, polycystic kidney disease, and amyloidosis have been recognized. Acquired causes include the chronic perpetuation of most causes of AKI including pyelonephritis, partial obstruction from ureteroliths, glomerulonephritis, neoplasia, and renal infarctions.

Regardless of the cause, the decline in functional nephrons causes a decrease in glomerular filtration rate (GFR). Compensatory mechanisms allow for maintenance of water and electrolyte balance despite the loss of kidney function by increasing the excretory load of each surviving nephron. Ultimately, these compensatory mechanisms are insufficient to maintain adequate secretion, and the resulting decompensation manifests as hypertension, edema, hyperphosphatemia, and metabolic acidosis [1]. This loss of excretory ability also results in the gradual increase in serum uremic solutes.

A staging system for CKD has been proposed by the International Renal Interest Society (IRIS) [3]. This system is based on evaluation of the patient's serum creatinine, proteinuria, and blood pressure as measured multiple times over the course of several weeks. Therefore, staging cannot be appropriately applied in the emergency setting. In addition, it is not appropriate to stage animals who may have a component of acute disease, as

Table 102.1 Differentiation of CKD and AKI.

Features of CKD	Features of AKI
Polyuria/polydipsia for > 3 months	Recent increased or decreased urination
Inappetence for > 3 months	Recent inappetence
Weight loss	Normal body condition score
Poor quality hair coat	
Small kidney size	Normal or large kidneys
Renal osteodystrophy	
Non-regenerative anemia	
History of azotemia for > 3 months	Normal bloodwork in last 3 months
History of proteinuria for > 3 months	Normal urinalysis in last 3 months

their status may improve with time. A separate clinical scoring system has been proposed for cats and dogs with AKI [4,5] (see Chapter 94).

Presentation

Cats and dogs with CKD generally present with a collection of clinical signs, including polyuria, polydipsia, weight loss, anorexia, vomiting, lethargy, halitosis, and weakness. Initial physical exam may reveal dehydration, muscle atrophy, emaciation, small and irregular kidneys, hypothermia, oral ulcers, and pallor.

Diagnostics

Laboratory Tests

The acquisition of patient samples prior to treatment is essential in determining the cause and severity of disease in these patients. Priority should be given to running a venous blood gas or other rapid analyzer of acid–base and electrolyte status, with samples for a serum chemistry panel and complete blood count also being collected at this time. Frequently identified abnormalities include azotemia and metabolic acidosis (see Chapter 107). Hypokalemia is found in 18% of cats with uremic CKD, although hyperkalemia is seen in 22% of cats with end-stage disease [6] (see Chapter 109). Calcium homeostasis is also significantly affected by CKD, with ionized hypocalcemia being reported in 56% of cats with end-stage CKD [7]. Total and ionized calcium in dogs with CKD can be decreased, normal, or elevated [8] (see Chapter 110).

The chemistry panel will typically reveal azotemia and hyperphosphatemia in addition to the electrolyte abnormalities described above. It is important to get a baseline measurement of blood urea nitrogen (BUN) and creatinine on admission in order to monitor for any improvement with correction of prerenal azotemia as targeted by initial therapy. Degree of hyperphosphatemia has been shown to be related to increased mortality in cats with CKD [9] and is correlated with worsening stage of disease in dogs [10].

The most significant finding on complete blood count for animals with CKD is anemia. This is typically a normocytic, normochromic, non-regenerative anemia (see Chapter 65). The cause of the anemia is associated with impaired production of erythropoietin (EPO), and dogs with CKD have been shown to have a relative deficiency of EPO (low or normal despite anemia) [11]. However, the anemia may be multifactorial with other causes including shortened red blood cell lifespan, poor nutrition, and gastrointestinal blood loss due to uremic gastroenteritis.

Ordering a reticulocyte count can help to further characterize the cause of the anemia in these patients.

A sterile urine sample should be acquired from all patients before starting fluid therapy. A standard urinalysis as well as a urine culture should be performed regardless of clinical signs, as cats have been shown to have positive urine cultures despite a lack of lower urinary tract signs [12] (see Chapter 96). Antibiotics should be considered until culture results are available. Other important findings on urinalysis include urine specific gravity, which should be isosthenuric in most cases of CKD, and proteinuria. Some cats (and rarely dogs) may have concentrated urine despite renal azotemia, which is suspected to be related to glomerular disease and is termed “glomerulotubular imbalance” [13]. Proteinuria is best evaluated with a urine protein:creatinine ratio (UPC) as long as there is no active sediment. Degree of UPC elevation has been shown to correlate with mortality in both cats and dogs [14,15].

Imaging

Abdominal ultrasonography is recommended for evaluation of all patients with CKD. In the emergency setting, imaging may be reserved for animals with a high suspicion of obstructive ureteral disease, such as cats with acute elevations in kidney values. At a minimum, these patients should have orthogonal abdominal radiographs taken to evaluate for the presence of ureteroliths (see Chapter 98).

Monitoring

It is important to acquire a set of baseline parameters to facilitate continued monitoring during hospitalization. Important parameters include body weight, which is essential for monitoring hydration status, and frequency of urination. In polyuric animals, placement of an indwelling urinary catheter is not necessarily required, but should be performed if there is concern regarding potential oliguria (see Chapter 95). In addition, blood pressure should be obtained in all animals presenting with CKD. Hypertension is seen in 19% of cats [16] and 31% of dogs [17] presenting with CKD and has been correlated with a worse prognosis (see Chapter 63). Urine specific gravity should not be used as a measure of hydration status in animals with CKD as their urine is typically isosthenuric despite dehydration.

Stabilization and Initial Therapy

Fluid Therapy

Cats and dogs with severe kidney disease are usually polyuric and may present with severe dehydration or

hypovolemia, generally necessitating intravenous fluid therapy. Rates should be determined based on a calculation of fluid deficit ($\text{body weight (kg)} \times \text{percent dehydration}$) and by taking into account any ongoing losses due to vomiting or diarrhea. The fluid deficit should be replaced over 6–24 hours depending on other variables that may require slower replacement (such as the identification of heart disease) or faster replacement (such as cardiovascular instability) (see Chapter 167).

Electrolyte and acid–base abnormalities are also addressed with fluid therapy. Potassium supplementation is frequently required in patients with CKD, and high rates may be required to normalize serum potassium (see Chapter 109). Metabolic acidosis is also frequently found in these patients. While this is largely corrected by improving perfusion with fluid therapy, a blood pH below 7.2 after correction of volume deficits is an indication for intravenous sodium bicarbonate supplementation [13] (see Chapter 174).

The primary risk with fluid therapy is volume overload or the development of edema. Screening for heart disease should be performed prior to high rates of fluid therapy if at all possible. In addition, animals with significant proteinuria may have hypoalbuminemia and low colloid oncotic pressure. In these patients, high rates of fluid therapy can cause fluid loss into pleural, abdominal, pulmonary, or interstitial spaces, so cautious fluid therapy rates are advised. Ideally, rates above 25 mL per kg of body weight per day should be avoided.

Management of Anemia

Patients with CKD frequently develop anemia as a consequence of an impaired ability to synthesize endogenous EPO. Typically, this anemia develops slowly as the CKD progresses, so these animals are able to tolerate more severe levels of anemia. However, if the patient is severely anemic (hematocrit less than 15%) and is displaying clinical signs of anemia such as tachycardia, tachypnea, or weakness, then a transfusion may be required. Whole blood or packed red blood cells may be used, with packed red blood cells preferred if volume overload is a concern (see Chapter 176).

If the patient is anemic but not significantly clinically affected, EPO products are recommended to stimulate erythropoiesis. Currently, darbepoietin alpha (DPO) is the preferred product due to anecdotal reports of lower risk of anti-EPO antibody development compared to the use of recombinant human EPO products. A retrospective study on DPO use in cats determined an ideal starting dose to be 1 $\mu\text{g/kg}$ subcutaneously once weekly [18]. Weekly monitoring of hematocrit is recommended in order to determine when dosing frequency can be reduced to every other week or once every 3 weeks.

Target hematocrit is roughly 30–40% (closer to 30–35% for cats and 35–40% for dogs) [1,19]. DPO treatment can cause hypertension, so regular blood pressure monitoring is recommended during therapy [18].

The erythropoiesis stimulated by EPO analogues requires ready availability of iron, and iron concentrations have been shown to be low in many animals with CKD [20]. This may be due to reduced intake, iron sequestration from inflammation, or increased loss due to gastrointestinal bleeding. Therefore, iron supplementation is recommended concurrently with EPO administration. An initial intramuscular injection of iron dextran (50 mg for a cat and 50–300 mg for a dog) is recommended, and monthly dosing may be required in some animals [21].

Hypertension (see Chapter 63)

Hypertension is a common sequela to CKD, and the presence of hypertension is one of the criteria for sub-staging in the IRIS system [3]. However, unless systolic blood pressure exceeds 200 mmHg or there are clinical signs representative of end-organ damage (retinal lesions or neurological signs), initiation of antihypertensive therapy is not required on an emergent basis [21].

If rapid reduction of hypertension is required in an emergency setting, a calcium channel blocker such as amlodipine is recommended. Multiple studies have shown that amlodipine is an effective and safe antihypertensive agent in cats [22–24] and dogs [25,26]. Starting daily doses of 0.625–1.25 mg for cats and 0.1–0.5 mg/kg for dogs are recommended.

Management of Gastrointestinal Signs

Many animals with CKD present with decreased appetite, nausea, vomiting, and diarrhea. Antiemetics such as ondansetron, dolasetron, or maropitant are frequently warranted. Cats with CKD have been shown to have increased gastrin concentrations, suggesting a potential role of CKD in promoting gastric hyperacidity [27]. The use of histamine-2-receptor antagonists or proton pump inhibitors to suppress gastric acid secretion is often recommended, although conclusive evidence of their efficacy in reducing morbidity associated with CKD has not been established.

Management of anorexia can include the use of appetite stimulants or assisted feeding. Mirtazapine has been used to stimulate appetite in cats and dogs with CKD with recommended dosing of 15–30 mg every 24 hours in dogs and 1.875–3.75 mg every 48–72 hours in cats [19]. A pharmacokinetic study has validated every other day dosing frequency in cats with CKD [28]. Despite appetite stimulation, many animals with CKD will require supplemental feeding via placement of a feeding tube.

Placement of an esophagostomy tube is recommended since many animals will require long-term nutritional support, although nasoesophageal or nasogastric tubes can be placed for short-term supplementation. Early placement of a feeding tube is strongly recommended.

Dose Reduction

Many commonly used medications are eliminated through the kidney, and the reduced renal function associated with CKD can prolong the half-life of these medications. This can lead to drug accumulation and an increased rate of adverse reactions. Ideally, dosage reductions are made based on calculations using the patient's GFR, but this is rarely measured in veterinary patients and is never available on an emergency basis, so other methods of dose reduction have been described [1].

One option is to decrease total dose by either halving the drug dosage or doubling the dosing interval, and this is used for drugs that have low risks of toxicity. A second method is to increase the dosage interval or decrease the dosage based on the use of serum creatinine as an estimation of GFR. In this method, the dosing interval is multiplied or the dosage is divided by the patient's serum creatinine. With this method, a cut-off of serum creatinine of 5 mg/dL is recommended to avoid decreasing dose to subtherapeutic levels, as higher creatinine concentrations are not well correlated with GFR. This method is used with drugs that are more likely to be toxic. The third option is to precisely adjust doses based on calculation of the percentage reduction in GFR and is recommended for drugs that have a high risk of toxicity. Examples of drug doses that should be adjusted and the recommended methods of adjustment are shown in Table 102.2.

Prognosis and Long-Term Management

A patient with CKD is considered stable when the serum creatinine has reached a baseline and they are no longer threatened by severe anemia, hypovolemia, hypertension, or electrolyte imbalances. Longer term management includes transitioning to a restricted protein and phosphorus diet, using phosphate binders, administering subcutaneous fluids, and continuing antiemetic therapy as needed. Additional considerations include control of persistent hypertension and proteinuria. More advanced therapeutic modalities, including renal transplantation, hemodialysis, and peritoneal dialysis, are available at a small number of veterinary hospitals, but the cost and availability of these options limit the number of animals with CKD that are managed in this fashion.

Table 102.2 Drug dosage adjustments for patients with CKD (adapted from [1]). Method 1: decrease dose by half or double dosage interval. Method 2: adjust according to serum creatinine concentration. Method 3: precise dosage modification using GFR (see text for more details).

Drug	Dosage adjustment method
Amikacin	3
Amoxicillin	1 or 2
Amphotericin B	3
Ampicillin	1 or 2
Cephalexin	2
Clindamycin	None
Chloramphenicol	None
Cyclophosphamide	None
Corticosteroids	None
Doxycycline	None
Enrofloxacin	1 (increased dosing interval)
Furosemide	None
Gentamicin	3
Heparin	None
Nitrofurantoin	Contraindicated
Penicillin	1 or 2
Propranolol	None
Tetracycline	Contraindicated
Tobramycin	3
Trimethoprim/sulfamethoxazole	2

Regardless of which management strategies are employed, CKD is a progressive disease. IRIS staging has been used to provide estimates of survival time in patients with CKD. In cats, median survival time (MST) was found to be 1151 days in stage 2 (although this study only included cats on the more severe end of stage 2), 679 days in stage 3, and 35 days in stage 4 [9]. The MST in dogs with CKD is less well defined, but one study demonstrated that dogs with CKD who were fed a renal diet had a MST of 594 days, while those kept on a normal maintenance diet had a MST of 188 days [29]. Another study showed that being underweight significantly reduced survival time as well as demonstrating that dogs with IRIS stage 4 CKD had shorter survival times than dogs with stage 2 or 3 disease [30]. The magnitude of proteinuria has been associated with a reduced survival time in both dogs [15] and cats [14,31]. Hypertension has been shown to increase the risk of uremic crisis and death in dogs [17].

Overall, CKD is a serious, chronic illness that requires dedicated monitoring and treatment by the owner and

rigorous follow-up with a veterinarian. Most animals with CKD will eventually succumb to the disease or its sequelae, but many can live for meaningful periods of time after diagnosis with sufficient owner dedication and supportive care.

Conclusion

In summary, cats and dogs with CKD will frequently present on an emergency basis. Initial goals in evaluating

these patients are to identify azotemia as well as pinpoint life-threatening complications including hypovolemia, hypertension, metabolic acidosis, anemia, and derangements in serum potassium. Taking blood and urine samples for characterization of kidney disease is an important first step and should precede implementation of first-line therapies, including intravenous fluid administration, blood transfusion, and management of profound hypertension. While lifelong monitoring and management of CKD will be required, substantial improvement can be made in the initial emergency period of patient hospitalization.

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Uroabdomen

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Etiology and Pathogenesis

Uroabdomen, or leakage of urine into the peritoneal and/or retroperitoneal space, occurs due to loss of integrity of the urinary tract anywhere from the kidneys to the distal end of the intra-abdominal portion of the urethra. The term *uroabdomen* incorporates both uroperitoneum and uroretroperitoneum. The former results from rupture of the intra-abdominal urethra, bladder or distal ureters, while the latter results from rupture of the proximal ureters or kidneys.

Causes of disruption to the urinary tract include trauma – blunt, penetrating, and iatrogenic – urinary obstruction, neoplasia, and dehiscence following urinary tract surgery [1–7]. In cats, trauma has been reported to be the cause of urinary tract rupture in 84.6–100% of study populations, with approximately half of these traumatic events being iatrogenic, and the bladder being the most common site of rupture [1,3]. In dogs, there is a similar incidence of traumatic etiologies, though a smaller proportion of canine cases were iatrogenic [2,4,6]. Concurrent injuries such as pelvic fractures may be present in as many as 70% of cases [1,4,6]. Male animals are over-represented [1,2,4], a finding attributed to the difference in urethral anatomy from females. The urethra of male cats and dogs is narrower than that of their female counterparts, and has greater attachments to bone; thus it is less adept at coping with fast and profound increases in intravesicular pressure [1,4,8,9]. Additionally, males may be more likely to roam and therefore be involved in trauma.

Regardless of the inciting cause, the pathophysiological consequences of uroabdomen are the same. As hyperosmolar, potassium-rich urine accumulates in the abdominal cavity, there is an osmotic pull of extracellular fluid (ECF) into the peritoneal space due to the concentration

gradient of sodium and chloride between the ECF and peritoneal fluid, favoring diffusion into the abdominal cavity. This third spacing combined with likely decreased fluid intake and increased losses through vomiting contribute to the dehydration and possible shock that may ensue.

The urine in the abdominal cavity also results in a concentration gradient of urea and creatinine across the peritoneum. Urea is a relatively small molecule at 60 daltons, and equilibrates fairly rapidly [2]. Creatinine has a molecular weight of 112 daltons, and takes longer to diffuse into the systemic circulation [2]. Due to the body's inability to excrete urea and creatinine, progressive azotemia develops. Metabolic acidosis occurs from a combination of accumulation of uremic acids, severe dehydration and/or hypovolemia resulting in a lactic acidosis, and from retention of hydrogen ions within the peritoneal or retroperitoneal space with subsequent reabsorption into the circulation and impairment of the intrinsic buffering system (see Chapter 107).

The kidneys are the primary mechanism for excretion of potassium from the body. The high potassium content of urine accumulating in the abdomen ultimately results in hyperkalemia with the potential to cause increased membrane excitability and subsequent cardiac arrhythmias [10]. Because potassium is typically excreted via the Na⁺/K⁺/ATPase pumps in the renal collecting ducts and distal tubules faster than reabsorption across the peritoneal cavity can occur, the concentration of potassium in the abdominal fluid will be higher than in the blood [2,11,12].

In addition to the metabolic derangements described above, the chemical peritonitis that results from direct contact of urine with the peritoneum causes substantial pain (see Chapter 87).

Clinical Signs and Physical Examination Findings

Clinical signs may be vague and non-specific, including vomiting, anorexia or lethargy, depending on when in the course of the disease a diagnosis of uroabdomen is made. Physical examination findings may include signs of shock or impaired perfusion, a palpable fluid wave and/or abdominal distension, abdominal pain, dehydration, cardiac arrhythmias or signs of concurrent trauma such as inguinal or perineal bruising, or pelvic fractures [1,3,6,7,9,13].

It should be noted that *palpation of a seemingly intact bladder does not rule out the diagnosis of uroabdomen* [1].

Diagnosis and Laboratory Evaluation

The diagnosis of uroabdomen is made based on a combination of clinical signs, physical examination findings, laboratory assessment of peripheral blood in comparison with abdominal fluid, and imaging techniques.

Laboratory Findings

As with many emergencies, a complete blood count and serum chemistry with an electrolyte panel are invaluable in assessing the systemic health of a patient. Laboratory findings may include [1,3,5,6,9]:

- azotemia
- hyperkalemia
- hyponatremia and hypochloremia
- hyperphosphatemia
- metabolic acidosis
- hemoconcentration (if dehydrated)
- neutrophilia (+/- left shift)
- hematuria (macroscopic or microscopic).

The rise in blood urea nitrogen (BUN) may be disproportionately greater than the rise in creatinine due to the more rapid equilibration of urea between the intra-abdominal urine and the systemic circulation. In people, BUN:creatinine ratios greater than 30:1 have been reported in cases of uroabdomen, with the normal ratio being approximately 10–15:1 [14,15].

Abdominocentesis with subsequent evaluation of the fluid is arguably the most useful tool in definitively diagnosing uroabdomen, though it gives no information as to the location of the rupture (see Chapter 186). It may be performed with the guidance of ultrasound or as a blind tap. The pathophysiology of uroabdomen results in an elevated creatinine and potassium in the abdominal fluid relative to the peripheral blood. Ideally, the same serum

Table 103.1 Reported abdominal fluid potassium and creatinine to peripheral blood ratios in dogs and cats [1,2].

	Abdominal fluid: peripheral blood creatinine	Abdominal fluid: peripheral blood potassium
Dogs	>2:1 (86%, 100%)*	>1.4:1 (100%, 100%)*
Cats	>2:1**	>1.9:1**

*Sensitivity, specificity.

**Sensitivity and specificity not reported.

chemistry or electrolyte analyzer should be used for the peripheral blood as abdominal fluid to avoid confounding results. Benchtop analyzers are available, but many do not provide consistent and reliable results [16].

The published ratios consistent with uroabdomen in dogs and cats are reported in Table 103.1.

The more azotemic an animal, the lower the gradient is expected to be [2,9]. Full analysis of the abdominal fluid is also recommended, including cytology. The fluid may range from a pure transudate, modified transudate to an exudate depending on chronicity, severity, and presence of any infectious agents [17]. If the latter were found, criteria for a septic uroabdomen would be satisfied (see Chapter 87).

Imaging Findings

Ultrasound is a valuable tool in diagnosing uroabdomen. Though originally developed for use in trauma patients, the focused assessment with sonography for trauma (FAST) (see Chapter 182) examination may be useful, regardless of the etiology of the free abdominal fluid. An abdominal FAST involves evaluating four areas – caudal to the xiphoid, around the urinary bladder, and around each kidney – for presence of free fluid [18]. Contrast cystography has been described in two dogs and an *in vitro* model whereby injection of microbubbled saline allowed visualization of bladder tears with ultrasound. In this study, microbubbles were created in saline by manually injecting sterile saline and air vigorously, back and forth, between two syringes through a three-way stopcock. Larger air bubbles were expelled, and the remaining solution was infused promptly through a urinary catheter into the bladder. The presence of a bladder tear was confirmed by ultrasonographic visualization of microbubbled saline leaking outside the bladder and passing into the peritoneum [19].

Plain radiographs may show a loss of intra-abdominal serosal detail. This may be confined to the peritoneal or retroperitoneal space, or may be generalized [1,6,9,20]. The bladder or kidneys may or may not be visible [1,9]. Depending on the cause, additional abnormalities such as urinary calculi or pelvic fractures may be seen [1].

Contrast radiographic studies are easy to perform on an emergency basis and can help to definitively diagnose

a uroabdomen or determine the exact location of the rupture [20]. The choice of contrast study will be determined by the suspected location of disruption. For suspected bladder or urethral tears, positive contrast cystography and urography are indicated respectively [1,20]. For renal damage or suspected ureteral rupture, excretory urography is the contrast study of choice [5,6,20]. False negatives can occur and are most commonly due to insufficient volume of contrast agent [6,9,20]. Contrast agents should be used with caution in azotemic or dehydrated patients, due to the risk of acute kidney injury [9,20] (see Chapter 94).

Advanced imaging modalities such as CT urography and MR urography are being utilized more frequently in human medicine, but limited availability and higher costs constrain their widespread application in veterinary medicine [21].

Emergent Stabilization

Initial evaluation and treatment should be directed towards achieving and/or maintaining systemic stability. Fluid therapy should be utilized as indicated to restore perfusion and normalize heart rate, pulse quality, capillary refill time, and blood pressure. These traditional endpoints of resuscitation, together with mentation and body temperature, are typically considered the standard of care, though it should be noted that ongoing oxygen debt may be sustained past normalization of these [22]. Peripheral lactate concentration, pH, base deficit, and central venous oxygen saturation may also provide valuable information about the patient's hemodynamic status (see Chapters 152 and 153).

Fluid type may depend on co-morbidities and severity of shock, and choices could include isotonic, hypertonic or colloid solutions, or combinations of the above (see Chapters 167–169). It has been suggested that avoidance of potassium-containing fluids in a hyperkalemic animal is warranted [23]. However, a study by Drobatz and Cole showed that a balanced electrolyte solution such as lactated Ringer's solution improved acid–base status after 12 hours of fluid therapy in a population of hyperkalemic cats with urethral obstructions with no difference in serum potassium, when compared to 0.9% saline, suggesting that a balanced electrolyte solution may be preferable [24].

It is important to fully evaluate the patient for concurrent injuries that may affect means of stabilization. Additionally, analgesia is an important component of initial therapy, both for the pain associated with chemical peritonitis and any concurrent orthopedic or soft tissue injuries (see Chapter 193). Opioids, specifically pure mu-agonists, are ideal due to superior pain relief and minimal risk for toxicity [25]. Non-steroidal anti-inflammatories should

be avoided in patients with hemodynamic compromise and altered renal function. Ketamine should be used cautiously in these patients, since it may have a prolonged duration of action due to its excretion in urine [26,27].

Due to the potential for electrolyte derangements, particularly hyperkalemia, an electrocardiographic assessment (ECG) is warranted in all patients with diagnosed or suspected uroabdomen. ECG abnormalities reported with hyperkalemia include peaked T-waves, decreased P- and R-wave amplitude, prolonged QRS and P-R intervals, S-T segment depression, and increased Q-T intervals. With rising potassium concentration, this may progress to atrial standstill, sinoventricular rhythm, and ventricular fibrillation or asystole [10,28,29].

Symptomatic treatment (see below) of hyperkalemia is definitely warranted with ECG changes, but there is no reliable correlation between presence or absence of ECG changes and serum potassium levels [10]. Treatment has been advocated should serum potassium exceed 7.5 mmol/L, or earlier if the animal is showing any clinical signs [30].

In addition to intravenous fluid therapy, options for emergency treatment of hyperkalemia include the following [9,30–32].

- Calcium gluconate: 0.5–1.5 mL/kg of a 10% solution given slow IV (over approximately 5–10 minutes), with ECG monitoring. This does not reverse hyperkalemia but it does act as a “cardioprotectant” by raising the threshold potential in cardiomyocytes, speeding impulse propagation in the sinoatrial and atrioventricular node, and returning cardiomyocyte excitability to normal. The duration of action of calcium gluconate is 30–60 minutes.
- Drugs promoting intracellular flux of potassium.
 - *Regular insulin*: 0.25–0.5 U/kg IV followed by an infusion of 50% dextrose (1–2 g/unit of insulin administered) to prevent hypoglycemia. Insulin stimulates the Na⁺/K⁺/ATPase pump, which moves potassium intracellularly in exchange for sodium in a 2:3 ratio [30,31]; this effect is independent of insulin's effect on glucose. The onset of action of insulin is < 15 minutes and its effect is maximal at 30–60 minutes following a single dose [32]. Serial monitoring of blood glucose is recommended following insulin administration to monitor for hypoglycemia. Should hypoglycemia occur, dextrose supplementation (2.5–5%) in intravenous fluids can be instituted.
 - *Terbutaline*: 0.01 mg/kg slow IV or SC. Catecholamines activate Na⁺/K⁺/ATPase pumps through beta-2-receptor stimulation in a manner that is additive to the effect of insulin. Alternatively, nebulized albuterol may be used. The effect of beta-agonist therapy is apparent at 30 minutes and persists for at least 2 hours. Mild tachycardia is the most common side-effect of

nebulized albuterol or terbutaline. The effect of insulin is additive with that of albuterol, and a combination of the two can result in a decline in serum potassium by about 1.2 mEq/L in about 60 minutes [32].

- *Sodium bicarbonate*: 1 mEq/kg slow IV. Sodium bicarbonate infusion can shift potassium from the extracellular to intracellular space by increasing blood pH. This therapy should be employed with caution as the possibility for paradoxical CNS acidosis and hyperosmolality from the high sodium concentration exists. There is additional risk of lowering ionized calcium which may counteract the effects of calcium gluconate administration [30]. Therefore sodium bicarbonate administration is typically considered as a last-line therapy.

Ultimately, urinary diversion or definitive repair will be required to prevent recurrence hyperkalemia.

Treatment

The two main components of treatment are urinary diversion followed by, or performed at the same time as, definitive repair of the site of rupture.

Assuming at least one of the ureters and kidneys is intact and functional, a urinary catheter should be placed into the bladder to allow emptying and prevent accumulation of urine within the abdomen [9]. In cases of urethral tears, fluoroscopic guidance may be required to facilitate correct placement [9]. Peritoneal drainage should also be performed. This may be accomplished by draining with a needle, over-the-needle catheter or placement of a peritoneal dialysis or abdominal drainage catheter [1,9] (Figure 103.1). Placement should be aseptic

Pigtail catheter placed for peritoneal drainage of urine

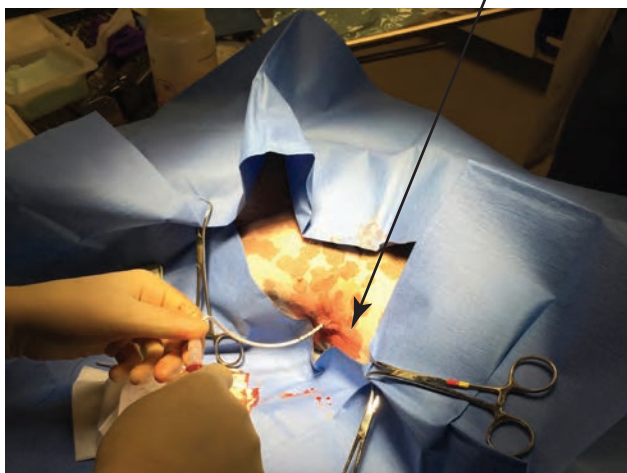


Figure 103.1 Placement of a peritoneal drainage catheter in a dog.

and the catheter should be attached to a closed collection system. A cystostomy tube may be utilized as a method of urinary diversion in cases of urethral rupture [3,9,33].

Peritoneal dialysis may be used in the preoperative period to treat severe hyperkalemia or azotemia [34]. Full discussion of this is beyond the scope of this chapter, but in brief, dialysate solution is infused into the abdominal cavity. The peritoneum acts as a selectively permeable membrane and solutes and water move between peritoneal capillaries and peritoneal fluid to equilibrate. Following a dwell time, the fluid is then removed from the peritoneal cavity and unwanted solutes can thus be eliminated [4].

Published survival rates in veterinary studies have been variable. In one study of 27 dogs and cats undergoing peritoneal dialysis, 24% survived to discharge [35]. One study evaluating dogs with leptospirosis that underwent peritoneal dialysis showed a survival rate of 80% [36]. In general, the overall survival rate with peritoneal dialysis is likely related more to the underlying disease than the actual technique of dialysis itself.

Medical management may be attempted by utilizing a urinary catheter for urethral tears, or potentially bladder rupture [9]. The urethra is reported to take 3–21 days to heal [4,37,38] (see Chapter 100), and a study by Burrows and Bovee showed healing of an iatrogenic cystostomy incision in 45 hours [11].

Surgery may be indicated for larger tears, those that have failed medical management or tears in a location that renders urinary diversion alone insufficient. Options for surgical management vary depending on the location of the tear, but include ureteronephrectomy, ureteroureterostomy, neoureterocystostomy, nephrectomy, urethral anastomosis, stent placement, subcutaneous ureteral bypass implantation, repair of bladder laceration or permanent urethrostomy [5,9,37]. For a detailed description of these techniques, the reader is referred to a surgical textbook.

Complications and Prognosis

Complications of uroabdomen include development of severe chemical peritonitis, septic peritonitis if the urine is infected, and complications associated with surgery [1,3,4,39] (see Chapter 87).

Dehiscence or delayed healing may result from urine in direct contact with recovering tissues [38]. Strictures, incontinence, ongoing urine leakage, and urinary tract infections are all possible complications that may be encountered postoperatively [1,3,4].

The published literature reports a poor outcome in 35% of dogs with urethral rupture and in 17.2–28.6% of cats [1] (see Chapter 100). In both dogs and cats, the presence of multiple traumatic injuries is associated with a higher mortality rate [3,4].

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Urethral Prolapse

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Urethral Prolapse

Urethral prolapse is a condition in male dogs where the urethral mucosa everts beyond the external urethral orifice. The mucosa is susceptible to trauma and these patients often present for blood dripping from the penis. Alternatively, patients may present for a red or purple mass located at the tip of the penis. The most common breeds affected by this condition are English bulldogs and other brachycephalic breeds. Several reports also document the condition in the Yorkshire terrier [1].

The exact cause of urethral prolapse remains unknown, but several theories exist. Respiratory difficulty, sexual excitement, urogenital or prostatic conditions such as prostatomegaly and urinary calculi, and developmental diseases have all been proposed [2]. In addition, increased abdominal pressure causing impaired venous return to the distal urethra secondary to upper airway obstruction, chronic vomiting, or dysuria has also been suggested [2].

Diagnosis

Diagnosis of urethral prolapse is made by observation of a fleshy mass on the distal urethra through which a urinary catheter can be placed (Figure 104.1). Determining the underlying cause of urethral prolapse may be challenging diagnostically and includes bloodwork, urinalysis, urine culture, abdominal radiographs, and abdominal ultrasound. In many cases an underlying cause cannot be determined.

Treatment

Treatment of urethral prolapse in the emergent setting is directed at controlling bleeding. This can be



Figure 104.1 Urethral prolapse in a dog.

accomplished by sedating the patient and preventing further self-trauma. Both acepromazine and butorphanol are common sedatives used for this reason [3]. There is evidence to suggest that sedation given in the perioperative period may contribute to a more optimal long-term outcome following surgery [3]. Although not reported, the author had used topical vasoconstricting agents with some success to control bleeding until surgical intervention can occur.

Definitive treatment is directed at replacing prolapsed urethral mucosa. This can be done in the emergent setting by manual reduction of the prolapsed tissue and placement of a purse-string suture. Clients should be warned that prolapse may recur over time with this method.

Surgery is recommended when medical management is unsuccessful or when protracted bleeding occurs. Surgical correction involves resection of prolapsed urethral mucosa, urethropexy [4], or a combination of the two. The most common complications following surgery include

continued bleeding (39%) and recurrence of the condition (57%) [3]. Concurrent castration has been recommended to help control underlying causes of the disease. However, a recent study found no correlation between castration status and recurrence of prolapse following surgery [3].

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Discolored Urine

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Introduction

Normal urine is transparent and ranges from a light yellow to amber color. The color of normal urine is attributed to the presence of urochrome and urobilin, byproducts of normal metabolic processes [1]. Urine discoloration results from the presence of cells or free pigment of endogenous or exogenous origin. Abnormally colored urine might appear red, brown, orange, or another color that is less commonly observed. Once an abnormal urine color is observed, further investigation should be performed as this finding could be an indicator of systemic disease or conditions of the upper or lower urinary tract.

Examination of the Urine Specimen

In the initial steps of performing a standard urinalysis, the examiner makes note of the turbidity and color of the urine sample prior to further sample processing. Following centrifugation, the color of the supernatant and sediment (or pellet) should again be noted. When cellular components such as red blood cells (RBCs) cause gross discoloration of urine, the abnormal color will be localized to the pellet and the supernatant should become colorless or yellow. The sediment is then examined microscopically to determine the types of cells present. If the urine supernatant remains abnormally colored following centrifugation, further consideration of the patient's history and/or diagnostic tests are required to determine the source of the pigment.

Abnormal Urine Sediment Color

Hematuria

Hematuria is the term which describes the presence of intact RBCs in urine. Only a low number of RBCs

(5–10 RBCs/ μ L) are necessary to produce a positive heme reaction on a urine chemistry reagent strip, but a large number of RBCs must be present to cause gross discoloration of the urine. With urine sample centrifugation, the supernatant typically becomes clear, although storage of dilute or alkaline urine may lead to lysis of RBCs, lending a light pink tint to the supernatant.

The presence of RBCs in the urine implies their escape from circulation at some level within the urogenital system. Hematuria can be due to macroscopic or microscopic vascular damage or spontaneous hemorrhage secondary to an abnormality of hemostasis. Vascular damage might be caused by infection or inflammation (pyelonephritis, bacterial cystitis, idiopathic cystitis), trauma (blunt trauma, presence of urinary calculi, recent surgery, cystocentesis, manual bladder expression, urinary catheterization), neoplasia of the upper or lower urinary tract or reproductive tract, normal estrus, urethral prolapse, prostatic disease, or other spontaneous etiologies such as primary renal hematuria. Hemostatic disorders causing spontaneous urinary tract hemorrhage include marked thrombocytopenia (e.g. immune-mediated thrombocytopenia), platelet dysfunction (e.g. von Willebrand's disease, excessive antiplatelet therapy), and acquired or congenital coagulopathy (e.g. anticoagulant rodenticide ingestion, excessive heparin therapy, hemophilia A or B).

Some common causes of gross hematuria are urinary tract infection in dogs and idiopathic cystitis in cats (see Chapter 96). Urine sediment examination aids in the diagnosis of urinary tract infection by demonstrating pyuria, the presence of an abnormally high number of white blood cells (WBCs), and possibly also the presence of rods or cocci. Urine culture and susceptibility testing provides additional information regarding the specific type of bacteria present. Cats presenting with idiopathic cystitis might have a low number of WBCs in the urine, but infrequently have bacterial urinary tract infections.

If a voided sample of urine is discolored due to hematuria, comparison of the sample to one obtained via cystocentesis might help to localize the source of blood. If the voided sample is hematuric and the sample obtained shortly thereafter via cystocentesis is clear, the blood is thought to originate from a source distal to the urinary bladder, such as the urethra, prostate, uterus or vulva. Cystocentesis should be performed following collection of the voided sample because of the possibility of causing iatrogenic hemorrhage. Performing cystocentesis is contraindicated when a hemostatic disorder is suspected, and relatively contraindicated when urinary bladder neoplasia is suspected.

Other tests that might help determine the cause of hematuria include urine culture, complete blood count, tests of hemostatic function, abdominal radiography or ultrasound, and cystoscopy.

Other Cells or Particles

Marked pyuria or crystalluria can lead to a turbid and discolored urine appearance that clears with centrifugation. Further examination of the urine sediment confirms the presence of WBCs, crystals, or other debris within the urine sediment.

Abnormal Urine Supernatant Color

Endogenous Pigments

Bilirubinuria

Bilirubinuria occurs in the presence or absence of hyperbilirubinemia and clinical signs of icterus. Because of its low threshold for renal excretion, bilirubinuria might be detected early in the course of disease processes before hyperbilirubinemia is evident. Trace to mild bilirubinuria is common in normal dogs, as dogs have the unique ability to conjugate bilirubin in their renal tubular cells [2]. Its presence in the urine can correspond to prehepatic (hemolysis), hepatic (hepatocellular disease), or posthepatic (biliary tract and gall bladder disease) causes of hyperbilirubinemia.

Although concentrated normal urine often has an intense yellow or amber coloration, bilirubinuria should be suspected when urine is dark yellow to brown and minimally concentrated. With prolonged storage at room temperature and/or with exposure to ultraviolet light, bilirubin becomes oxidized into biliverdin, which contributes a green color to the urine sample. Once oxidized to biliverdin, the sample will test negative for bilirubin on reagent pad analysis so the presence of bilirubin should be determined on fresh urine samples [3]. Diagnostics that might help determine the cause of bilirubinuria include plasma color inspection, complete blood

count with manual differential, serum biochemistry, liver function testing, and abdominal ultrasound. A further review of hyperbilirubinemia is provided in Chapter 11.

Hemoglobinuria

The presence of free hemoglobin causes a pale pink to dark red discoloration of the urine. Unless RBCs are lysed due to *in vitro* storage conditions, true hemoglobinuria is expected to come from *in vivo* hemolysis. On urine chemistry test strips, occult blood/hemoglobin strips contain an organic peroxide [4,5] which yields a positive result in the presence of intact RBCs, free hemoglobin, and myoglobin. Examination of the urine sediment helps to exclude hematuria, but further investigation is necessary to differentiate hemoglobinuria from myoglobinuria. Hemoglobinuria is suspected when the patient's plasma or serum color is light pink to red, while serum in patients with myoglobinuria is typically colorless. Other distinguishing diagnostic findings seen in patients with myoglobinuria are found in Table 105.1 and discussed later in this chapter.

Hemolytic anemia is suspected when hemoglobinuria occurs concurrently with anemia, hemoglobinemia, and/or hyperbilirubinemia. Causes of hemolytic anemia are divided into immune-mediated (primary or secondary immune-mediated hemolytic anemia (IMHA)) and non-immune etiologies (e.g. zinc intoxication, envenomation, osmotic lysis, RBC metabolic defects, among many others). Once hemoglobinuria is confirmed, further testing is required to determine the underlying cause. A complete blood count with manual differential, examination of red blood cell morphology, and reticulocyte count are essential in the work-up of patients with hemolytic anemia. The saline agglutination test or Coombs test may aid in the differentiation of immune-mediated and non-immune-mediated causes of hemolysis. Further testing might include radiography or other diagnostic imaging, chemistry panel analysis, and serology or PCR for infectious organisms. A more detailed review of hemolytic anemia is presented in Chapter 66.

Myoglobinuria

Myoglobin, an oxygen-carrying protein present in muscle cells, causes a red to brown discoloration when present in the urine. Myoglobinuria occurs when severe muscle damage causes myoglobin to be released from the sarcoplasm of myocytes into circulation. Although there is greater understanding of conditions resulting in myoglobinuria in human medicine, etiologies reported in veterinary species include malignant hyperthermia, heat stroke, blunt trauma or crush injury, drug- and toxin-induced rhabdomyolysis, tetanus, *Babesia canis* and *Neospora caninum* infection, and snake or bee envenomation [6–11].

Table 105.1 Distinguishing features of hematuria, hemoglobinuria, and myoglobinuria.

Origin of pigmenturia	Urine color			Plasma color	Other laboratory findings		
	Prior to centrifugation	Supernatant following centrifugation	Urine sediment findings		CBC	Biochemistry	Other
Hematuria	Light to dark red	Clear	Intact RBCs; few to TNTC. ± WBC, bacteria, RBC casts*	Normal	Normal to decreased PCV,* normal to decreased platelet count,* inflammatory leukogram*	Normal protein to panhypoproteinemia*	Abnormal tests of coagulation or platelet function*
Hemoglobinuria	Light to dark red	Light to dark red	± Red-brown casts	Light to dark red	Anemia ± Heinz bodies, schistocytes, RBC parasites, autoagglutination*	Hyperbilirubinemia	Positive infectious disease testing, metallic foreign object on abdominal radiographs, positive Coombs test*
Myoglobinuria	Red to brown	Red to brown	± Red-brown casts	Normal	No specific abnormalities expected	Severely elevated CK and AST	Soluble in 80% ammonium sulfate

*Depending on specific etiology.

AST, aspartate aminotransferase; CBC, complete blood count; CK, creatine kinase; RBCs, red blood cells; TNTC: too numerous to count.

Because the appearance of myoglobinuria is similar to hematuria and hemoglobinuria, diagnostic clues must be utilized to differentiate these three pigments (see Table 105.1). Helpful diagnostics include inspection of serum or plasma color, which should be clear in patients with myoglobinuria and light pink to dark red in patients with hemolysis and hemoglobinuria. Other diagnostic clues present in patients with muscle damage significant enough to result in myoglobinuria include muscle pain on physical examination, marked elevations in creatine kinase (CK) and/or aspartate aminotransferase (AST), absence of hyperbilirubinemia or pink to red plasma discoloration.

Tests to confirm the presence of myoglobin in the serum or urine are not commonly performed bedside or in most veterinary hospital laboratories. One clinical laboratory procedure performed in veterinary medicine is differential solubility testing, in which an 80% ammonium sulfate solution is added to a urine sample and the mixture is observed for precipitation of the colored substance. In this test, hemoglobin is insoluble and myoglobin remains soluble [6]. Other confirmatory tests include latex agglutination [11], electrophoresis, and fluorometric or radiometric immunoassay [8,12] methods.

Other Endogenous Pigments

Other endogenous pigments which can be found in urine include porphyrins, methemoglobin, and melanin. Porphyrinuria, the presence of porphyrin pigments in the urine, is a normal finding which causes red-brown-colored urine in rabbits. In this species, the origin of these porphyrin pigments is metabolic breakdown of chlorophyll and other plant-based pigments [13]. Porphyrinuria also occurs rarely in other species due to porphyria, an acquired or inherited disorder of one or more enzymes within the pathways involved in heme biosynthesis [13]. These conditions have been reported in cats, cattle, rabbits, hedgehogs, and other veterinary species [14–17]. Porphyrin pigments fluoresce under ultraviolet light, which helps to differentiate this type of pigment from others which cause red or brown urine discoloration.

Methemoglobin causes a dark brown to black discoloration of urine and indicates the presence of methemoglobinemia *in vivo*, or the oxidation of hemoglobin to methemoglobin in acidic urine [18]. Suspicion of methemoglobinuria should be addressed by thorough review of patient history for risk factors such as ingestion of acetaminophen or phenazopyridine, or exposure to skunk musk.

Also causing a dark brown to black urine color, melanin pigment has been identified in the urine of human patients with metastatic melanoma [19]. At this time, there are no reports of melanuria in veterinary species.

Exogenous Pigments

Medications

Administration or accidental ingestion of drugs can also lead to urine discoloration. Phenazopyridine, a urinary tract analgesic used in human and large animal medicine, contains a dye which causes red-orange urine discoloration. This drug has toxic potential in dogs [7] and cats [20], causing hepatotoxicity, rhabdomyolysis, and oxidative RBC injury. Considering these possible effects of intoxication, myoglobinuria, bilirubinuria, hemoglobinuria, and methemoglobinuria could also be present. Any pigmenturia that might be attributed to phenazopyridine ingestion should be further investigated to ensure that no other evidence of toxicity is present.

Numerous other drugs are known to cause urine discoloration in humans. Administration of rifampin causes red urine discoloration and isoniazid administration or riboflavin supplementation can lead to orange-colored urine [21]. Blue or green urine might be the result of methylene blue, propofol, or cimetidine administration [21,22]. The extent to which these drugs cause urine discoloration in veterinary patients is unknown.

Foods

Abnormal urine color is also observed in humans following consumption of various foods. The consumption of beets, blackberries, and carrots is known to cause red urine discoloration and the consumption of fava beans and rhubarb contributes a brown color to urine [21]. Beeturia, the name for red urine discoloration that results from the consumption of beets, has been most extensively studied as it does not occur uniformly in humans. It appears that, although beeturia occurs in a proportion of clinically normal humans, its incidence is higher in patients with iron deficiency anemia [23]. As with drug-induced urine discoloration, it is unknown if these foods cause similar changes in urine color in veterinary patients.

Multifactorial Urine Discoloration

Interestingly, purple urine discoloration has only been documented in human patients with “purple urine bag syndrome,” a condition which requires a combination of endogenous and exogenous processes to occur. In order to produce the purple urine color, dietary tryptophan is initially converted to indole by intestinal bacteria, followed by hepatic metabolism to indican, and further metabolism to indigo and indirubin by bacteria involved in urinary catheter-associated urinary tract infection or colonization of a urinary collection system [24]. This syndrome has not yet been documented in veterinary patients.

Pigment-Induced Renal Injury

In addition to its utility as a diagnostic clue, the presence of pigmenturia is also of clinical significance because of its ability to induce or worsen renal injury. Hemoglobinuria and myoglobinuria are most well known as risk factors for pigment-induced renal injury. Other causes of pigmenturia, such as melanuria, might also be able to produce a similar clinical syndrome.

Hemoglobinuria and the associated inflammatory reaction that occurs with *in vivo* hemolysis can precipitate acute kidney injury. Experimental induction of hemoglobinuria has led to greater understanding about its pathophysiology. Intravenous administration of hemolyzed RBCs appears to cause changes in renal function secondary to intratubular obstruction and toxic renal tubular damage [25]. Despite these findings, renal injury does not appear to be induced by the presence of hemoglobin alone. Combined renal ischemia and intravenous infusion of hemolyzed RBCs have induced acute kidney injury in an experimental setting [26]. In studies in which red cell stroma has been removed from hemolyzed blood prior to infusion, kidney injury was not produced [27], even in canine subjects with experimentally induced renal ischemia [28] or acidemia [18]. These studies suggest that the pathophysiology of hemoglobin-induced kidney injury is multifactorial. Nonetheless, patients with rapid intravascular hemolytic processes should be monitored for evidence of acute kidney injury.

Myoglobinuria has also been associated with the development of acute kidney injury. As with hemoglobinuria, the pathophysiology is also likely multifactorial.

An experimental study performed in 1989 demonstrated that concurrent myoglobinuria and renal ischemia resulted in acute kidney injury, while neither myoglobinuria nor transient renal artery occlusion alone was sufficient to induce acute kidney injury in dogs [29]. Since patients at risk for myoglobinuria (e.g. dogs with heat stroke) frequently have concurrent hypovolemia and ischemic renal injury, renal values should be monitored during the management of such cases.

Although hemoglobinuria and myoglobinuria have been most extensively studied, the presence of other endogenous pigmenturia might also lead to kidney injury. In a case report of a human patient with metastatic melanoma and melanuria, histological evidence of renal tubular damage was found in association with an accumulation of melanin pigment in tubular epithelial cells [19]. The importance of melanin-induced kidney injury in dogs and cats is unknown, since melanuria is not well documented in these species.

Conclusion

The finding of abnormal urine color in a veterinary patient should not be ignored. This observation might indicate the presence of urinary tract disease, systemic disease, or exposure to a potentially toxic substance, or it might be a sign of a benign process such as known ingestion of a food or medication. Performing a thorough history, physical examination, and urinalysis can give the clinician initial clues in determining the origin of the abnormal color, which might guide further work-up and treatment of the patient.

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Urinary Diversion in the Emergency Room

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Urinary Catheterization

Indications

There are several indications for the placement of urinary catheters within the emergency setting. Temporary catheterization may be indicated to obtain urine samples for urinalysis and aerobic culture, contrast imaging such as a cystourethrogram, to facilitate bladder emptying in patients with urinary retention or temporary inability to void (e.g. postoperative patients), or to relieve urethral obstruction. In cases of urethral obstruction secondary to calculi, catheters may be used to bypass the stones or displace them into the bladder using the catheter or concurrent hydropulsion, pending more definitive treatment.

Indwelling urinary catheters can both be therapeutic and aid with monitoring (see Chapter 187). In feline patients, urethral obstruction secondary to feline interstitial cystitis is a very common reason for emergency evaluation. However, urethral obstruction may also be secondary to calculi, neoplasia, or stricture formation in both canine and feline patients, and mucous plugs in feline patients. Trauma patients, particularly those with pelvic trauma, may also benefit from placement of an indwelling urinary catheter. Maintaining patient comfort during recumbency and monitoring urinary output can be important aspects of managing these patients. In addition, patients with pelvic trauma may also suffer concurrent bladder or urethral trauma or rupture, resulting in uroabdomen or urine leakage into the perineal tissues (see Chapters 100 and 103). Many patients with urethral tears secondary to trauma or catheterization injury can achieve urethral healing with 7 days of indwelling catheter placement. Other recumbent, sedated, or anesthetized patients may also benefit from urinary catheterization. Urine production must be closely monitored in certain animals, particularly

those with oliguria, anuria, or severe polyuria (e.g. post-obstructive diuresis); indwelling catheterization provides an essential monitoring tool in these patients (see Chapter 95).

Contraindications

The placement of a urinary catheter is not without risk so the benefit to the patient must be weighed against possible complications. Even in patient populations where catheterization would improve monitoring and ease nursing care, the risk of an acquired urinary tract infection may outweigh the monitoring and management benefits. In addition, those with known bacterial infection or at increased risk of infection (diabetics, animals with urinary tract implants) have decreased ability to clear infections and are predisposed to resistant bacterial species or urosepsis. Since catheterization can be traumatic to the urethral mucosa and predispose to continued irritation, thrombocytopenic patients may be at increased risk for hematuria. Patients with diarrhea, especially female patients, are at risk for continued catheter contamination and ascending bacterial infections (see Chapters 96 and 187).

Complications

Several complications may be encountered during or after placement of a urinary catheter (see Chapter 100). Difficult placement and rigid catheters or stylets may result in trauma or tearing of the urethra. Patients with prior trauma or friable mucosa may be at increased risk. Mucosal trauma prevention is typically achieved with adequate analgesia or sedation, generous lubrication, compatible stylets contained within the catheter, and gentle technique. Other complications include kinking or knotting of the catheter, which is generally the result

of excessive catheter length within the bladder [1]. Measurement of the catheter prior to placement to determine the appropriate length and visualization via radiographs, fluoroscopy, or ultrasound help to determine appropriate placement.

The development of catheter-associated infection or pyuria is common in hospitalized patients (see Chapter 96). The rate of catheter-associated infection in cats with feline urethral obstruction varies. In a pilot study, one-third of cats with obstructive lower urinary tract disease developed pyuria after catheterization whereas other studies have found lower rates of infection [2,3]. In catheterized female dogs, 20% developed a urinary tract infection in one study, whereas other studies have shown the risk to be as high as 52% in dogs and cats. Seeding of bacteria during catheter placement or the development of an ascending bacterial infection is typically implicated as the source of infection.

The development of a biofilm increases the risk of ascending infection, and decreases the ability of both the immune system and antimicrobials to clear bacteria adhered to the catheter. Biofilm is a complex network of bacterial colonies, host supplied ions, and extracellular mucopolysaccharides that begins to form along the inside and outside portions of the catheter almost immediately after insertion [4]. Recent studies have suggested that the use of hydrophilic urinary catheters with silver or chlorhexidine coating may help to prevent biofilm formation and may be considered in the future for veterinary patients requiring long-term catheterization [4–6].

Strict aseptic technique during catheter placement and regular urinary catheter care should be implemented. Urinary tract infections have been associated with the length of catheterization, age, and administration of antimicrobials [7–9]. Common bacterial isolates include *Escherichia coli*, *Enterobacter*, *Staphylococcus* spp, *Streptococcus* spp, *Pseudomonas* spp, *Serratia*, and *Klebsiella*. Fungal infections have also been reported [9–11]. Prevention of infection is paramount, so the duration of urinary catheterization should be minimized and limited to patients for whom the catheter is an absolute necessity. Studies suggest that the use of pre-emptive antimicrobials is not effective in preventing infection, and therefore is not recommended [9,12,13].

Percutaneous Nephrostomy Tube

Indications

Ureteral disease has become increasingly identified in both canine and feline patients and may necessitate immediate intervention. Ureteral obstruction can be

unilateral or bilateral, and may be secondary to calculi, neoplasia, inadvertent ligation, mucus plugs, edema, stricture, or trauma [14–19]. The urgency of treatment is dependent on the degree of metabolic derangements, urine production, and cardiovascular stability. Although some animals may initially respond to medical management, those with hyperkalemia, severe metabolic acidosis, and fluid overload often need emergent intervention.

Life-threatening abnormalities are most frequently noted in animals with bilateral disease or those with limited renal reserve, such as “big kidney, little kidney” (BKLLK) patients. In critically ill animals with ureteral obstructions, bypass of the obstruction with nephrostomy tube drainage, along with medical management and/or hemodialysis, can improve patient stability and provide information about the function of the obstructed kidney via a closed collection drainage system attached to the catheter [20]. This also quickly allows for retrieval of urine from the renal pelvis for culture to determine if infection is present.

Once patient stability is improved, definitive treatment may be pursued if indicated. Typical definitive treatments in patients with obstructive ureteral disease include both interventional methods, such as ureteral stenting or placement of a subcutaneous ureteral bypass (SUB) system, and surgical techniques, such as ureterotomy, ureteral reimplantation, and ureteronephrectomy (see Chapter 98).

The use of locking loop pigtail catheters for percutaneous nephrostomy tube placement in veterinary patients has become more prevalent due to availability and improved comfort with placement procedures. The technique does not require general anesthesia and can be performed with ultrasound guidance, making this minimally invasive procedure beneficial in patients that are too unstable for general anesthesia or definitive management [19]. Due to the size and mobility of feline kidneys, percutaneous placement is not always possible, so general anesthesia and laparotomy with fluoroscopic guidance are often needed. However, where available, this technique can be performed much more rapidly than other definitive procedures. Renal pelvis size can dictate the feasibility of a locking loop catheter placement since the coil size of many commercially available catheters is at least 1 cm, making percutaneous catheter placement in a renal pelvis less than 5 mm challenging, potentially resulting in hemorrhage into the pelvis. In smaller renal pelvis sizes, placement via laparotomy is often recommended [19].

Various percutaneous placement techniques using both ultrasound and fluoroscopic guidance have been described, including a modified Seldinger technique and direct trocar induction technique. The modified

Seldinger technique is preferable due to the safety of a smaller access needle and improved placement stability from the wire coiled in the renal pelvis. Removal can be performed rapidly under fluoroscopic guidance after releasing the suture locking mechanism [19].

Complications

Placement of a locking loop nephrostomy tube has been shown to have infrequent complications; however, complications that do arise can be severe. In people, many complications are secondary to the percutaneous site, including pain, hemorrhage or hematoma formation, as well as hematuria, infection, urine leakage, obstruction of the tube, dislodgment, intestinal injury, septicemia, pneumothorax or hemothorax, and, rarely, loss of the kidney [21–24]. As with any surgical procedure, electrolyte and coagulation abnormalities should be addressed prior to placement. Severely uremic patients may have an acquired coagulopathy attributable to platelet dysfunction (see Chapter 70). Patients that require emergency surgical procedures have been shown to benefit from the administration of desmopressin. A recent study involving uremic people having central lines or percutaneous nephrostomy tubes placed showed that desmopressin improved platelet closure time. No patients within this study had significant hemorrhage or required any intervention due to bleeding [25].

There are few studies regarding percutaneous nephrostomy tube placement in veterinary medicine. In a retrospective study of 20 veterinary patients undergoing nephrostomy tube placement, with two feline patients having bilateral nephrostomy tubes placed, for a total of 22 kidneys, the overall rate of major complications was low, with 1/4 dogs and 1/18 cats found to have a major complication, including subcutaneous urine leakage, entrapment of other ureteral implants, dislodgment, or the need for multiple placement attempts [19]. Minor complications were also noted, including hematuria in 14 patients and bacterial infection in six patients [19].

Percutaneous Antegrade Urethral Catheterization

Indications

Urethral catheterization, as previously discussed, is the gold standard of treatment for urethral obstruction or tears due to a variety of disease processes. However, in some animals, a retrograde catheter cannot be passed due to stricture, small patient size, neoplastic obstruction, or urethral tear. Continued attempts at

placement may lead to prolonged sedation, progressive urethral irritation and risk of perforation, and increase the risk of decompensation from metabolic derangements.

If a urethral catheter cannot be placed, or rupture has occurred, percutaneous antegrade urethral catheterization (PAUC) should be considered. This technique was first described in 1984 in people, and has since been described in male cats with urethral obstruction [26,27]. Animals are placed under general anesthesia, positioned in lateral recumbency, and a peripheral catheter is inserted percutaneously into the bladder for decompression, sample collection, and facilitation of a contrast cystourethrogram using fluoroscopic guidance. An angled hydrophilic guidewire is fluoroscopically guided percutaneously through the catheter into the bladder and urethra. A urinary catheter is then inserted over the wire for retrograde catheterization (Figure 106.1). Cystostomy tubes may also be indicated in this patient population, but percutaneous antegrade urethral catheterization (PAUC) can often be completed more quickly, therefore decreasing the length of general anesthesia and more rapidly relieving urethral obstruction. It also eliminates the need for a percutaneous cystostomy tube, which can be dislodged and lead to a uroabdomen (see Chapter 103).

Complications

Brief general anesthesia is required for this procedure, which is often indicated in hemodynamically unstable patients. Medical management may be required prior to induction to address severe hyperkalemia and hemodynamic compromise (see Chapter 109). Urine leakage from the cystocentesis site, bleeding, and bladder rupture are possible complications, particularly in patients with abnormal or inflamed bladder tissue from the underlying disease, severe infection, or prolonged obstruction. However, in a recent study, cystocentesis in male cats with urethral obstruction was not associated with urine leakage or rupture [28]. Other side-effects seen in human patients include contrast leakage or extravasation and anaphylactoid or anaphylactic type reactions.

Previous literature has shown high success rates in a small population of cats with feline urethral obstruction [29]. In this study, 7/9 cats were successfully catheterized with this technique. The only complication noted was inability to manipulate and pass a guidewire through the urethra in two patients due to the presence of urethral calculi and stricture. In cases where guidewire passage is not possible, conversion to cystostomy tube placement or exploratory laparotomy may be necessary to relieve the obstruction.

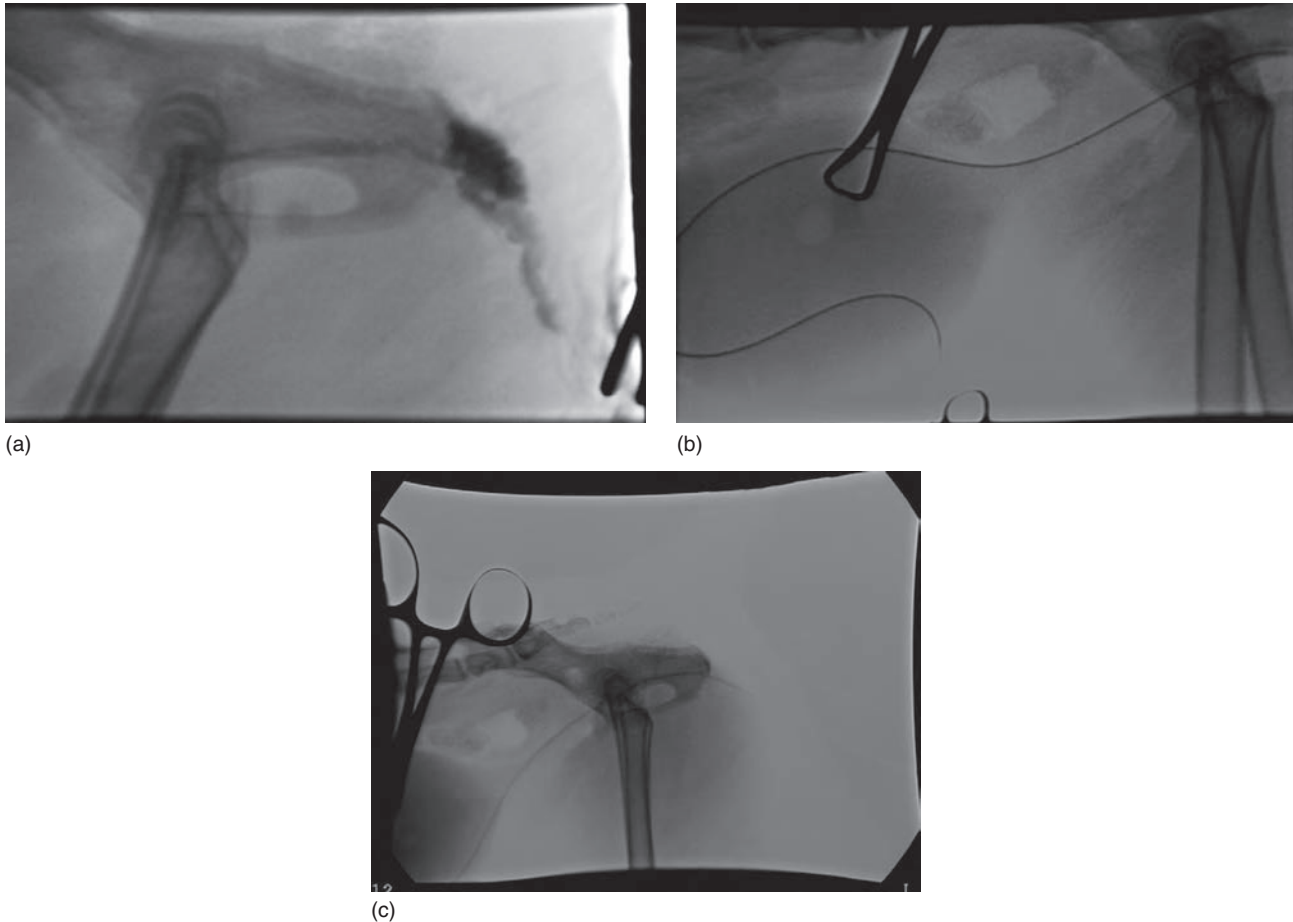


Figure 106.1 Retrograde cystourethrogram using fluoroscopic guidance in a male cat documenting contrast extravasation consistent with a urethral tear (a). Placement of a hydrophilic guidewire into the bladder and urethra via percutaneous bladder catheterization (b). Retrograde placement of a urethral catheter over the wire, bypassing the urethral tear (c).

Cystoscopy and Urethroscopy

Indications

The use of endoscopy for visualization of the urinary system has become widespread as a diagnostic tool in veterinary and human medicine. Both rigid and flexible scopes can be used to rapidly identify urethral obstructions, neoplasia, or trauma. In human patients, this can be performed under local anesthesia, though general anesthesia is required in veterinary patients. Urethroscopy can help facilitate catheterization in difficult cases using over-the-wire techniques and direct visual guidance (Figure 106.2). This may be particularly useful in small female patients, neoplastic obstructions, and those with urethral tears. Other emergent applications include fragmentation of

calculi using laser lithotripsy, ureteral stent placement or removal, assistance for urethral stent placement, and foreign body retrieval.

Complications

For cystoscopic procedures in veterinary patients, the use of general anesthesia is required due to discomfort and need for patient immobility. This may not be practical in critically ill patients. Other possible complications include irritation or trauma (including urethral or bladder perforation), hemorrhage, and lower urinary tract discomfort postoperatively. Use of cystoscopy in patients with urethral trauma can result in fluid extravasation into the surrounding soft tissues due to the pressurized saline ingress used to facilitate distension and visualization.

Figure 106.2 Appearance of the urethral papilla using rigid cystoscopy.



Cystostomy Tubes

Indications

Cystostomy tubes may be used for temporary or permanent purposes in both dogs and cats. Temporary indications include traumatic or iatrogenic rupture of the urinary tract, urolithiasis or other cause of urethral obstruction, and feline lower urinary tract diseases. Cystostomy tubes are often used as part of long-term management in veterinary patients with spinal cord or other neurological disease and secondary bladder dysfunction, postsurgical diversion, and obstructive neoplasia [30]. Historically, general anesthesia and surgical placement of the cystostomy

tube have been performed. With this technique, a celiotomy is carried out followed by cystostomy, tube placement, and cystopexy to the abdominal wall.

There are various types of cystostomy tubes, including Foley catheters, mushroom-tipped catheters, and low-profile gastrostomy tubes. Both a minimally invasive inguinal technique and laparoscopic techniques have been described for permanent cystostomy tube placement with relatively low complication rates [31,32].

In the emergency setting, many patients presenting with urethral obstruction are not stable enough for long periods of general anesthesia and surgery. In these patients, percutaneous cystostomy tubes or suprapubic catheterization can be performed (Figure 106.3). Often

Figure 106.3 Percutaneous locking loop catheter placed in the bladder to act as a cystostomy tube in a dog with a urethral obstruction secondary to a mineralized prostatic mass.



these techniques can be performed under fluoroscopic or ultrasound guidance, although the placement of a suprapubic catheter has been performed bedside without additional imaging in people with few complications using a trocar and Foley catheter method [30]. As with nephrostomy tubes, locking loop or Foley catheters can be placed quickly with injectable and local anesthesia.

Complications

Complication rates for cystotomy tube placement as high as 49% have been reported in this patient population, but rates may be lower with less invasive techniques [31,32]. Despite the high rate of occurrence, most complications are easily managed. In one study, inadvertent removal of the tube or displacement from the bladder was the most common complication, which may be reduced by the use of low-profile gastrostomy tubes. Urinary tract infection is another common complication, with one study showing that 85.7% of patients developed a bacterial infection [30]. Other risks include urine leakage or uroperitoneum, hematuria, patient trauma to the tube, breakage of a portion of the catheter during removal, subcutaneous infection at surgical site, and fistula formation after removal [30,33].

Percutaneous cystotomy tubes have been documented in human patients, with few studies describing their use in veterinary patients [34]. It has been suggested that the use of temporary cystotomy tubes may help to alleviate and prevent further obstruction to the urethra in cats with urethral obstruction secondary to feline interstitial cystitis. However, high rates of complications have been noted in a small study involving cats with urethral obstruction, including migration of the catheter allowing for urine leakage into the peritoneum, and a single incident of omental entrapment [35]. Additional studies

are needed to further characterize complications, rates of complications, and potential benefits in this patient population.

Other potential adverse events that may occur during placement include hemorrhage, damage or penetration to other abdominal viscera, or bladder wall rupture, particularly in bladders that may already be diseased.

Peritoneal Drainage

Indications

Locking loop pigtail catheters may also be useful in patients with a uroabdomen. Many uroabdomen patients can be stabilized and effectively managed until definitive intervention with a urethral catheter. However, in patients with uroabdomen secondary to ureteral injury, large bladder defects, or those in which a urethral catheter cannot be placed, peritoneal drainage using a percutaneously placed abdominal locking loop catheter can be quickly placed with sedation and ultrasound guidance.

Complications

The main concern for placement of a locking loop catheter within the peritoneal cavity is injury to other abdominal structures during placement, especially the spleen and intestines, particularly when the sharp trocar supplied with the locking loop catheter system is used. Hemorrhage from the bladder or body wall, or inadvertently traumatized abdominal organs, can result during placement. In the presence of urinary tract infections, urine leakage during catheter placement can lead to intra-abdominal infection. Like other catheters in the urinary tract, ascending infections can result from external catheter contamination.

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G. Acid-base, Electrolyte and Endocrine Disorders

107

Acid–Base Disorders

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Introduction

Acid–base disorders are common in emergency room patients. Identifying and understanding acid–base abnormalities can play a valuable role in diagnosis, evaluation of disease severity, and patient monitoring. There are now affordable blood gas machines that allow acid–base analysis on a very small quantity of blood, making them a very useful tool in the emergency room. This chapter will review the traditional approach to acid–base analysis. There are alternative approaches to acid–base analysis described, such as the Stewart approach and the semi-quantitative approach that may provide added insight into the mechanisms of acid–base abnormalities. These approaches do not lend themselves to rapid, patientside application and require more laboratory values than those obtained from the blood gas machine. As a result, their application in the emergency room patient may be limited.

Sample Considerations

Although there are small differences in acid–base values when arterial, central venous, and peripheral blood samples are compared in healthy research dogs, this agreement is lost in cardiovascularly unstable patients where venous PCO_2 (and hence pH) can vary greatly from arterial values [1–4]. However, there is often value in venous blood gas analysis in unstable patients, but the clinician must realize that elevated PvCO_2 values in the shock patient may be a product of poor cardiac output, not hypoventilation. When possible, central venous blood samples are recommended.

Acid–Base Regulation

Changes in hydrogen ion concentration can have important physiological consequences. It can alter the structure

and function of proteins and nucleic acids, modify hormone and drug-binding affinities, and impair enzymatic function. By convention, the hydrogen ion concentration is expressed as pH. It is important to note that pH has an inverse relationship with hydrogen ion concentration. The normal range of hydrogen ion concentration in the extracellular fluid of a mammalian system is in the range of 35–45 nmol/L, which corresponds to a pH of 7.35–7.45.

Acid–base balance in the healthy animal is primarily affected by nature of the diet and the acid byproducts of cellular metabolism. Homeostasis is maintained by chemical buffering as well as active responses of the lungs and the kidneys to alter hydrogen ion concentration. Chemical buffering includes reactions with hemoglobin, plasma proteins, phosphate, and bicarbonate. The most important buffer system is the bicarbonate buffer system as shown in the following equation.



The Henderson–Hasselbalch equation for the bicarbonate buffer system (Table 107.1) illustrates that pH is proportional to the ratio of bicarbonate to PCO_2 ($\text{pH} \sim [\text{HCO}_3^-]/\text{PCO}_2$). This relationship is the basis of the traditional approach to acid–base balance. In this approach, PCO_2 represents the respiratory component of acid–base balance while bicarbonate represents the metabolic component. From this relationship, it can be appreciated that an acidemia (decrease in pH) may be due to a decrease in bicarbonate concentration, an increase in

Table 107.1 Acid–base equations.

Acid–base	Equation
pH	$\text{pH} = -\text{Log} [\text{H}^+]$
Henderson–Hasselbalch equation	$\text{pH} = 6.1 + \text{Log} [\text{HCO}_3^-] - (0.03 \times \text{PCO}_2)$
Anion gap	$\text{AG} = (\text{Na}^+ + \text{K}^+) - (\text{HCO}_3^- + \text{Cl}^-)$

PCO_2 , or both. Alternatively, an alkalemia (increase in pH) may be due to an increase in bicarbonate concentration, a decrease in PCO_2 , or both.

Active regulation of acid–base balance involves regulation of PCO_2 by the lungs and changes in bicarbonate handling by the kidneys in response to an abnormality in pH. These changes are known as “compensatory” responses. Compensation will return the pH towards normal, but will not completely normalize it. This is an important distinction when performing acid–base analysis (see below).

Acid–Base Analysis

A stepwise approach can simplify acid–base analysis. All acid–base analyses require comparison of the measured patient values to a reference range for that species and ideally specific to the blood gas machine in use.

Evaluate pH

If the measured pH is less than the normal range, it is categorized as acidemia (increased hydrogen ion concentration), while increases in pH are an alkalemia.

Determine the Primary Disorder

Acid–base balance is divided into the respiratory and metabolic contributions. The respiratory contribution is evaluated by PCO_2 while the metabolic contribution can be assessed by the bicarbonate concentration, total carbon dioxide (TCO_2) or base excess/base deficit. From the relationship described above, it can be appreciated that elevations in PCO_2 will decrease pH, representing a respiratory acidosis. Conversely, a decreased PCO_2 is a respiratory alkalosis.

The parameter used to assess the metabolic contribution to acid–base balance depends on what values are provided by the blood gas machine as well as the choice of the interpreter [5]. Bicarbonate concentration is a value calculated by the blood gas machine and usually not provided by chemistry analyzers. As described by the relationship above, elevations of bicarbonate concentration indicate a metabolic alkalosis while decreases in bicarbonate concentration are a metabolic acidosis. Base excess (or base deficit) is also calculated by the blood gas machine and is defined as the quantity of strong acid (or strong base) that would be needed to add to a liter of oxygenated whole blood in order to return the pH to 7.4 at a temperature of 37 °C and a PCO_2 of 40 mmHg [6]. The terms *base excess* and *base deficit* are essentially interchangeable and for the sake of simplicity, the term *base excess* will be used for the remainder of this chapter.

Bicarbonate concentration is directly altered by changes in PCO_2 whereas base excess provides a

measure of the metabolic component, independent of changes in PCO_2 . As such, base excess is the parameter of choice when evaluating acid–balance in animals with substantial changes in PCO_2 . The algorithm for base excess used in commercial blood gas machines was derived for human patients. In the healthy human, normal base excess is 0 mmol/L (–2 to +2 mmol/L). The normal range of base excess varies with species (due to variations in diet). Herbivores tend to have a positive value while carnivores normally have a negative base excess, when compared to humans. When interpreting base excess, values more negative than the reference range for that species represent a metabolic acidosis (the animal is missing base), while values more positive than the reference range represent a metabolic alkalosis (gain of base).

Total CO_2 is also a measure of the metabolic component. It is calculated by many blood gas machines and measured by many chemistry analyzers. Total CO_2 , as the name suggests, is a measure of the total quantity of CO_2 in the blood. As the vast majority of CO_2 is carried in the blood as bicarbonate, TCO_2 is an estimation of blood bicarbonate concentration and is interpreted in a similar manner. It generally runs 1–2 mmol/L higher than the true bicarbonate concentration.

Once the contribution of the respiratory and metabolic systems has been determined, the system responsible for the abnormality in pH needs to be identified. The nature of the pH abnormality defines the disorder. So if the pH is acidemic, the system with an acidosis (respiratory or metabolic or both) is the cause. See the case example provided at the end of the chapter.

Compensation

The final step in acid–base analysis is to determine if appropriate compensation is present. When there is a single disorder in one system, then the changes in the opposing system should be evaluated to determine whether it is consistent with the degree of compensation expected, given the primary disorder. For example, if the primary disorder is metabolic in origin then it is expected that respiratory compensation will be evident at the time of acid–base analysis. The degree of respiratory compensation for a given change in bicarbonate concentration can be estimated by the values given in Table 107.2 [7]. If the measured value of PCO_2 is not similar to this estimated value, appropriate compensation is not present and the animal has two acid–base disorders (both a metabolic and a respiratory abnormality). When the primary abnormality is respiratory in origin, metabolic compensation is expected but the degree of change in bicarbonate concentration depends on the chronicity of the respiratory abnormality (see Table 107.2). Acute

Table 107.2 Expected compensatory changes to primary acid–base disorders [7].

Primary disorder	Expected compensation
Metabolic acidosis	↓ PCO ₂ of 0.7 mmHg per 1 mmol/L decrease in [HCO ₃ [−]] ± 3
Metabolic alkalosis	↑ PCO ₂ of 0.7 mmHg per 1 mmol/L increase in [HCO ₃ [−]] ± 3
Respiratory acidosis – acute	↑ [HCO ₃ [−]] of 0.15 mmol/L per 1 mmHg ↑ PCO ₂ ± 2
Respiratory acidosis – chronic	↑ [HCO ₃ [−]] of 0.35 mmol/L per 1 mmHg ↑ PCO ₂ ± 2
Respiratory alkalosis – acute	↓ [HCO ₃ [−]] of 0.25 mmol/L per 1 mmHg ↓ PCO ₂ ± 2
Respiratory alkalosis – chronic	↓ [HCO ₃ [−]] of 0.55 mmol/L per 1 mmHg ↓ PCO ₂ ± 2

[HCO₃[−]], bicarbonate concentration measured in mmol/L; PCO₂, partial pressure of carbon dioxide measured in mm Hg, ↑ increased; ↓, decreased.

respiratory acid–base disorders will have minimal metabolic compensation evident at the time of analysis.

Acid–base compensation in cats is poorly understood. There are no published guidelines at this time. There is some evidence that metabolic compensation in cats is similar to dogs but there is some suggestion in the literature that cats may not develop respiratory compensation [8–11].

Primary Versus Mixed Disorders

When there is only one acid–base abnormality present (respiratory or metabolic, but not both), and there is appropriate compensation present in the opposing system, it is considered a primary or simple acid–base disorder. When there are abnormalities present in both systems, a mixed disorder is present. If a primary disorder with appropriate compensation is not present, it is a mixed disorder. See the case examples provided at the end of the chapter.

Acid–Base Disorders

Once the acid–base diagnosis is made, the differential diagnoses for the disorder(s) should be considered for the specific patient. This will provide greater understanding of the animal's disease process and may help guide therapy.

Respiratory Alkalosis

Respiratory alkalosis is a product of increased alveolar minute ventilation generated by increased respiratory rate, increased tidal volume or both [12]. Potential causes include respiratory tract disease stimulating hyperventilation or changes to the respiratory center of the brain, altering control of alveolar ventilation. Anxiety, pain, and excitement may drive an increase in alveolar ventilation in some animals. Treatment of respiratory alkalosis is primarily focused on resolution of the underlying disease.

Respiratory Acidosis

Respiratory acidosis can be the result of decreased alveolar minute ventilation, increased CO₂ production or increases in inhaled CO₂ [12]. In the cardiovascularly stable animal, venous PCO₂ will be slightly higher than arterial values. In states of shock there can be substantial increases in PvCO₂ that do not reflect alveolar ventilation. As a consequence, poor tissue perfusion can be a cause of an apparent respiratory acidosis when evaluating venous blood gases [13]. See Box 107.1 for a list of specific causes of respiratory acidosis.

Box 107.1 Major causes of respiratory acidosis.

Decreased alveolar ventilation

- Respiratory center depression
 - Drugs, e.g. opioids
 - Organic brain disease
- Cervical spinal cord injury or disease
- Disease of the peripheral nerves
- Disease of the neuromuscular junction
 - Generalized myasthenia gravis
 - Polyradiculoneuritis
 - Tick paralysis
 - Botulism
- Upper airway obstruction
- Lower airway obstruction

Increased CO₂ production*

- Fever
- Malignant hyperthermia

Increased inhaled CO₂ concentration

- Rebreathing (anesthesia machine or ventilator)
- Poor tissue perfusion
- Cause of elevated PvCO₂, but not PaCO₂

*Increased CO₂ production will only be a cause of respiratory acidosis if the animal is unable to increase alveolar ventilation appropriately (e.g. anesthetized animals).

Elevations in PaCO_2 will lower the alveolar PO_2 , and hence lower PaO_2 . This can cause hypoxemia in animals breathing room air. When severe respiratory acidosis is evident ($\text{PCO}_2 > 60 \text{ mmHg}$), oxygen therapy should be provided immediately to alleviate hypoxemia. Specific therapy to lower PCO_2 will require treatment of the underlying disease. When respiratory acidosis is severe and there is no rapidly effective therapy for the underlying disease (such as brain injury, cervical spinal cord disease or polyradiculoneuritis), mechanical ventilation is indicated in order to restore adequate alveolar ventilation.

Metabolic Alkalosis

Metabolic alkalosis is far less common than metabolic acidosis in clinical medicine [14]. The two main mechanisms of metabolic alkalosis are gain of base or loss of acid. Base can be gained by renal retention of bicarbonate or by iatrogenic administration of bicarbonate. Renal retention of bicarbonate will occur in response to chronic respiratory acidosis. The most common cause of a metabolic alkalosis in dogs and cats in one study was respiratory disease. The metabolic alkalosis in these cases was likely due to compensation for a respiratory acidosis [14].

If a patient with respiratory acidosis receives therapy to improve the PCO_2 , the elevated bicarbonate from compensation will be persistent for some time, as changing renal handling of bicarbonate is a slow process. A metabolic alkalosis from loss of acid can occur from selective loss of gastric fluid or from renal loss of acid. Selective gastric acid loss can occur with pyloric outflow obstructions or proximal duodenal obstructions or with nasogastric tube aspiration. Selective gastric acid loss is usually associated with hypochloremia. Renal acid loss can occur secondary to hypokalemia and decreased effective circulating volume through the stimulation of aldosterone.

Treatment of metabolic alkalosis, like all acid–base disorders, focuses on treatment of the underlying disease. In addition, electrolyte disorders such as hypochloremia and hypokalemia must be addressed and decreases in effective circulating volume treated in order to resolve the metabolic alkalosis. Fluid therapy with 0.9% saline may be a valuable part of the treatment plan.

Metabolic Acidosis

Metabolic acidosis is considered the most common acid–base disorder in emergency room patients and it has been found to have both diagnostic and prognostic relevance [15]. Metabolic acidosis can be the result of gain of acid or loss of bicarbonate. Calculation of the

anion gap (AG) may help differentiate between these two mechanisms.

Anion Gap

The AG estimates the quantity of unmeasured anions present (see Table 107.1). The majority of the cations in circulation can be readily quantitated but the total charge quantity of several anions is not easy to determine. The charge of these substances (primarily albumin and phosphorus) is estimated by calculating the AG.

The normal range for the AG will depend somewhat on the laboratory normal values for the parameters in the equation, but is generally in the range of 12–20 mmol/L [16]. In metabolic acidosis, a decreased bicarbonate concentration will need to be balanced by an increase in either chloride concentration or the AG in order to maintain electroneutrality. Diseases associated with a gain of acid will classically cause a decrease in bicarbonate concentration and an increase in AG. There are many possible gained acids that can cause a high AG metabolic acidosis but the four most common causes are diabetic ketoacidosis (DKA), uremia, ethylene glycol intoxication, and lactic acidosis. These can be remembered with the acronym DUEL (Box 107.2). Evaluation of blood glucose and lactate will allow confirmation or dismissal of DKA and lactic acidosis as potential causes. The likelihood of ethylene glycol intoxication can be further assessed with consideration of the patient history and other emergency room tests (see Chapter 131). There are many other less common causes of metabolic acidosis that can be considered if these four more common causes are ruled out.

It is very important to recognize that the AG has limitations and can be normal in some cases of acid gain. Albumin is the major contributor to the normal AG quantity. When there is a gain of acid, the anionic component of that acid accumulates and the result is an increase in AG. If the patient has hypoalbuminemia, the AG quantity will be smaller and the increase in AG associated with the

Box 107.2 Common causes of metabolic acidosis.

High anion gap metabolic acidosis (gain of acid)*

D = Diabetic ketoacidosis

U = Uremia

E = Ethylene glycol intoxication

L = Lactic acidosis

Hyperchloremic metabolic acidosis (loss of bicarbonate)

- Diarrhea
- Renal tubular acidosis
- Dilutional acidosis
- Hypoadrenocorticism

*Note – elevation of anion gap may not be evident in all cases of metabolic acidosis due to a gain in acid.

gain of acid may not lead to a value that is out of the reference range [17,18]. When an elevated AG is present, it tends to be a valuable tool in assessment of metabolic acidosis. A normal or decreased AG should not rule out the possibility of a gain in acid.

Treatment of metabolic acidosis due to a gain in acid is focused on resolution of the underlying cause. Bicarbonate therapy is generally considered contraindicated in the treatment of DKA and lactic acidosis [19,20]. Bicarbonate therapy may be beneficial in the management of animals with uremic acidosis (see Chapter 174).

Bicarbonate loss can occur through diarrhea or through inappropriate renal acid–base handling. Abnormal renal acid–base handling can be due to one of several defects collectively known as renal tubular acidosis. These processes of bicarbonate loss are usually associated with a concomitant gain in chloride. These animals are expected to have a normal AG, hyperchloremic metabolic acidosis. Dilutional acidosis is another cause of a normal AG metabolic acidosis and is most commonly seen following large-volume administration of IV fluids, in particular 0.9% sodium chloride [21]. Animals presenting with significant clinical signs due to

hypoadrenocorticism frequently have a metabolic acidosis. This can be due to both a lactic acidosis from poor perfusion as well as impaired urine acidification [16]. Bicarbonate therapy is often indicated in the treatment of bicarbonate-losing diseases.

Acid–Base and Prognosis

Acid–base parameters have been found to have good predictive ability in human emergency room patients [22–24]. There is some evidence to support a prognostic value of acid–base abnormalities in veterinary patients, although more studies are needed to define this further in small animal patients [25,26]. Evaluation of lactate concentration in addition to acid–base analysis may provide even more valuable information.

Case Example 1

The following is the venous blood gas result from a dog on presentation to the emergency room for trauma.

Parameter	Patient value	Reference range	Interpretation
pH	7.210	7.351–7.463	Acidemia
PCO ₂ mmHg	30	31–43	Respiratory alkalosis
Bicarbonate mmol/L	10	18.8–25.6	Metabolic acidosis
Base excess mmol/L	–12	–4.5 to 0.3	Metabolic acidosis
Sodium mmol/L	148	143–151	Normal
Chloride mmol/L	115	108–115	Normal
Potassium mmol/L	4	3.6–4.8	Normal
Anion gap mmol/L	27	12–20	Elevated

The acid–base disorder is defined by the pH. In this example, the pH tells us the animal has an acidemia. It is clear that the respiratory system cannot be causing this abnormality so the cause of the abnormal pH is the metabolic acidosis. The concurrent respiratory alkalosis could represent compensation. When the calculations in Table 107.2 are used, the PCO₂ value in this patient is consistent with appropriate compensation. So the final acid–base diagnosis is a simple metabolic acidosis. The elevated AG suggests this animal has a gain of acid.

Given the history of trauma, a lactic acidosis is highly likely, and direct measurement of blood lactate concentration would allow confirmation of this diagnosis.

Case Example 2

The following is the venous blood gas result from a dog on presentation to the emergency room for trauma.

Parameter	Patient value	Reference range	Interpretation
pH	7.394	7.351–7.463	Normal pH
PCO ₂ mmHg	25	31–43	Respiratory alkalosis
Bicarbonate mmol/L	16	18.8–25.6	Metabolic acidosis
Base excess mmol/L	–8	–4.5 to 0.3	Metabolic acidosis

Similar to Case 1, this patient has both a respiratory alkalosis and a metabolic acidosis. Although it may be tempting to consider this a primary metabolic acidosis with very good respiratory compensation, this would break the rule that compensation will not return the pH to normal. The diagnosis is a mixed disorder with both a respiratory alkalosis and a metabolic acidosis. The animal has two acid–base abnormalities and a list of

rule-outs should be generated for each (see Boxes 107.1 and 107.2).

Case Example 3

The following is the venous blood gas results from a dog on presentation to the emergency room for trauma.

Parameter	Patient value	Reference range	Interpretation
pH	7.059	7.351–7.463	Acidemia
PCO ₂ mmHg	41	31–43	Normal
Bicarbonate mmol/L	11	18.8–25.6	Metabolic acidosis
Base excess mmol/L	–17	–4.5 to 0.3	Metabolic acidosis

This case has an acidemia which is clearly due to the metabolic acidosis but there is no respiratory compensation evident. As respiratory compensation occurs soon after the onset of a metabolic acid–base abnormality, the lack of respiratory compensation is always considered abnormal. It is interesting to note that the bicarbonate concentration in this example is similar to that in Case 1, yet the pH in this example is substantially lower. This reflects the

benefits of compensation in protecting the pH from severe abnormalities. The lack of compensation in this example exposes the animal to a severe acid–base disorder. This patient therefore has two abnormalities, metabolic acidosis and a lack of respiratory compensation (something is making the PCO₂ higher than it should be). As this is a venous blood gas, hemodynamic instability is a possible cause for the PCO₂ to be higher than expected.

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108

Sodium and Water Balance

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Introduction

Sodium and water balance are regulated separately in the body. Sodium balance regulates the extracellular fluid (ECF) volume while abnormalities in water balance cause changes in sodium concentration. In clinical medicine, changes in serum sodium concentration are almost always a reflection of abnormal water balance. Total body water (TBW) is distributed between the intracellular (ICF) and ECF compartments.

As water moves freely across cell membranes, the distribution of water between the ICF and ECF compartments depends on the quantity of osmotically active substances in each compartment. ECF osmolality can be

determined by Formula 1 shown in Box 108.1 [1–3]. As urea has high membrane permeability, it does not alter the distribution of water between the cells and the extracellular fluid, making it an ineffective osmole. Effective ECF (plasma) osmolality (P_{osm}) (Formula 2 in Box 108.1), also known as “tonicity,” is mainly composed of sodium and glucose osmoles and their accompanying anions [2]. Under normal conditions, glucose contributes less than 10 mOsm/kg and the plasma sodium concentration is the main determinant of the effective P_{osm} . Thus, hypernatremia represents hypertonicity although hyponatremia does not always reflect hypotonicity.

The relationship of the serum sodium concentration to water balance is illustrated by the manner in which

Box 108.1 Formulae.

Formula 1: Calculated osmolality (mOsm/kg) = $2 [\text{Na}^+] + \frac{[\text{Glucose}]}{18} + \frac{[\text{BUN}]}{2.8}$

Formula 2: Calculated effective P_{osm} (Tonicity) (mOsm/kg) = $2 [\text{Na}^+] + \frac{[\text{Glucose}]}{18}$

Formula 3: Osmol gap (mOsm/kg) = measured P_{osm} – calculated P_{osm}

Formula 4: Na deficit (mEq) = $0.6 \times \text{BW (kg)} \times ([\text{Na}^+]_{\text{normal}} - [\text{Na}^+]_{\text{patient}})$

Formula 5: Change $[\text{Na}^+]$ /1L infusate (mEq) = $\left(\frac{[\text{Na}^+]_{\text{infusate}} + [\text{K}^+]_{\text{infusate}} - [\text{Na}^+]_{\text{patient}}}{0.6 \times \text{BW (kg)} + 1} \right)$

Formula 6: Electrolyte-free water clearance (mL) = $V_{\text{urine}} (\text{mL}) \times \left(1 - \frac{[\text{Na}^+]_{\text{urine}} + [\text{K}^+]_{\text{urine}}}{[\text{Na}^+]_{\text{serum}}} \right)$

Formula 7: Water deficit (L) = $0.6 \times \text{BW (kg)} \times \left[\left(\frac{[\text{Na}^+]_{\text{patient}}}{[\text{Na}^+]_{\text{normal}}} \right) - 1 \right]$

$[\text{Na}^+]$, $[\text{K}^+]$, mEq/L; $[\text{Glucose}]$, mg/dL; $[\text{BUN}]$, mg/dL.

$[\text{BUN}]$, blood urea nitrogen concentration; BW, body weight; $[\text{K}^+]$, potassium concentration; $[\text{Na}^+]$, sodium concentration; P_{osm} , plasma osmolality; V_{urine} , volume of urine.

the serum sodium concentration and effective P_{osm} are normally regulated by alterations in the intake and excretion of water. This regulatory response is mediated by osmoreceptors in the hypothalamus, which sense changes in the effective P_{osm} of as little as 1% [2]. When the effective P_{osm} increases, it increases water intake via thirst and decreases water excretion via the secretion of antidiuretic hormone (ADH) from the posterior pituitary gland. When the effective P_{osm} decreases, it decreases water intake and increases water excretion by excreting dilute urine in the absence of ADH. In addition, there are non-osmotic factors that can influence hypothalamic function and override the effects of osmolality. In particular, effective circulating volume (ECV) depletion is a potent stimulus for ADH release and thirst. As a result, hypovolemic patients may have persistent thirst and ADH secretion, even in the presence of hyponatremia.

The volume status also affects the rate of urinary sodium excretion, which is primarily regulated by aldosterone, angiotensin II, and natriuretic peptides [4,5]. It is important to understand the difference between osmoregulation and volume regulation. The effective P_{osm} is determined by the ratio of solutes, primarily sodium, and water, whereas the extracellular volume is determined by the absolute quantity of sodium and water present [2]. Thus, knowledge of the serum sodium concentration gives no predictable information regarding volume status, including interstitial hydration and intravascular volume status.

Hyponatremia

Etiology

Hypotonic Hyponatremia

Hyponatremia is categorized according to the concurrent effective P_{osm} . Hyponatremia with hypotonicity may be further classified based on the volume status of the patient; hypovolemic, normovolemic, or hypervolemic. Patients with hypotonic hyponatremia and hypovolemia have non-osmotic stimulation of ADH (i.e. decreased ECV), resulting in water retention and development of hyponatremia [4,5]. Hypotonic hyponatremia with normovolemia is most commonly due to inappropriate ADH secretion, psychogenic polydipsia or iatrogenic mechanisms. Hypervolemic hyponatremia with hypotonicity is due to inadequate water excretion as evidenced by a urine osmolality >200 mOsm/kg, or decreased ECV despite increased TBW. Disease mechanisms leading to hypervolemic hyponatremia include kidney failure, nephrotic syndrome, and congestive heart failure. Figure 108.1 provides a list of causes of hyponatremia.

Isotonic Hyponatremia

Hyponatremia with normal effective P_{osm} can be an erroneous finding with severe hyperlipidemia or hyperproteinemia when serum sodium concentration is measured by a flame photometry [6].

Hypertonic Hyponatremia

Hyponatremia with hypertonicity occurs with an elevation of effective P_{osm} due to high plasma glucose or administration of hyperosmolar agents such as mannitol [4]. They retain the water content in the extracellular fluid space by a transcellular osmotic gradient and lower the serum sodium concentration by dilution. The relationship between blood glucose and serum sodium concentration has been found to be non-linear. Below glucose concentrations of 400 mg/dL, sodium concentration falls by approximately 1.6 mEq/L for every 100 mg/dL rise in the serum concentration of glucose [7]. At higher glucose concentrations, it should fall by 2.4 mEq/L for every 100 mg/dL rise in the glucose concentration [8].

Clinical Signs

The clinical signs directly attributable to hypotonic hyponatremia primarily reflect neurological dysfunction due to cerebral edema induced by hypo-osmolality [9–11]. In general, patients may develop nausea, lethargy, obtundation, seizures, and coma with severe acute hyponatremia [12,13]. In comparison, a similar degree of chronic hyponatremia results in a lower degree of cerebral edema and neurological signs. This is due to osmotic adaptation in the brain. The initial adaptation consists of the loss of potassium and sodium, followed by the loss of organic solutes such as myoinositol and amino acids [14,15]. Although less severe, chronic hyponatremia can also cause neurological signs that are likely mediated by the serum sodium concentration rather than by hypotonicity, perhaps reflecting the importance of sodium in neural function [16,17]. Overly rapid elevation of the chronic hyponatremia may also cause neurological signs; this issue will be discussed in the section on treatment. Hyponatremia associated with normal or elevated effective P_{osm} is not believed to have specific clinical signs associated with hyponatremia.

Diagnosis

The history and physical examination can provide important clues to the correct diagnosis. In addition, the initial laboratory evaluation should include measurements of serum concentrations of sodium, potassium, urea, and glucose. If hyponatremia is noted, measurement of P_{osm} , osmol gap, urine sodium concentration, and urine osmolality may help determine the cause of hyponatremia. If

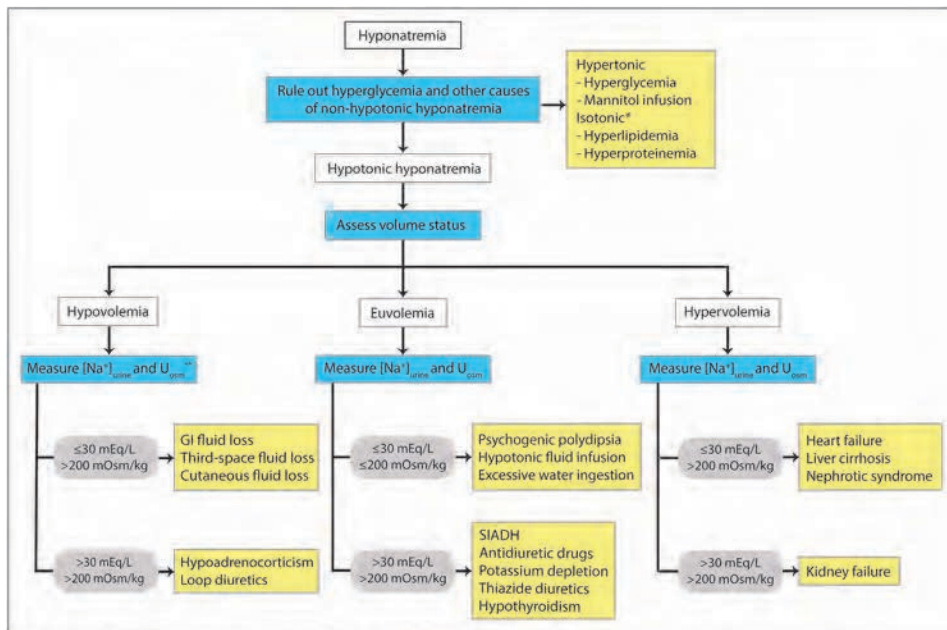


Figure 108.1 Clinical diagnostic approach to the patient with hyponatremia [72–89].

* Only if serum sodium concentration is measured using the flame photometry

** Multiplying the last two digits of the urine specific gravity by 30–40 gives a rough estimate of urine osmolality

[Na⁺]_{serum}, urine sodium concentration; U_{osm}, urine osmolality; GI, gastrointestinal; SIADH, syndrome of inappropriate antidiuretic hormone secretion

the effective P_{osm} (measured $P_{\text{osm}} - \text{BUN}/2.8$) is normal or elevated, evaluation for hyperglycemia or existence of unmeasured osmolar agents (e.g. mannitol) should be considered. In addition, determination of the osmol gap (Formula 3 in Box 108.1) may reveal the existence of unmeasured osmolar agents in the plasma [4].

As discussed above, urinary sodium retention and excretion is one of the important regulatory mechanisms of volume status. Hyponatremia associated with decreased ECV or excess water intake should occur in conjunction with a low urine sodium concentration ($\leq 30 \text{ mEq/L}$), while hyponatremia due to water retention is likely to occur in conjunction with a high urine sodium concentration ($> 30 \text{ mEq/L}$) (see Figure 108.1) [13,18]. An important exception to this may be hypoadrenocorticism and diuretic (e.g., loop diuretics) administration, which can result in decreased ECV without low urine sodium concentration [19]. Measurement of urine osmolality aids in determining the activity of ADH. Appropriate renal water excretion in the face of hyponatremia would be associated with a low urine osmolality ($\leq 200 \text{ mOsm/kg}$). The presence of hyponatremia with urine osmolality $> 200 \text{ mOsm/kg}$, suggests that ADH is active and causes of appropriate or inappropriate ADH release should be considered.

Treatment

There are two basic principles involved in the treatment of hyponatremia: raising the serum sodium concentration at a safe rate and treating the underlying cause. In patients with hypertonic hyponatremia, the total body sodium content is usually normal and removal of the osmotic substance (usually glucose) from the ECF will resolve the hyponatremia. For hypotonic hyponatremia, the amount of sodium required to raise the serum sodium concentration to a desired value can be estimated from Formula 4 in Box 108.1 [4]. You can also calculate how much volume of a specific sodium-containing fluid is needed to increase the serum sodium to the normal value using Formula 5 [12,20]. However, these formulae are only estimates and serial measurement of the serum sodium concentration is necessary. In addition, these calculations do not include any ongoing losses that may occur, and thus starting with the administration of 1/4–1/3 of the calculated fluid rate using Formula 5 is suggested [21].

In patients with hypovolemic hyponatremia, restoration of euvolemia will remove the stimulus for ADH release and is usually associated with resolution of hyponatremia. In an attempt to reduce the rate of change of serum sodium concentration, use of a crystalloid fluid

with a sodium concentration similar to the patient is recommended (within 10 mEq/L of the patient's serum sodium concentration). Alternatively, administering desmopressin acetate (dDAVP) to suppress water excretion into urine can be considered [22].

In patients with asymptomatic chronic (>48 hours) hyponatremia, special attention must be paid to the rate of correction. Acute elevations of the serum sodium concentration may lead to osmotic shrinkage of axons, severing their connections with the surrounding myelin sheaths. This may lead to central pontine and extrapontine demyelinating lesions, called osmotic demyelination syndrome, characterized by various neurological signs that develop within one to several days following a rapid increase in serum sodium concentration [23–28]. Experimental and clinical observations suggest that the degree of correction over the first 24 hours is much more important than the hourly rate. It thus seems advisable to raise the serum sodium concentration in asymptomatic patients by less than 10 mEq/L on the first day and less than 18 mEq/L over the first 48 hours (Box 108.2) [12,13,29,30].

If patients show neurological signs due to either acute (<48 h) or chronic hyponatremia, the risk of untreated hyponatremia is greater than the potential harm of overly rapid correction. If severe clinical signs are evident, 3% hypertonic saline (1–2 mL/kg, can be repeated 2–4 times) should be given over 10–20 minutes to raise the serum sodium concentration by 4–6 mEq/L (see Box 108.2) [13,29–31]. If the signs are mild, 3% hypertonic saline can be given at a rate of 1–3 mL/kg/h (or alternative hypertonic solution) at a correction rate of 0.5–2 mEq/L/h for 2–3 hours or until the neurological signs disappear [13,29,30]. Even with this initial rapid rate of correction, the elevation in the serum sodium concentration should not exceed 10 mEq/L in the first 24 hours [13].

There are a few reports showing that administration of hypotonic solutions or water may abate development of neurological signs when the hyponatremia is corrected more rapidly than recommended, as long as it is administered within 24 hours [32,33]. Correction of potassium depletion, if present, is another important component of therapy [34]. The exogenous potassium will primarily

Box 108.2 Treatment summary for hypotonic hyponatremia.

Hyponatremia with clinical signs (both acute and chronic)

- Severe clinical signs: Administer 3% hypertonic saline 1–2 mL/kg (can be repeated 2–4 times) (or alternative hypertonic saline solution at a rate calculated using Formula 5 in Box 108.1) over 10–20 min to increase $[\text{Na}]_{\text{serum}}$ by 4–6 mEq/L
- Mild clinical signs: Administer 3% hypertonic saline at a rate of 1–3 mL/kg/h (or alternative hypertonic saline solutions) at a correction rate of 0.5–2 mEq/L/h for 2–3 h or until the neurological signs are resolved
- Limit the increase in $[\text{Na}]_{\text{serum}}$ to a total of 10 mEq/L during the first 24 h and 18 mEq/L for the first 48 h, regardless of whether hyponatremia is acute or chronic
- Start cause-specific treatment and treat underlying causes
- Check the $[\text{Na}]_{\text{serum}}$ after 20–30 min, 1 h, 2 h, and every 4–8 h until hyponatremia is resolved

Acute (<48 h) hyponatremia without clinical signs

- Correct $[\text{Na}]_{\text{serum}}$ promptly by using a hypertonic crystalloid solution (no limit on the correction rate)
- Start cause-specific treatment and treat underlying causes
- Check the $[\text{Na}]_{\text{serum}}$ after 1 h, 2 h, and every 4–8 h until hyponatremia is resolved

Chronic (>48 h) hyponatremia without clinical signs

- Start treatment to increase $[\text{Na}]_{\text{serum}}$ slowly by <0.5 mEq/L/h
- Limit the increase in $[\text{Na}]_{\text{serum}}$ to a total of 10 mEq/L during the first 24 h and 18 mEq/L for the first 48 h
- Start cause-specific treatment and treat underlying causes
- Check the $[\text{Na}]_{\text{serum}}$ after 1 h, 2 h, and every 4–8 h until hyponatremia is resolved

Hyponatremia with hypovolemia

- Restore intravascular volume by administering a crystalloid solution with $[\text{Na}]_{\text{serum}}$ similar to the patient (≤ 10 mEq/L difference)
- Follow the treatment protocols described above depending on the presence of clinical signs and chronicity of hyponatremia.
- Check the $[\text{Na}]_{\text{serum}}$ after 10–20 min, at the end of resuscitation, and every 2–4 h until hemodynamic stability is achieved

$[\text{Na}]_{\text{serum}}$, serum sodium concentration.

enter the cells, and electroneutrality will be maintained by shifting the sodium from the intracellular to extracellular space. The net effect is that potassium is as effective as sodium in correcting hyponatremia. Thus, administered potassium must be included when calculating the volume of fluid to be given to increase the serum sodium concentration at a safe rate using Formula 5 in Box 108.1 [12,35].

Therapy of normovolemic or hypervolemic patients with hypotonic hyponatremia is aimed at decreasing water intake and/or increasing water removal by enhancing water excretion using diuretics (e.g., loop diuretics) [13,29]. In these patients, several novel therapies, including a urea or vasopressin receptor antagonist, have been investigated as adjunctive treatment for hyponatremia, but their clinical benefits are controversial or cost prohibitive [36–39]. If clinical signs of hyponatremia develop in patients with normovolemia or hypervolemia, the serum sodium concentration can be raised by the use of a loop diuretic in combination with hypertonic saline [29,30]. No specific treatment is necessary for hyponatremia with normal to high effective P_{osm} . The serum

concentration of sodium should be normalized as the underlying cause is resolved.

Hypernatremia

Etiology

The major causes of hypernatremia are listed in Figure 108.2, and it can also be classified according to the volume status of the patient [5,40]. It must be emphasized here that the majority of patients with these conditions or diseases maintain water balance with a near normal serum sodium concentration because their thirst mechanism is intact.

Hypernatremia develops when animals cannot replace the water loss with water intake for any reason. Insensible fluid losses are usually hypotonic to plasma [40]. Any condition that increases these losses (e.g. fever, respiratory distress) predisposes toward the development of hypernatremia. Gastrointestinal losses, due to osmotic diarrhea (e.g. lactulose, sorbitol administration) can also

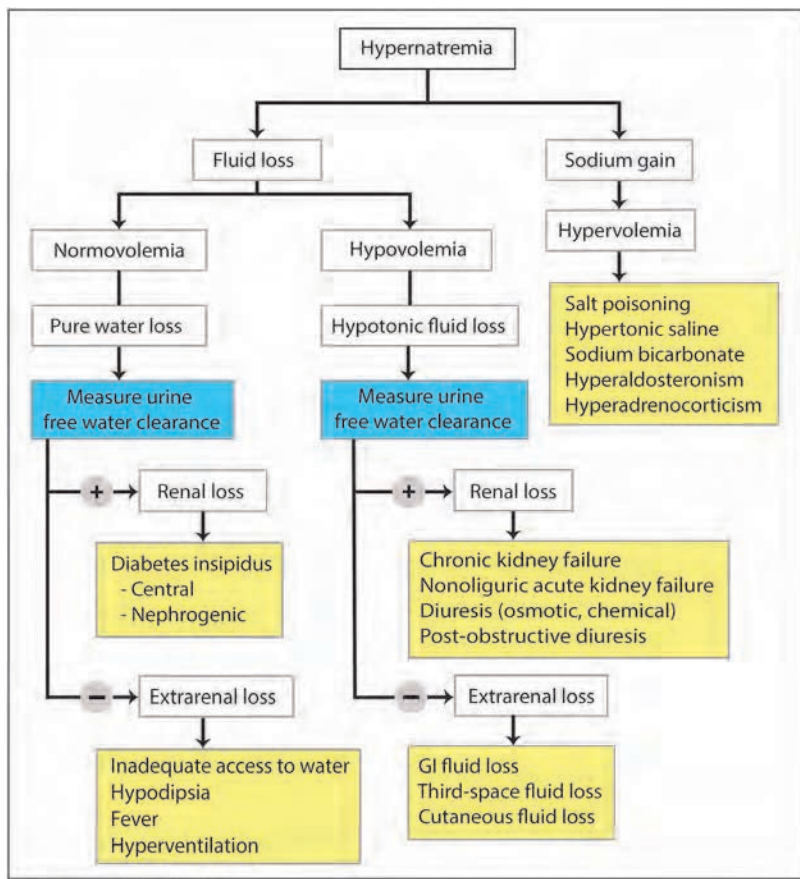


Figure 108.2 Clinical diagnostic approach to the patient with hypernatremia [43,44,90–99].

produce a similar effect [41,42]. Diabetes insipidus is characterized by the complete or partial failure of ADH secretion (central diabetes insipidus (CDI)) or loss of the renal response to ADH (nephrogenic diabetes insipidus (NDI)). As a result, renal water reabsorption is inadequate or absent, and a diuresis of dilute urine ensues. Hyponatremia can also result from the ingestion or infusion of sodium salts. This problem can occur in hospital if patients are given hypertonic saline or sodium bicarbonate. There are also case reports of hyponatremia due to ingestion of sodium salts such as homemade play dough [39,43–45].

Clinical Signs

The clinical signs of hyponatremia are primarily neurological. Lethargy and weakness are commonly reported findings, which can progress to tremor, seizure, coma, and death in severe cases [5,40,46,47]. These signs are related to the movement of water out of the brain cells down the osmotic gradient created by the rise in effective P_{osm} . This cerebral dehydration may result in focal intracerebral and subarachnoid hemorrhages [48,49]. It can also result in demyelinating brain lesions similar to those associated with overly rapid correction of chronic hyponatremia [50,51].

Within several hours of the onset of hyponatremia, the brain will begin to adapt to the hyperosmolar state with an increase in brain cell osmolality, resulting in water movement back into the brain and the return of brain volume toward normal. This increase of brain cell osmolality is potentially due to sodium and potassium uptake by brain cells [14]. Intracellular osmolytes also accumulate and increase the osmolality. Because of this osmotic adaptation, patients with chronic hyponatremia may be relatively asymptomatic [52,53]. Although the evidence is less obvious than for hyponatremia, overly rapid correction of chronic hyponatremia can cause cerebral edema and possible neurological deterioration [49,53,54].

Diagnosis

As for hyponatremia, the history and physical examination can provide important information. Initial laboratory tests should include measurements of serum sodium and potassium concentrations. If hyponatremia is noted, measurement of urine osmolality, urine sodium, and urine potassium concentrations may help diagnose the cause of hyponatremia (see Figure 108.2) [40]. Using Formula 6 in Box 108.1, free water clearance into the urine can be calculated. Based on this evaluation, renal water loss can be assessed [5,55].

Treatment

Hyponatremia is considered acute if the rise in serum sodium has a documented onset within the last 48 hours [56]. If this is the case, rapid correction of hyponatremia is indicated by administering 5% dextrose solution at a rate of 3–6 mL/kg/h, or alternative hypotonic solutions (e.g. 0.45% saline) at a rate calculated using Formula 5 or 7 in Box 108.1, at a correction rate of 1–2 mEq/L/h, and complete correction within 24 hours because hyponatremia can lead to irreversible neurological injury (Box 108.3). If patients show clinical signs of acute hyponatremia, the correction rate should be increased by administering 5% dextrose solution at a rate of 7–10 mL/kg/h, or alternative hypotonic solutions, given for a correction rate of up to 2–3 mEq/L/h for the initial 2–3 hours or until the signs are resolved.

In the case of chronic hyponatremia (>48 h), osmotic adaptation has been completed and too rapid correction may result in cerebral edema [53,57]. Although no definitive trials have been performed, the maximum safe rate at which the serum sodium concentration should be lowered in chronic cases is <0.5 mEq/L/h or 10 mEq/L/day for the first 24 hours and 18 mEq/L for the first 48 hours in the absence of clinical signs [49,56]. One study suggests that excessively slow correction (<0.25 mEq/L/h) should also be avoided because of the potential increase in mortality [58].

Most cases of hyponatremia are due to water loss [5]. Gradual correction of this deficit with fluid replacement requires calculation of the water deficit using Formula 7 in Box 108.1 [40,49]. Free water can be given orally or intravenously as 5% dextrose in water. Alternatively, hypotonic solutions such as 0.45% saline can be used. The volume of water available for oral intake must be closely monitored to avoid a rapid, uncontrolled decrease in the animal's sodium concentration. Free water administration does not provide appropriate isotonic replacement of vascular volume deficits or interstitial dehydration [56]. If large-volume fluid resuscitation is needed to treat hypovolemia, it is safest to use a crystalloid with a sodium concentration that is similar to the patient (within 10 mEq/L of the patient's serum sodium concentration) (see Box 108.3). This may necessitate making a specific fluid by the addition of hypertonic saline to a commercially available crystalloid.

The most physiological therapy for treatment of CDI is exogenous ADH. This is typically achieved by the administration of dDAVP (1 drop or 1.5–4 μ L in the conjunctival sac OU q8–12h) [59]. Since patients with NDI do not usually have a major response to ADH, dDAVP is ineffective. The major form of therapy for patients with NDI is the treatment of underlying causes. Thiazide diuretics, non-steroidal anti-inflammatory drugs, and a

Box 108.3 Treatment summary for hypernatremia.**Acute (<48h) hypernatremia**

- Clinical signs present: Administer 5% dextrose solution at a rate of 7–10 mL/kg/h (or alternative hypotonic solutions at a rate calculated using Formula 5 in Box 108.1) at a correction rate of 2–3 mEq/L/h for the initial 2–3 h or until the neurological signs are resolved
- No clinical signs: Administer 5% dextrose solution at a rate of 3–6 mL/kg/h (or alternative hypotonic solutions) at a correction rate of 1–2 mEq/L/h
- Correct hypernatremia within 24 h of initial therapy
- Start cause-specific treatment and treat underlying causes
- Check the $[\text{Na}]_{\text{serum}}$ after 20–30 min, 1 h, 2 h, and every 4–8 h until hypernatremia is resolved

Chronic (>48h) hypernatremia

- Severe clinical signs present (usually acute on chronic hypernatremia): Administer 5% dextrose solution at a rate of 7–10 mL/kg/h (or alternative hypotonic solutions at a rate calculated using Formula 5 in Box 108.1) at a correction rate of 2–3 mEq/L/h for the initial 2–3 h or until the neurological signs are resolved
- No clinical signs present: start 5% dextrose solution at a rate of 1–1.5 mL/kg/h (or alternative hypotonic solutions) or oral water at a correction rate of 0.5 mEq/L/h
- Limit the decrease in $[\text{Na}]_{\text{serum}}$ to a total of 10 mEq/L during the first 24 h and 18 mEq/L for the first 48 h, regardless of whether clinical signs are present or absent
- Start cause-specific treatment and treat underlying causes
- Check the $[\text{Na}]_{\text{serum}}$ after 1 h, 2 h, and every 4–8 h until hypernatremia is resolved

Hypernatremia with hypovolemia

- Restore intravascular volume by administering a crystalloid solution with $[\text{Na}]_{\text{serum}}$ similar to the patient (≤ 10 mEq/L difference)
- Follow the treatment protocols described above depending on the presence of clinical signs and chronicity of hypernatremia.
- Check the $[\text{Na}]_{\text{serum}}$ after 10–20 min, at the end of resuscitation, and every 2–4 h until hemodynamic stability is achieved

$[\text{Na}]_{\text{serum}}$, serum sodium concentration.

low-sodium diet may decrease the severity of water loss due to NDI [40,60,61].

Therapy in patients with sodium overload is best aimed at removing the excess sodium. When renal function is normal, the sodium load will usually be excreted rapidly in the urine. This process can be facilitated by inducing a sodium and water diuresis with loop diuretics and replacing the urine output with fluid that is hypotonic to the urine [5,40]. Intravenous 5% dextrose or hypotonic crystalloid solutions can also be used in patients presenting with marked hypernatremia. However, careful monitoring is necessary, since these patients are volume expanded and the excess fluid may lead to fluid overload and pulmonary congestion or edema in susceptible cases.

Prognosis

Both hyponatremia and hypernatremia are associated with increased mortality in human patients [62–64]. More recent evidence suggests that even mild abnormalities and fluctuations in sodium values are significantly associated with poor outcome [65,66]. In dogs and cats, a retrospective study found the magnitudes of hyponatremia and hypernatremia were linearly associated with a higher mortality rate [67,68]. This was true even with the borderline to mild abnormalities. Some studies in human patients found that abnormal sodium concentration is an independent risk factor for poor prognosis and that early correction may improve outcome [69–71]. Therefore, hyponatremia and hypernatremia should be corrected carefully, but promptly.

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Potassium Disorders

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Introduction

Disorders of potassium homeostasis are associated with a wide range of disease types including urological, renal, toxic, and endocrine disorders. As such, altered serum potassium concentrations are considered common in both critically ill hospitalized patients and in those presenting to an emergency room. Moderate to severe hyperkalemia as well as hypokalemia can have immediately life-threatening consequences and ER clinicians must be adept at rapid recognition and correction of dyskalemias. This chapter discusses the most common causes of potassium disorders and how they may be addressed in the emergency room setting.

Potassium Homeostasis

Potassium is the major intracellular cation in mammalian cells and more than 95% of total body potassium is located within cells, predominantly in skeletal muscle cells [1,2]. Normal extracellular potassium concentration is approximately 4 mEq/L, while intracellular concentration is approximately 140 mEq/L and it is important to realize that serum potassium levels do not reflect whole-body potassium content in some settings [1,2].

The potassium concentration gradient between the intracellular and extracellular space is maintained by the active Na⁺-K⁺-ATPase pump that transports potassium ions into the cell and sodium out of the cell in a 3:2 ratio [3]. Potassium regulation must adapt to both the addition of potassium to the extracellular compartment by oral potassium intake in the diet and parenteral administration in intravenous fluids in hospitalized patients [2].

Two mechanisms are of great importance in maintaining a normal serum potassium concentration: the distribution of potassium between the intra- and extracellular fluid compartment (internal potassium balance), and the renal excretion of excess potassium (external potassium

balance) [3]. Abnormalities in serum potassium concentrations can therefore arise from abnormal potassium intake disturbances in internal potassium balance, or abnormal external potassium balance [3].

Hypokalemia

Definition and Etiology

Normal serum potassium values for dogs and cats are expected to range from 3.5 mEq/L to 5.5 mEq/L and hypokalemia is therefore defined as serum potassium concentrations less than 3.5 mEq/L [1,2]. An abnormality in any of the processes of potassium homeostasis outlined above can lead to hypokalemia and the three general causes for hypokalemia are decreased daily potassium intake, disorders of internal potassium balance (increased intracellular shift of potassium), and disorders of external potassium balance (increased renal and, more rarely, gastrointestinal potassium losses) [1,2,4]. Box 109.1 summarizes the most common conditions associated with hypokalemia in veterinary medicine.

Due to renal adaptation and increased renal potassium reabsorption in states of low serum potassium, decreased dietary intake of potassium alone is unlikely to lead to significant hypokalemia [1,4]. Over a period of days, the kidney typically alters excretion to match intake when dietary potassium load is altered. However, an abrupt absence of dietary potassium intake in a patient that typically has a high daily intake could conceivably result in transient hypokalemia during the period when renal adaptation is yet incomplete. However, administration of intravenous fluids with an isotonic crystalloid that does not contain sufficient potassium to meet maintenance potassium needs can lead to iatrogenic hypokalemia, especially in chronically anorexic animals [1]. Potassium absorption in the gastrointestinal tract

Box 109.1 Causes of hypokalemia [1,4–21].**Decreased intake**

Decreased oral intake

Intravenous administration of potassium deficient fluids

Clay ingestion (cat litter)

Disorders of internal balance (intracellular movement)

Metabolic alkalosis

Refeeding syndrome

Hypokalemic periodic paralysis

Hypothermia

Rattlesnake envenomation

Insulin excess (endogenous and exogenous)

Beta-adrenergic agonism

Disorders of external balance (renal and gastrointestinal losses)

Gastrointestinal losses

Vomiting

Diarrhea

Urinary losses

Chronic kidney disease (cat > dog)

Postobstructive diuresis

Diuretics

Renal tubular acidosis

Diabetic ketoacidosis

Hyperaldosteronism

Hyperadrenocorticism

Dialysis

can rarely be impaired by chronic ingestion of clay in humans, and hypokalemia in a cat due to the ingestion of clay cat litter containing bentonite has also been reported [5,6].

An increased flux of potassium into cells can lead to hypokalemia, as observed with metabolic or respiratory alkalosis, refeeding syndrome, periodic hypokalemic paralysis, hypothermia, rattle snake envenomation, or activation of the $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump due to increased endogenous or exogenous insulin, increased endogenous catecholamines, or beta-adrenergic agonist therapy or toxicosis [1,7–12].

Increased gastrointestinal and urinary losses are the most important causes of hypokalemia due to increased potassium loss in small animals [1,2]. An overview of conditions most commonly leading to urinary and gastrointestinal losses of potassium can be found in Box 109.1 [1,4,13].

Symptoms

The severity of symptoms resulting from hypokalemia usually correlates with the degree of hypokalemia and symptoms are generally not seen until potassium

concentrations reach 3.0 mEq/L to 2.5 mEq/L [4]. Hypokalemia can have a major effect on acid–base balance and glucose metabolism, neuromuscular function, cardiovascular, and renal function, and abnormalities induced by hypokalemia can therefore be divided into those four categories [1,2,4].

In dogs, acute potassium depletion leads to metabolic acidosis, which is reversible as soon as potassium is reintroduced to the diet [22]. Similar effects have been shown in cats with chronic potassium depletion [23]. Hyperglycemia is another adverse metabolic effect of total body potassium depletion and is thought to occur secondary to impaired beta-cell insulin release [24].

Hypokalemia can induce skeletal muscle weakness or paralysis, as well as cardiac arrhythmias and conduction disturbances. The mechanisms by which alterations in cell membrane excitability occur are complex but ascribed to the fact that potassium is necessary to maintain a normal resting membrane potential in skeletal and cardiac muscle [1,4,25]. Clinically, pelvic limb weakness can be observed in hypokalemic dogs and cats [1]. In cats specifically, hypokalemic myopathy frequently manifests as ventroflexion of the neck and head and occurs most commonly with chronically decreased dietary potassium intake and increased urinary potassium excretion [26,27]. Feline hyperaldosteronism has also been recognized as a cause of marked hypokalemia and associated muscle weakness [13,28]. In severe cases, respiratory muscle fatigue can require ventilatory support until hypokalemia and associated polymyopathy have resolved [29].

A variety of electrocardiographic (ECG) changes and cardiac arrhythmias have been observed in hypokalemic dogs and cats. The mechanisms by which arrhythmias develop is incompletely understood, but might be similar to the enhanced automaticity described in skeletal muscle of dogs with severe hypokalemia [4,25]. Hypokalemia also delays ventricular repolarization, prolonging the ventricular refractory period and predisposing the heart to re-entry arrhythmias [1,4]. Arrhythmias and ECG changes in hypokalemic dogs are less predictable than in dogs with hyperkalemia but can include atrial and ventricular tachyarrhythmias, ST segment depression, decreased amplitude of T-waves, prolongation of the QT interval, and the appearance of U-waves [1,30,31]. Increased P-wave amplitude and prolongation of the QRS complex have also been described [4]. Hypokalemia leaves the myocardium refractory to the effects of class I antiarrhythmic agents (e.g. lidocaine) and serum potassium concentrations should be corrected in patients with ventricular arrhythmias non responsive to therapy [1].

Potassium depletion can interfere with several renal functions. Polyuria and polydipsia along with decreased urinary concentration ability have been described in

hypokalemic patients, which are thought to be due to decreased renal ADH responsiveness in states of potassium depletion [1,4].

Treatment

The main goal in managing patients with hypokalemia is to correct the primary disease process and to rapidly decrease the risk of hypokalemia-associated adverse events.

Potassium deficits should be corrected, but immediate correction of the full deficit is not commonly urgent and monitoring of the clinical consequences of potassium depletion (e.g. ECG changes and muscle strength) should guide the rate of initial potassium replacement. Potassium replacement can generally be administered as enteral forms of potassium or parenteral.

Parenterally administration of potassium solutions (e.g. potassium chloride, potassium phosphate) is indicated in patients with moderate (2.5–3.4 mEq/L) to severe (<2.5 mEq/L) hypokalemia [1,2]. The rate of intravenous potassium administration should generally not exceed 0.5 mEq/kg/h of potassium to avoid potential life-threatening effects of iatrogenic hyperkalemia [1]. In profoundly hypokalemic patients, the rate can cautiously be increased to 1.0–1.5 mEq/kg/h long as close ECG monitoring is available [2]. In human patients, it is recommended that the concentration of potassium in intravenous fluids administered through a peripheral vein should not exceed 60 mEq/L due to the risk of pain associated with administration and peripheral venous sclerosis [4]. It is unknown if these issues are relevant to dogs and cats. Furthermore, administration of infusions containing high potassium concentrations through a central venous line should be performed with caution due to the risk for direct effects on cardiac conduction [4].

Guidelines for potassium supplementation based on degree of hypokalemia are provided in Table 109.1 [32]. Potassium supplementation should be conservative and closely monitored in patients suffering from oligoanuria, hypoaldosteronism, or those in which potassium-sparing diuretics are administered concurrently (e.g. spironolactone), as these conditions can predispose patients to development of hyperkalemia [2]. Patients that present in shock or dehydrated should be resuscitated or rehydrated with isotonic crystalloid fluids prior to the addition of potassium so as not to exceed a rate of 0.5 mEq/kg/h of potassium at the high necessary fluid rates [2].

Only in severely hypokalemic animals should potassium repletion be started at the time of rehydration. This can be achieved by staying within safe margins for potassium supplementation (<0.5 mEq/kg/h) or by an infusion containing potassium supplementation separate from the isotonic crystalloid used for rehydration

Table 109.1 Guidelines for intravenous potassium supplementation in dogs and cats [32].

Serum potassium concentration (mEq/L)	mEq KCL to add to 250 mL fluid	mEq KCL to add to 1 L fluid	Maximal fluid rate (mL/kg/h)
<2.0	20	80	6
2.1 to 2.5	15	60	8
2.6 to 3.0	10	40	12
3.1 to 3.5	7	28	18
3.6 to 5.0	5	20	25

KCL, potassium chloride.

[2]. Similarly, the administration of sodium bicarbonate and insulin to patients in diabetic ketoacidosis should be delayed until rehydration is achieved and serum potassium levels are >3.5 mEq/L, as sudden correction of acidemia and insulin replacement can worsen hypokalemia by enhancing intracellular potassium shifts [2,4]. In a subset of hypokalemic patients, simultaneous correction of magnesium deficits is likely to allow for more rapid and thorough correction of potassium deficit [33].

When supplementing flexible intravenous fluid bags, extreme care must be taken to sufficiently mix the content of the bag to avoid inadvertent administration of fluids containing life-threateningly high potassium concentrations [34]. The clinician must also bear in mind that reduced insulin release in hypokalemic patients can lead to reduced Na⁺-K⁺-ATPase activity, which in turn leads to elevated intracellular sodium concentrations. As potassium is provided and pump activity increases, sodium export from the cell will increase. Thus, in the initial stages of potassium repletion, parallel increases in serum sodium concentration may be observed.

Oral potassium most commonly is administered in the form of potassium gluconate powder or tablets with food. The recommended dose is 0.5 mEq/kg body weight orally once to twice daily and should be titrated to effect [35]. Oral potassium substitution is limited to patients experiencing mild hypokalemia (serum potassium concentration >3.4 mEq/L) and patients that voluntarily intake food or can be fed by esophageal or gastroenteral feeding tubes.

Hyperkalemia

Definition and Etiology

Hyperkalemia is defined as serum potassium concentrations that exceed 5.5 mEq/L and can be life-threatening at concentrations greater than 7.5 mEq/L [1]. As outlined

above, potassium intake occurs orally, by intravenous infusion, or by increased potassium release from intracellular sites. Initially, most excess potassium is taken up and transiently stored intracellularly and then excreted primarily by the kidneys [3]. Therefore, an abnormality in any process of potassium intake or generation, translocation from cells into extracellular fluid, or decreased renal excretion can lead to hyperkalemia [3]. Box 109.2 lists the most common causes of hyperkalemia in veterinary patients. In chronic, persistently hyperkalemic patients, reduced renal excretion is nearly always the underlying mechanism. However, such reductions in potassium clearance can be the result of extrarenal (e.g. hypoadosteronism, urethral obstruction) or intrinsic renal (e.g. CKD) causes.

Hyperkalemia occurs more commonly due to excessive potassium supplementation in intravenous fluids (by addition of potassium chloride or potassium phosphate) than with increased oral intake. However, the authors have observed severe, yet transient hyperkalemia during oral potassium bromide loading in small animal patients. Patients with impaired renal potassium excretion due to any of the causes listed in Box 109.2 are at an increased risk of hyperkalemia secondary to increased

potassium intake [36]. Rapid rates of intravenous fluid administration as well as inadequate mixing when preparing potassium-supplemented intravenous fluid bags can lead to inadvertent potassium overdose and hyperkalemia [34,37]. To avoid adverse effects, administration of intravenous potassium should not exceed 0.5 mEq/kg/h [1].

Increased potassium concentrations in the supernatant of stored human red blood cell products is recognized and can lead to potentially fatal hyperkalemia during blood transfusions. The majority of adult canine and feline erythrocytes lack $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump activity and intracellular potassium concentration is low. Newborn puppies of all breeds still have the $\text{Na}^+\text{-K}^+\text{-ATPase}$ present in their red blood cells (RBC) membranes, as do reticulocytes in adult dogs. The Asian dog breeds retain the transporter in adult RBC membranes even into adulthood. However, since puppies and Asian dog breeds rarely serve as blood donors, it is unlikely that significant potassium accumulation occurs in canine and feline stored blood products. Nonetheless, one case of potential transfusion-related hyperkalemia has been reported in a dog [41,42].

Hyperkalemia occurs frequently in patients with chronic kidney disease and has been described to persist in a subset of dogs even after initiation of feeding of a commercial renal diet [43]. Potassium-reduced diets specifically formulated by a veterinary nutritionist have been shown to be an effective alternative to correct persistent hyperkalemia [43].

Transcellular shift of potassium out of cells is another common cause of hyperkalemia in which the rise in plasma potassium is too rapid to be corrected by increased renal excretion. Metabolic acidosis due to inorganic acid accumulation (uremic acids, respiratory acidosis, hydrogen chloride, or calcium chloride infusions) results in buffering of excess hydrogen ions intracellularly and, in exchange, an extracellular shift of potassium occurs in order to maintain electroneutrality [2,36,44]. Release of potassium from the intracellular space can further occur when the rate of tissue breakdown is increased such as in severe exercise (especially with concurrent hypothyroidism), trauma (rarely; hypokalemia more common), heat stroke, administration of cytotoxic agents or radiation therapy to patients with malignant lymphoma (tumor lysis syndrome), and during spontaneous reperfusion of the limbs or following treatment with thrombolytic agents in cats that suffer from aortic thromboembolism [41,45–53]. Treatment with or accidental ingestion of angiotensin converting enzyme inhibitors, beta-adrenergic blockers (e.g. atenolol, propranolol), or $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump inhibitors such as digitalis can also lead to hyperkalemia [54].

Diabetic ketoacidosis and non-ketotic states of hyperglycemia and hyperosmolarity in patients with

Box 109.2 Causes of hyperkalemia [1,34,36–41,43, 45–75].

Increased intake

Oral

Intravenous potassium-containing fluids

Packed red blood cell transfusions

Disorders of internal balance (extracellular movement)

Metabolic acidosis

Insulin deficiency with ketoacidosis or hyperosmolarity

Tissue catabolism

Reperfusion injury (e.g. aortic thromboembolism)

Pseudohyperkalemia

Thrombocytosis or leukocytosis

In vitro hemolysis in Japanese breed dogs

Disorders of external balance (decreased renal excretion)

Anuric or oliguric renal failure

Ureteral obstruction

Urethral obstruction

Uroabdomen

Decreased effective circulating volume

 Cavitary effusions with drainage

Hypoadrenocorticism

Pseudohypoadosteronism

 Gastrointestinal disease (trichuriasis)

insulin deficiency can further lead to shift of potassium in the extracellular space [1]. Hyperkalemia occurs due to a decreased uptake of potassium intracellularly secondary to a decreased $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump activity in the absence of insulin, while hyperosmolar states lead to water shifts out of the cell which raise the intracellular potassium concentration and promote a favorable gradient for passive potassium exit out of the cell [3,36]. Additionally, frictional forces from water leaving the cell to the hyperosmolar extracellular space can result in potassium being carried along (“solvent drag”) [36].

It is important to realize that total body potassium stores in states of insulin deficiency are commonly depleted and the extracellular hyperkalemia is a relative hyperkalemia. Correction of concurrent acidemia as well as insulin replacement enables relocation of the potassium to the intracellular space and can lead to severe hypokalemia [2,4].

Pseudohyperkalemia is an artifactual increase in serum potassium in which potassium shifts out of the cells during or after blood sample acquisition [36]. Potassium can be released from several different circulating blood cells (e.g. blood platelets, leukocytes, and erythrocytes) and pseudohyperkalemia is seen most commonly in patients with severe thrombocytosis [55]. Akita dogs and other dogs of Japanese origin have a functional erythrocyte membrane $\text{Na}^+\text{-K}^+\text{-ATPase}$ and therefore high intracellular potassium concentrations and artifactual hyperkalemia can be observed if hemolysis occurs during or following blood sampling [56,57]. Pseudohyperkalemia due to thrombocytosis or leukocytosis can be confirmed by comparison of plasma potassium levels with the initially acquired serum potassium levels [36]. Plasma potassium levels should not be affected by thrombocytosis and leukocytosis as the extracellular fluid gets separated from the cells before coagulation has occurred and intracellular potassium is released. Reducing the time plasma is in contact with red cells in Japanese breed dogs prior to potassium measurement can help reduce the occurrence of pseudohyperkalemia [57].

Renal potassium excretion is usually so efficient that an increase in potassium intake alone will not cause hyperkalemia in a normal subject [1]. For hyperkalemia to develop, urinary excretion of potassium must be reduced and prerenal (e.g. decreased effective circulating volume), renal (e.g. acute or chronic renal disease, hypoaldosteronism), and postrenal diseases (e.g. ureteral obstruction, urethral obstruction, uroabdomen) are the most common causes for persistent hyperkalemia in companion animals [1,3]. Effective circulating volume depletion such as from excessive fluid losses or third spacing of fluid into a non-circulating body cavity will

lead to reduced distal renal tubular flow and decreased urinary potassium excretion [3]. Urinary potassium excretion can be improved by restoring effective circulating volume, renal perfusion, and urine output. By reducing effective circulating volume, chylothorax, non-chylous pleural effusion, and peritoneal effusion, especially when managed with intermittent drainage, can result in hyperkalemia and hyponatremia [58–63]. In renal failure, adequate potassium excretion is maintained by increased potassium excretion per functioning nephron, which is dependent on aldosterone and enhanced $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity and maintained urine flow rate and, therefore, the ability to excrete potassium decreases once oliguria develops [36].

Most commonly, oliguria and anuria are associated with acute insults to the kidneys leading to tubular damage, but oliguria and subsequent hyperkalemia can also occur with end-stage chronic kidney disease [64–66]. Hyperkalemia has been reported due to decreased potassium excretion in feline and canine uroabdomen, ureteral, and urethral obstruction [67–71].

Hyperkalemia in conjunction with hyponatremia and sodium to potassium ratios of $<27:1$ are highly suggestive of hyperkalemia due to hypoaldosteronism (Addison’s disease) and hyperkalemia has been reported in the majority of canine and feline patients suffering from hypoaldosteronism [72,73]. Natriuresis, vomiting, and anorexia in hypoaldosteronism patients commonly worsen the ability to excrete sufficient amounts of potassium in the face of inadequate endogenous mineralocorticoids by decreasing effective circulating volume and distal tubular flow rate [1]. Initial therapy aimed at restoring effective circulating volume often can decrease potassium concentrations into the normal range [1]. Treatment with exogenous mineralocorticoids (e.g. desoxycorticosterone) is begun immediately after a presumptive diagnosis of hypoaldosteronism is made, but definitive diagnosis is achieved by measuring resting cortisol levels and adrenocorticotropin hormone (ACTH) stimulation test [1,2].

Pseudohypoaldosteronism with a reduced sodium to potassium ratio of $<27:1$ can be found in dogs with gastrointestinal disease, especially patients suffering from trichuriasis, salmonellosis, and perforated duodenal ulcers [74,75].

Symptoms

The clinical manifestations of hyperkalemia are limited to skeletal muscle weakness and abnormal cardiac conduction and reflect the physiological effect of potassium on resting membrane potential as well as cell membrane excitability [1,36]. Skeletal muscle weakness can develop

Table 109.2 Electrocardiographic changes secondary to hyperkalemia [82].

Serum potassium concentration	Electrocardiographic change
>5.5 mEq/L	Peaked, narrow T-wave
>6.5 mEq/L	Prolonged QRS complex and PR interval
	Depressed R-wave amplitude
	Depressed ST segment
>7 mEq/L	Depressed P-wave amplitude
>8.5 mEq/L	Atrial standstill
	Sinoventricular rhythm
>10 mEq/L	Biphasic QRS complex
	Ventricular flutter
	Ventricular fibrillation
	Asystole

in hyperkalemic states, usually when serum potassium concentration exceeds 8.0 mEq/L [1]. Severe hyperkalemia can lead to atrial standstill, bradycardia, and ventricular asystole due to impaired membrane excitability of the cardiac conduction system [36]. Rarely, wide complex tachycardia can be seen in cats with severe hyperkalemia [76]. The electrocardiographic changes caused by hyperkalemia have been studied in experimental dogs and cats and typically follow a similar pattern, but do not always correlate with serum potassium concentrations in the critically ill patient [1,77–80].

One must bear in mind that the manifestation of hyperkalemia at any given serum potassium level will be dependent on other factors as well (e.g. ionized calcium). The progressions of waveform and conduction changes are summarized in Table 109.2.

Treatment

The most appropriate treatment for hyperkalemia is dependent on the degree of hyperkalemia, the timeframe of onset, and the underlying cause.

An ECG should be performed in every patient with moderate to severe hyperkalemia as rapid onset of even moderate hyperkalemia can cause cardiac arrhythmias [1,2]. Animals capable of normal urine potassium excretion (i.e. with normal urine output) and without clinical signs associated with hyperkalemia in the range of 5.5–6.5 mEq/L might not require immediate treatment, but exogenous potassium administration should be discontinued and the cause for the hyperkalemia investigated [1]. Potassium-free (e.g. 0.9% NaCl) or potassium-deficient fluids (e.g. lactated Ringer's) can be administered to patients with normal urinary output to promote diuresis and may be sufficient to decrease serum potassium concentrations to normal ranges.

The goals of treatment of patients suffering from severe hyperkalemia or exhibiting clinical signs associated with hyperkalemia are aimed at restoring the resting membrane potential of cells, normalizing cardiac action potential conduction velocities, and ultimately lowering the serum potassium concentration. Ten percent calcium gluconate antagonizes the effect of hyperkalemia on myocardial resting membrane potential, but will not lower the potassium concentration [1]. Regular insulin with dextrose to prevent hypoglycemia or the sole administration of dextrose solutions to increase endogenous insulin levels, sodium bicarbonate, and beta-adrenergic agonists can all be successfully used to decrease serum potassium concentrations by promoting increased intracellular shifts of potassium [2,81]. A summary of treatments for life-threatening hyperkalemia is provided in Table 109.3.

Table 109.3 Treatment of severe hyperkalemia [1,2,81].

Drug	Dosage	Mechanism of action	Comment
10% Calcium gluconate	0.5–1.5 mL/kg IV over 5–10 min with ECG monitoring	Reduces cardiac excitability by re-establishing the normal gradient between the resting membrane and threshold potentials	Cardioprotective but will not lower serum potassium concentration
Insulin and 50% Dextrose	Regular insulin 0.5 U/kg IV with dextrose 2 g/U of insulin (4 mL of 50% dextrose)	Promotes intracellular shift of potassium through activation of Na ⁺ -K ⁺ -ATPase	
50% Dextrose	0.7–1 g/kg IV over 3–5 min	Same as above	
Sodium bicarbonate	1–2 mEq/kg IV slowly over 15 min	Increases extracellular pH and promotes intracellular shift of potassium in exchange for H ⁺ ions	
Terbutaline	0.01 mg/kg IV slowly	Promotes intracellular shift of potassium through activation of Na ⁺ -K ⁺ -ATPase	

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Calcium, Magnesium, and Phosphorus Disorders

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Introduction

The term *minerals* refers to all forms of inorganic nutrients. However, the most physiologically abundant of these elements (sodium, potassium, chloride) all nearly completely dissociate in water and are thus generally categorized as electrolytes and discussed separately from other minerals.

This chapter focuses on three minerals, calcium, magnesium, and phosphorus, (Ca, Mg, and P), that share several important features including hormonal regulation, renal excretion, abundant divalent forms, predominance of non-exchangeable mass, and extensive protein/macromolecule binding. The importance of mineral disorders in the veterinary emergency room setting is likely to be comparable to what is observed in human medicine (with the exception of alcohol-related disorders). A retrospective study of 1447 human emergency room (ER) patient records revealed the following: 17.6% of these patients had one or more abnormalities in Ca, Mg, and/or P, 0.3% required treatment in the ER, and 5.1% were treated only after hospital admission [1]. The authors also concluded that significant treatments were largely administered to just three main types of patients: diabetics, alcoholics, and patients with renal failure. They further recommended that STAT testing be largely restricted to those patient categories.

In veterinary medicine, ER clinicians are far more likely to encounter acute kidney injury (a largely hospital-acquired condition in humans), urinary tract obstruction, and poorly regulated diabetics than their MD counterparts. From this, one might predict that mineral disorders may, in fact, be slightly more common in a veterinary ER setting than in a human emergency department. This chapter discusses the most common causes of Mg, Ca, and P disorders and how they may be addressed in the emergency room setting.

Phosphorus Homeostasis

Phosphorus is essential to the function of lipid bilayer cell membranes. Mammalian lipid bilayers are constructed of phospholipids such as phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and sphingomyelin [2]. The phosphorylation of the lipid glycerol head is essential to the creation of a hydrophilic subregion and to the assembly of oriented bilayers. Phosphorylation is central to the processes of glycolysis and the generation of the high-energy compounds used to redistribute free energy (e.g. ATP, phosphocreatine) in living systems [3,4]. Phosphates play a key role in the activation of clotting factors (V and X) and platelet aggregation [5]. Phosphate moieties are extensively utilized to alter protein function. It has been estimated that up to 30% of all mammalian proteins have at least one phosphorylation site [6]. Phosphate is also a co-factor for many co-enzymes and is essential for the formation of 2-3 diphosphoglycerate (2-3DPG), which is utilized to modify hemoglobin's oxygen affinity within the erythrocytes of some mammals (not cows or cats) [7].

Eighty percent of whole-body phosphorus is complexed in (hydroxy)apatite biomineral in the skeleton, whereas 19–20% is found in the intracellular compartment where it is the most abundant anion. Less than 1% is found in the plasma where it may be bound to organic macromolecules or unbound in its ionic form. At normal physiological pH (i.e. 7.4), 80% of the unbound phosphate will be in its divalent (HPO_4^{2-}) form and the remaining 20% in its univalent (H_2PO_4^-) form. Clinical laboratories typically only measure the unbound portion of serum phosphate and thus the main screening test used to assess phosphate in the clinical setting is examining but a fraction of whole-body stores.

Ingested phosphate is taken up by the small bowel via both passive and active transport. Intestinal uptake of

both phosphorus and calcium is enhanced by vitamin D [8]. Parathyroid hormone (PTH), vitamin D, and calcitonin regulate the mobilization (or storage) of phosphorus in skeletal biomineral deposits [9]. At the level of the kidney, phosphate excretion is regulated by both PTH and fibroblast growth factor-23 (FGF-23) [10]. FGF-23 is secreted by osteoblasts in response to increases in phosphorus intake. In a negative feedback loop, FGF-23 inhibits the production and stimulates the degradation of 1,25-dihydroxyvitamin D, while promoting a concurrent increase in urinary phosphorus excretion in a manner independent of both PTH and vitamin D [10].

The renal tubular Na-PO₄ co-transporter is the predominant site of regulation for phosphate excretion [10]. This co-transporter is inhibited by metabolic acidosis [11]. Elevated serum phosphate or PTH promotes removal of this membrane co-transporter via endocytosis. Conversely, insertion of the transporter into the renal tubular membrane is stimulated by acute reductions in serum phosphate, whereas chronic hypophosphatemia promotes the synthesis of new transporters [11].

Hypophosphatemia

Definition and Etiology

Normal serum phosphate values for dogs and cats are expected to range from approximately 3.0 mg/dL up to 5.0 mg/dL (canine) or 6.0 mg/dL (feline). Assuming a Gaussian distribution of values from both diseased and non-diseased patients, one can assume that there will be overlap between serum phosphate concentrations obtained from these two groups [12]. This author typically views values that lie 15–20% above or below the reference interval to be reliably abnormal (and not due to the nature of reference interval generation). Hypophosphatemia may therefore be broadly defined as serum phosphate concentrations less than 2.5 mg/dL in both dogs and cats. An abnormality in any of the processes of phosphate homeostasis (as outlined above) can lead to hypophosphatemia. The three general causes for hypophosphatemia are internal redistribution/transcellular shifts, decreased intake or absorption, and increased urinary excretion [12–16]. Box 110.1 summarizes the most common conditions associated with hypophosphatemia in small animal practice.

Significant redistribution/intracellular shifts of phosphate are a common cause of hypophosphatemia. Respiratory alkalosis (hyperventilation, hypocapnia) has a potent effect, and can abruptly lower serum concentrations below the reference interval [16]. Refeeding syndrome, wherein insulin release in the face of a pre-existing phosphate deficiency causes phosphate (as well as potassium and magnesium) to be taken up intracellularly, can also cause a significant abrupt decline in serum phosphate

Box 110.1 Causes of hypophosphatemia.

Decreased gastrointestinal absorption

Vitamin D deficiency
Malabsorption
Vomiting and diarrhea
Phosphate binder administration
Antacids

Increased renal excretion

Diabetes mellitus
Diabetic ketoacidosis
Renal tubular defects
Diuretic administration
Hyperadrenocorticism
Eclampsia
Hyperaldosteronism
Early hypercalcemia of malignancy

Transcellular shifts

Insulin administration
Parenteral glucose administration
Bicarbonate administration
Total parenteral nutrition administration
Refeeding syndrome
Hypothermia
Respiratory alkalosis

concentrations [17]. The so-called “hungry bone syndrome” can potentially occur following parathyroidectomy or parathyroid ablation for chronic hyperparathyroidism, as the previously substrate-limited osteoblasts quickly resume their uptake of phosphate, although this is atypical and postoperative hyperphosphatemia has been described in this setting as well [18–20].

The restoration of effective insulin signaling during the treatment of diabetic ketoacidosis (DKA) will commonly reduce serum phosphate concentrations within the first 24 hours after insulin therapy is begun [20–23]. Serum phosphate levels should begin to return to the healthy steady-state values once the factors driving the translocation have been rectified. Treatment should generally be initiated if the serum phosphate concentration is below 1.5 mg/dL or if it is below 2.5 mg/dL and the patient is exhibiting compatible clinical signs [24].

Care must be taken with severe DKA patients. Patients with blood glucose concentrations of greater than 250 mg/dL *must* have a significant reduction in glomerular filtration rate (or their blood glucose would not be able to persist that far above the renal threshold) [22]. In this setting, serum phosphate may be markedly elevated due to impaired renal excretion. The author has cared for a DKA dog whose pretreatment serum phosphate was 22.6 mg/dL (in the absence of renal injury). Pre-emptively

administering phosphate supplementation to such a patient would only serve to drive the calcium-phosphorus product even further above the *in vivo* solubility saturation point and promote metastatic calcification of soft tissues. Phosphorus supplementation should be reserved for those cases in which recent total calcium and serum phosphate measurements are available for review.

Clinical Signs

The severity of symptoms resulting from hypophosphatemia often correlates weakly with the degree of the reduction and is generally not evident until phosphate concentrations reach 1.5–2.0 mg/dL [25–28]. Moderate hypophosphatemia (1.5–2.5 mg/dL) does not obligate correction if clinical signs are absent. The exception to this guideline would be patients on mechanical ventilation in whom even moderate hypophosphatemia may prevent successful weaning [25].

In dogs and cats, the clinical signs associated with hypophosphatemia are highly variable and include many organ systems [12,26]. Table 110.1 details the clinical signs associated with hypophosphatemia (and hyperphosphatemia which is covered below). Several of these complications can severely alter the path towards recovery for a patient whose primary problem is otherwise resolving. Prompt correction of hypophosphatemia has the potential to avoid serious complications and reduce reliance on expensive life support measures such as transfusion, hemodialysis, oxygen therapy, and mechanical ventilation.

Treatment

The main goal in managing patients with hypophosphatemia is to correct the primary disease process and rapidly decrease the risk of hypophosphatemia-associated adverse events. Phosphate deficits should be

Table 110.1 Clinical signs associated with extreme elevations or reductions in serum phosphorus concentrations (subcategorized by organ system).

Organ system	Clinical signs observed with:	
	Severe hypophosphatemia (<1.5 mg/dL)	Severe hyperphosphatemia (>8–10 mg/dL)
Central nervous system	Confusion	Decreased mentation
	Paresthesias	Seizures
	Seizure	
	Coma	
Cardiovascular	Congestive heart failure	Dysrhythmias
	Dysrhythmias	Q-T interval prolongation
Pulmonary	Acute respiratory failure	
	Tissue hypoxia	
Musculoskeletal	Myalgias	Weakness
	Weakness	Cramping
	Rhabdomyolysis	Hyperreflexia
		Tetany
Renal	Acute kidney injury	Renal injury
	Metabolic acidosis	Progression of pre-existing chronic kidney disease
Hematological	Hemolysis	
	Platelet dysfunction	
	Leukocyte dysfunction	
Gastrointestinal	Persistent ileus	Anorexia
	Nausea	Nausea
	Vomiting	Vomiting
Ocular		Reduced visual acuity
		Conjunctivitis
Dermatological		Pruritus

corrected, but immediate correction of the full deficit commonly is not urgent and monitoring of the visually apparent clinical consequences of phosphate depletion (e.g. seizures, muscle weakness, pigmenturia, ileus, hemolysis) should guide both the total quantity and rate of initial phosphate replacement. Phosphate replacement can generally be administered as enteral forms (mild to moderate) or through parenteral administration (moderate with clinical signs and severe).

Enteral phosphate supplementation in humans is typically in the range of 15–45 mg/kg/day. While well-established guidelines for oral supplementation in dogs and cats are lacking, staying well below the dose at which renal interstitial mineralization has been shown to occur (108 mg/kg/day) is advised [29]. Parenteral administration of phosphate solutions (e.g. potassium phosphates, sodium phosphates, or Glycophos) is indicated in patients with moderate (1.5–2.5 mg/dL) to severe (<1.5 mg/dL) hypophosphatemia [24]. For moderate hypophosphatemia, administration rates of 0.01–0.03 mmol PO₄/kg/h have been recommended, whereas in severe hypophosphatemia rates of 0.03–1.2 mmol PO₄/kg/h may be required [30,31]. Reassessment of serum phosphate concentrations every 8–12 hours while supplementation is ongoing is advised.

Hyperphosphatemia

Definition and Etiology

Hyperphosphatemia may be broadly defined as serum phosphate concentrations greater than 6 mg/dL (dogs) or 7 mg/dL (cats). An abnormality in any of the processes of phosphate homeostasis can lead to hyperphosphatemia. The three general causes for hyperphosphatemia are increased endogenous release, increased exogenous uptake, and decreased urinary excretion [32–40]. Box 110.2 summarizes the most common conditions associated with hyperphosphatemia in small animal practice.

Symptoms

The clinical manifestations of hyperphosphatemia are dependent on the severity of the elevation and the rate at which it has increased. Similar to hypophosphatemia, the clinical signs associated with hyperphosphatemia are highly variable and include many organ systems [32–34,36]. Table 110.1 details the clinical signs associated with hyperphosphatemia. Several of these complications can severely alter the path towards recovery for a patient whose primary problem is otherwise resolving. Prompt correction of hyperphosphatemia is often only achievable by extracorporeal therapies (e.g. hemodialysis) or by the prompt restoration of renal excretion.

Box 110.2 Causes of hyperphosphatemia.

Increased gastrointestinal absorption

Vitamin D toxicosis
Cholecalciferol
Calcipotriene
Phosphate enemas

Decreased renal excretion

Azotemia
Prerenal
Hypoadrenocorticism
Renal
Acute kidney injury
Chronic kidney injury
Postrenal
Uroabdomen
Obstructive uropathies
Hypoparathyroidism
Acromegaly
Hyperthyroidism

Transcellular shifts

Hemolysis
Tumor lysis syndrome
Crush injury/rhabdomyolysis

Physiological

Young, rapidly growing dogs
Postprandial

Treatment

Hyperphosphatemia is best addressed by treating the underlying disorder. In situations of increased intracellular phosphate release such as rhabdomyolysis and tumor lysis syndrome, the administration of calcium-poor fluids can accelerate renal excretion of phosphate. Loop diuretics such as furosemide may also promote phosphate excretion. Renal excretion is generally so efficient in patients with adequate renal function that balance can be maintained with only a minimal rise in serum phosphorus concentration even for a relatively large phosphorus load. Therefore, acute hyperphosphatemia usually resolves within a few hours if renal function is sufficiently preserved. Patients with chronic kidney disease (CKD) and mild asymptomatic hyperphosphatemia can be treated by reducing dietary protein intake and reducing intestinal absorption with phosphate-binding salts of aluminum, magnesium, or calcium. However, these agents have little role or no role to play in the emergency setting. Emergency room patients are often anorexic and dietary intake is of little concern in the immediate future.

Hemodialysis or peritoneal dialysis may be required to correct hyperphosphatemia in AKI or CKD patients and some have proposed that phosphate be a determining factor in timing the initiation of hemodialysis support [41].

Calcium Homeostasis

Calcium ion is an essential chemical factor in several essential body functions such as muscle contraction, nerve conduction, neurotransmitter release, hormone secretion, cell division and motility, enzyme activity, blood coagulation, action potentials, and pacemaker automaticity. Calcium homeostasis refers to the regulation of the concentration of calcium ions in the extracellular fluid environment ($\text{ECF}_{\text{Ca}^{2+}}$). Quite different mechanisms regulate the abundance and distribution of ionized and complexed calcium within the intracellular environment. Intracellular calcium ion is a major second messenger system and cytoplasmic levels must be tightly controlled to avoid cytotoxicity [42].

Extracellular calcium ion concentration is also tightly controlled due to the adverse effects of both elevations and decreases in this parameter. $\text{ECF}_{\text{Ca}^{2+}}$ greatly impacts the function of voltage-gated ion channels (VGIC). Decreases in $\text{ECF}_{\text{Ca}^{2+}}$ (hypocalcemia) lead to VGIC opening that is too easily triggered or spontaneous in nature. Clinically, this effect manifests as nerve and muscle dysfunction such as hypocalcemic tetany. Conversely, increases in $\text{ECF}_{\text{Ca}^{2+}}$ (hypercalcemia) can prevent or reduce VGIC opening and clinical manifestations include many types of depressed nervous system function. Due to its ability to form insoluble particulates with phosphate ions, increases in $\text{ECF}_{\text{Ca}^{2+}}$ can also lead to excessive accumulation of mineral deposits within soft tissues or within third spaces such as the bladder lumen or renal collecting system.

The regulation of $\text{ECF}_{\text{Ca}^{2+}}$ is complex and involves the interplay of several organ systems. However, ultimately $[\text{ECF}_{\text{Ca}^{2+}}]$ depends on three main factors [42,43]:

- the absorption of dietary calcium
- the extent of $\text{ECF}_{\text{Ca}^{2+}}$ excretion by the kidney

- the relative rate of release and uptake of $\text{ECF}_{\text{Ca}^{2+}}$ from the bony skeleton which contains a massive reservoir of 99% of $\text{ECF}_{\text{Ca}^{2+}}$. The mobilization of even a tiny portion of this skeletal reservoir can have major impacts on $[\text{ECF}_{\text{Ca}^{2+}}]$.

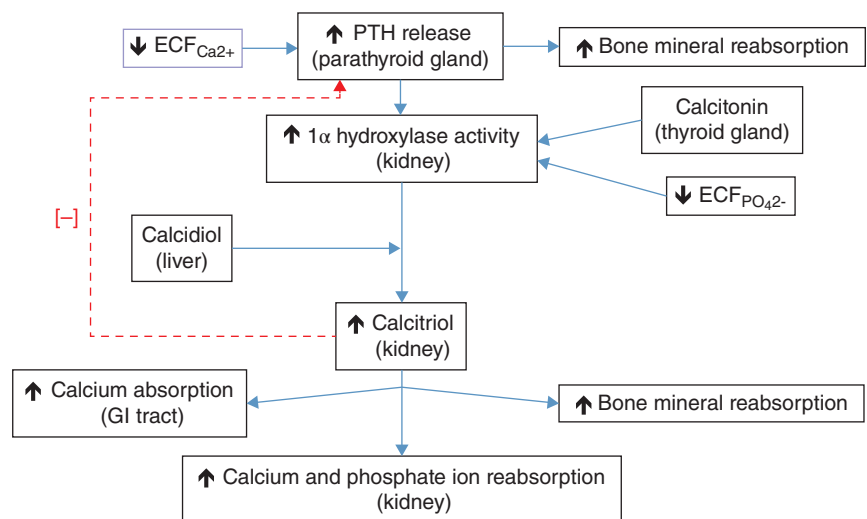
The major humoral factors and their roles in calcium homeostasis are outlined in Figure 110.1. The three major hormonal mediators are PTH, calcitriol, and calcitonin. PTH typically serves a key role in minute-to-minute regulation of $\text{ECF}_{\text{Ca}^{2+}}$ while calcitriol plays the central role in day-to-day $\text{ECF}_{\text{Ca}^{2+}}$ regulation. Calcitonin plays a relatively minor role involving the control of bone mineral mobilization and fine-tuning PTH release.

Hypocalcemia

Definition and Etiology

Hypocalcemia is defined as an abnormal reduction in the concentration of calcium in the extracellular fluid compartment. The recognition of such a reduction and the cut-off values used in identifying hypocalcemia will depend heavily on the means by which calcium is measured. Plasma calcium is present in three major forms: (1) ionized (~55% of total calcium present), (2) non-ionized chelated (~10% of total calcium present), and protein (largely albumin) bound (~35% of total calcium present) [42]. As just under half of the total calcium present in plasma is not in the form that is physiologically regulated, reductions in total calcium cannot always be assumed to be coincident with reductions in the ionized fraction. Reductions in ionized calcium are best identified by direct measurement rather than inference methods. The absolute value at which one will identify ionized hypocalcemia will vary between institutions but will typically be characterized as below the range of 1.0–1.2 mmol/L. When total calcium is used to identify

Figure 110.1 Calcium homeostasis overview.



Box 110.3 Causes of hypocalcemia.**Common**

Hypoalbuminemia
Chronic kidney disease
Eclampsia
Acute kidney injury
Acute pancreatitis

Occasional

Soft tissue trauma/rhabdomyolysis
Hypoparathyroidism
Ethylene glycol intoxication
Phosphate enema administration
Bicarbonate administration

Uncommon

Lab/anticoagulant error
Rapid IV phosphate administration
Dilutional
Intestinal malabsorption
Hypovitaminosis D
Blood transfusions
Hypomagnesemia
Intralipid infusion

hypocalcemia (not advised), cut-off values of <8 mg/dL are often used in the clinical setting.

Causes of hypocalcemia are outlined in Box 110.3. These causes have been broken down into three categories of common, uncommon, and rare for the reader; however, the relative prevalence of these underlying causes may vary by region and/or practice type. Among the causes of hypocalcemia considered common by this author, hypoalbuminemia is considered to be the least likely to result in concurrent ionized hypocalcemia and thus clinical signs reflecting nerve and muscle dysfunction. Both acute and chronic injury to the kidneys can result in hypocalcemia due to direct and indirect mechanisms. Eclampsia can be considered the cause of hypocalcemia most likely to be recognized due to its direct effects on muscle and nerve function. The hypocalcemia of acute pancreatitis has long been attributed to the saponification of peripancreatic fat but evidence of more widespread disruptions of calcium homeostasis in this setting bears consideration.

Clinical Signs

Clinical signs due to hypocalcemia may be subcategorized as due to muscle dysfunction, nervous system dysfunction, and cardiovascular dysfunction [42]. Manifestations of muscular dysfunction can include muscle tremors, fasciculation, twitching, and sustained contractions or tetany. Ineffective contractions may also manifest, as seen in some forms of dystocia. Nervous system

dysfunction manifestations can include disorientation, restlessness, parasthesias (particularly facial pruritus), panting, and hyperthermia. The CNS may also play a role in hypocalcemia-related arrhythmogenesis, but local effects on the cardiac tissue likely play a larger role. Cardiovascular manifestations of hypocalcemia include the aforementioned arrhythmias as well as arterial hypotension (see Chapter 53).

Treatment

Treatment options are based on addressing the underlying cause of the hypocalcemia and supplementing calcium in either enteral or parenteral form for an appropriate duration of time. When ionized hypocalcemia has been identified then treatment is advised if the $[iCa^{2+}] < 0.7\text{--}0.9$ mmol/L. If ionized hypocalcemia is to be inferred from total calcium measurements then treatment when the total $Ca < 6\text{--}7$ mg/dL could be justified if suitable clinical signs are evident.

Acute treatment typically involves the administration of parenteral calcium gluconate (10%). Dose ranges of the order of 0.5–1.5 mL/kg of 10% calcium gluconate administered over 1–5 minutes are generally required. Rechecking $[Ca^{2+}]$ before readministration is advised. For persistent hypocalcemia, a maintenance constant rate infusion at doses of 0.25–1.0 mL/kg/h of 10% calcium gluconate are often sufficient. Long-term supplementation often takes the form of calcium carbonate, which is inexpensive and widely available. In some instances, calcium citrate or oyster shell calcium may be preferable. Dosing requirements are widely variable and should be titrated based on individual patient responses to supplementation. Treatment precautions during any form of calcium supplementation include avoidance of extravasation of parenteral calcium solutions (particularly calcium chloride which can lead to local tissue necrosis), making every attempt to avoid a calcium $\times$ phosphate product of greater than 70, and the creation of a monitoring plan sufficiently intensive so as to avoid iatrogenic hypercalcemia.

Hypercalcemia**Definition and Etiology**

Hypercalcemia is an abnormal increase in $ECF_{Ca^{2+}}$. Increases in ionized calcium, total calcium, or both may be identified. The common causes of hypercalcemia in dogs and cats are summarized in Box 110.4. The most common causes of hypercalcemia in dogs are hypercalcemia of malignancy, hypoadrenocorticism, and chronic kidney disease. In cats, hypercalcemia of malignancy is highly prevalent, but idiopathic hypercalcemia is nearly as common (see Chapters 72 and 73). Renal causes of hypercalcemia are also quite common in feline patients.

Box 110.4 Causes of hypercalcemia.**More common (dogs)**

Hypercalcemia of malignancy
Hypoadrenocorticism
Chronic kidney disease

More common (cats)

Hypercalcemia of malignancy
Idiopathic
Chronic kidney disease

Less common (both)

Primary hyperparathyroidism
Hypervitaminosis D
Osteolysis
Iatrogenic
Granulomatous disease
Thiazide diuretics

Mechanisms underlying hypercalcemia often involve the overactivity of PTH or a hormonally active-related peptide. Bony destruction due to neoplasia, extensive bone inflammation, or infection can also cause persistent hypercalcemia. Certain medications (thiazides) and toxins (vitamin D analogue rodenticides) (see Chapter 130) are also causes of hypercalcemia that may be encountered in small animal practice [42].

Clinical Signs

The consequences of persistent hypercalcemia may be linked to calcium's role in determining cellular threshold potential and its ability to form relatively insoluble mineral complexes with phosphate ion. Hypercalcemia results in threshold potential becoming a less highly negative voltage. This shift increases the voltage gap between resting and threshold potentials and makes cells less excitable and more difficult to polarize. Hypercalcemia also increases muscle contractile state and increases ATP utilization while decreasing ATP production.

Clinical signs relating to CNS functions include obtundation, seizures, and lethargy. Cardiovascular signs of hypercalcemia include increased arteriolar tone (which may elevate arterial pressure in some patients), poor diastolic function, and arrhythmias. Muscle tremors or muscle weakness may be noted. Polyuria due to diminished urine concentrating ability can also occur in hypercalcemic patients.

In cases of chronic hypercalcemia, additional clinical manifestations may be noted. Gastric hyperacidity and vomiting are not uncommon in this setting. Calciuresis, urolithiasis, renal injury, and soft tissue mineralizations are also encountered in this clinical setting.

Treatment

Treatment of the underlying cause is always a priority in hypercalcemic patients. Thus, identification of the underlying etiology is a high priority in such cases. Options for non-specific treatment of hypercalcemia include the following [42]:

- ECF volume expansion and saline diuresis
- loop diuretics such as furosemide
- avoidance or discontinuation of thiazide diuretics
- bicarbonate administration (transient effect)
- corticosteroids (particularly in cases of hypoadrenocorticism, neoplasia, or granulomatous disease).

In cases of severe life-threatening hypercalcemia, additional treatment measures should be considered, including:

- calcium-chelating agents
- calcium channel blockers
- extracorporeal therapies such as hemodialysis or continuous renal replacement therapy
- bisphosphonate agents such as pamidronate.

For longer-term therapy, agents such as calcitonin and the antineoplastic antibiotic mithramycin may be employed.

Magnesium Homeostasis

The mechanisms underlying magnesium regulation are complex, poorly understood at present, and incompletely defined. The majority of the major transcellular transport proteins for magnesium have only recently been identified and our understanding of their regulation is an area of ongoing active research. While hormones do play a role in magnesium homeostasis, that role is quite minor when compared to their central importance in calcium homeostasis. Like calcium, magnesium is a divalent cation that can be found in ionized, complexed, or protein-bound forms.

The majority of body magnesium is found in the intracellular compartment where it is the second most abundant cation after potassium [44]. Much is often made of the fact that ionized magnesium is the most "biologically active" form. This is true of all electrolytes and is in no way unique to magnesium. Moreover, an argument can be made that it is in fact the common complexed form (i.e. Mg-ATP) that is the most biologically important form.

Magnesium homeostasis involves uptake of dietary magnesium. Magnesium is found in abundance in green plant matter as it is the central cation in chlorophyll, much as iron is in hemoglobin. In humans, enteral absorption of magnesium occurs in the small intestine, whereas fistula studies suggest that the major site of magnesium uptake in dogs is the colon. The site of feline magnesium uptake has not yet been defined.

Uptake of dietary magnesium follows a biphasic pattern. When whole-body magnesium stores are sufficient, magnesium uptake is limited and passive in nature. When whole-body magnesium is depleted, active uptake of magnesium from the bowel lumen becomes the predominant mechanism of absorption. Magnesium excretion occurs via the kidney with a minor contribution from the large bowel in certain circumstances. Fine-tuning of magnesium homeostasis occurs at the level of the distal convoluted tubule. As uptake of dietary magnesium is limited and passive when deficiency is absent, it is not surprising that reduced glomerular filtration is the principal cause for sustained elevations in plasma magnesium concentrations [44,45].

Hypomagnesemia

Definition and Etiology

The definition of hypomagnesemia is somewhat controversial. Many authors feel strongly that hypomagnesemia should only be defined by reductions in ionized magnesium [iMg] concentrations. Indeed, in the acute setting, [iMg] is an invaluable indicator of magnesium losses and shifts between the intracellular and extracellular compartments. However, in situations of chronic magnesium deficiency, [iMg] is not an ideal monitoring tool. In chronic deficiency, decreases in total serum magnesium [tMg] are large and [iMg] often remains within the reference interval. It has been suggested that in the setting of chronic inadequate magnesium intake, [tMg] is decreased in an attempt to preserve [iMg]. The mechanism most often proposed is down-regulation of an as yet unidentified magnesium-binding protein. In this author's practice, [tMg] is used as an initial screening test and [iMg] is used to further define magnesium imbalances in select patients. Causes of hypomagnesemia are outlined in Box 110.5 [44,45].

Clinical Signs

Magnesium is involved in over 300 enzymatic reactions as an essential co-factor. Surprisingly, the clinical signs are often associated (perhaps incorrectly) with only four major body systems: ECF composition (hypokalemia, hypocalcemia), neuromuscular, neurological, and cardiovascular, as shown in Box 110.6. This author would add additional hemostatic, respiratory, and gastrointestinal clinical signs as well. Specifically, magnesium acts as an endogenous calcium channel blocker and hypomagnesemia is a well-known cause of platelet activation secondary to increased cytosolic calcium. In addition, hypomagnesemia has been reported to cause weakness of accessory respiratory muscles and has been linked to sleep apnea manifestations. Lastly, hypomagnesemia can be associated with severe gastrointestinal ileus that is unresponsive to therapies other than enteral magnesium supplementation.

Box 110.5 Causes of hypomagnesemia.

Gastrointestinal

Malnutrition
Malabsorption
Chronic diarrhea
Nasogastric suction
Proton pump inhibitors

Renal

Congenital/heritable magnesium wasting syndromes
Postobstructive diuresis
Diuretic phase of acute kidney injury
Loop and thiazide diuretics
Cisplatin
Aminoglycosides
Cyclosporine A
Tacrolimus

Endocrine

Hyperparathyroidism
Hyperthyroidism
Syndrome of inappropriate antidiuretic hormone secretion
Hyperaldosteronism

Redistribution

Hungry bone syndrome
Acute pancreatitis
Blood transfusions
Insulin therapy

Miscellaneous

Diabetes mellitus
Chronic or recurrent hypercapnia (e.g brachycephalic syndrome)

Treatment

Treatment of hypomagnesemia is also an area where an understanding of the underlying physiology is essential. Uptake of enteral magnesium is passive unless whole-body deficiency is present. As such, excessive administration of enteral magnesium to patients without a magnesium deficit is likely to lead to a laxative effect with minimal alteration in serum magnesium concentrations. In addition, cellular uptake of magnesium is quite slow and cells may take 24 hours or more to equilibrate with ECF magnesium. As such, parenteral magnesium administration given as a single bolus is unlikely to alter intracellular magnesium concentrations. This author advises that bolus administration of magnesium (typically MgSO_4) be followed by constant infusions of at least 24 hours duration to address intracellular magnesium deficits. Total per day doses required in this setting are typically of the order of 0.5 g for small dogs/cats, 1 g for dogs 6–20 kg, and 2 g for larger dogs.

Box 110.6 Clinical signs associated with hypomagnesemia.**Alterations in ECF composition**

Hypokalemia
Hypocalcemia

Neuromuscular signs

Muscle cramps
Fasciculations
Tetany
Muscle weakness

Neurological signs

Nystagmus
Hemiparesis
Obtundation

Cardiovascular signs

Arrhythmias
Arterial hypertension

Hemostatic alterations

Increased platelet activation

Gastrointestinal signs

Ileus

Respiratory signs

Accessory muscle weakness
Reduced upper airway patency

Enteral supplementation of magnesium also requires some forethought. Not all forms of magnesium supplement are equally absorbable or bioavailable. The common Epsom salt (MgSO_4) is poorly absorbed and is thus often used as a cathartic and laxative. This author preferentially uses magnesium oxide and has observed no such laxative effect. Oral

maintenance doses are typically of the order of 200 mg per day for patients less than 20 kg, and 400 mg per day for larger patients. Magnesium excretion follows a diurnal rhythm and supplementation is likely to have greater impact if given with breakfast than with the evening meal.

Hypermagnesemia**Definition and Etiology**

Hypermagnesemia is defined as an increase in $[\text{iMg}]$, $[\text{tMg}]$, or both. Most often, elevations in serum magnesium are due to reductions in renal function and glomerular filtration rate. Due to the nature of magnesium uptake from the bowel, dietary excess is an infrequent and unlikely cause of hypermagnesemia. However, iatrogenic causes should be considered, such as administration of magnesium salts or certain magnesium-containing antacids and laxatives.

Clinical Signs

As hypermagnesemia is most often found in the setting of azotemia, the signs associated with it are often obscured by the underlying disorder. In cases of iatrogenic hypermagnesemia, clinical signs such as weakness, hypotension, and respiratory difficulty have been reported. In rare cases of severe acute hypermagnesemia, asystole may occur, likely due to the calcium channel-blocking properties of magnesium.

Treatment

The restoration of glomerular filtration rate with fluids and diuretics is the mainstay of treatment for hypermagnesemia. Insulin and dextrose can also help to accelerate the uptake of magnesium by cells. Parenteral calcium gluconate (10%), as described above in the section on treatment of hypocalcemia, can also be employed in patients experiencing severe signs.

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Hypoglycemia

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Introduction

Glucose, the breakdown product from carbohydrates, is an important source of energy in the animal body. It is the main energy source in cells such as red blood cells and the brain, so feedback mechanisms are in place to maintain normal glucose levels in the bloodstream (Figure 111.1). Small animals presenting to the emergency room frequently suffer from hypoglycemia. Hypoglycemia is associated with an increased risk of death in critically ill human patients [1].

Pathophysiology

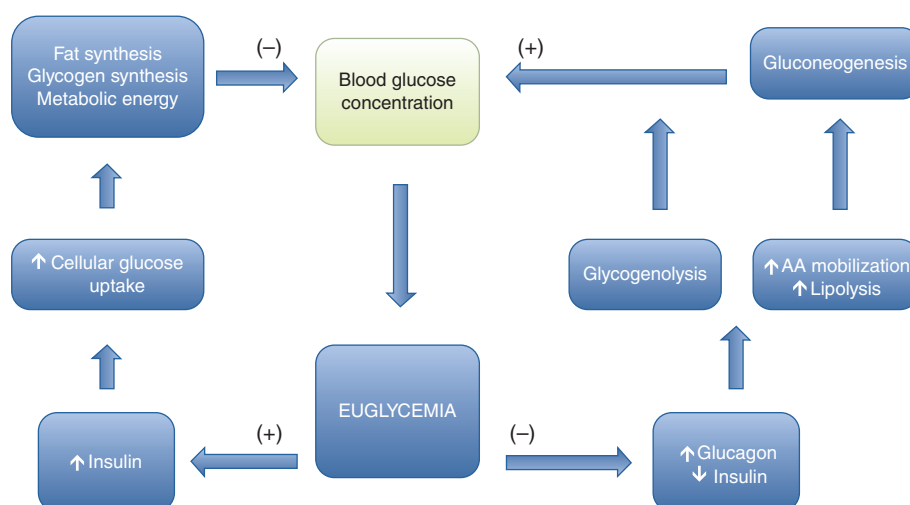
Glucose homeostasis requires a balance between absorption, production, and utilization. Glucose becomes available to the body via intestinal digestion and absorption of carbohydrates, the breakdown of glycogen via glycogenolysis, or the production of glucose via gluconeogenesis. Over

80% of the carbohydrate metabolism end-products are glucose; the remainder are fructose and galactose [2]. These are subsequently converted into glucose in the liver, leaving glucose as the final product of carbohydrate digestion.

Postprandially, glucose is stored in the liver as glycogen, a large polymer of glucose. As the only direct storage form of glucose, glycogen can be stored in all cells. However, most is stored in the liver and skeletal muscle. The amount of glycogen stored in the liver rarely exceeds 10% of the total weight of the liver in humans; it is assumed to be similar in dogs and cats [3]. The remainder of glucose is oxidized via glycolysis to form two molecules of pyruvate for each molecule of glucose. Pyruvate is converted to acetyl-CoA in the mitochondria and utilized in the Krebs cycle for final energy production. Alternatively, it can be converted to fatty acids for fat storage when intake of glucose exceeds demand.

Several key hormones play a role in the body with regard to glucose regulation. Insulin is produced via the beta-cells of the pancreas and is released when blood

Figure 111.1 Positive (+) and negative (–) feedback mechanisms to maintain normoglycemia.



glucose levels begin to increase. The counterregulatory hormones are released when glucose levels begin to decrease; they include glucagon, catecholamines, cortisol, and growth hormone. Glucagon is produced by the alpha-cells of the pancreas and stimulates glycogenolysis in the liver via cyclic AMP production and subsequent phosphorylation of glycogen phosphorylase. Epinephrine is released via sympathetic stimulation of the adrenal medulla and serves to potentiate glucagon's activation of phosphorylase.

Glycogenolysis by itself can only sustain the body's glucose demands for 6–12 hours [2]. The production of glucose via gluconeogenesis occurs in times of prolonged or increased demands. This process involves using the end-products of glycolysis, including lactic acid, pyruvate, glycerol and amino acids, to form glucose.

Cortisol helps mobilize proteins and adipocytes to ensure that amino acids and fatty acids are available for glucose production. Close to 60% of amino acids in the body can be converted to glucose [2]. Cortisol, along with growth hormone, also serves to inhibit the actions of insulin and potentiate the effects of glucagon and epinephrine in the liver. The kidney also has limited glucose production capabilities and can contribute up to 40% of total glucose production under certain conditions (ex. hepatic insufficiency) [4].

Clinical Signs

Normally, the central nervous system is entirely dependent on plasma glucose as a source of energy. Glucose concentrations in the brain are up to 30% lower compared to plasma and special facilitative glucose transporters are required for entry into the brain cells [5]. GLUT 1 is the predominant transporter in the brain vasculature, with other transporters (GLUT 1–GLUT 5) found throughout the body.

Hypoglycemia can cause severe neuronal damage, including a reduction in cerebral ATP, cellular swelling, and oxidative damage [6]. Although death is uncommon, irreversible brain damage may occur during hypoglycemic episodes. In the face of hypoglycemia, the brain has an adrenergic response system in place to raise blood glucose levels and stimulate counterregulatory hormones. This sympathoadrenal system is responsible for some of the initial clinical signs seen in hypoglycemic patients, including restlessness, muscle tremors or nervousness (typically seen when the plasma glucose level is <68 mg/dL) [6]. Neuroglycopenia, or lack of glucose supply to the brain, leads to lethargy, ataxia, seizures, and coma when plasma glucose levels fall below 18 mg/dL [6].

However, the progression and severity of clinical signs relating to hypoglycemia will vary with each patient's

rate of development, duration, and severity of the underlying disease process. Patients that have acclimated to a lower glucose level may not display the expected clinical signs of hypoglycemia.

Causes of Hypoglycemia

The differential diagnoses for hypoglycemia can be categorized into excess secretion of insulin or insulin-like factors, decreased glucose production, excess glucose consumption, drug-associated causes, and spurious causes (Box 111.1).

Excess Secretion of Insulin or Insulin-Like Factors

Insulinoma

Although rare, functional beta-cell tumors of the pancreas, known as insulinomas, are one of the most common neuroendocrine tumors in dogs [7]. These are malignant tumors which commonly metastasize to local lymph nodes and the liver. Middle-aged medium- to large-breed dogs are most commonly affected. Clinical signs commonly follow meals (due to increased insulin release) or exercise and can include seizures, weakness, collapse, ataxia, and muscle fasciculations.

Bloodwork may show hypokalemia (due to insulin-induced intracellular shifts) and elevated liver values, but hypoglycemia (<70 mg/dL) is the most consistent finding. Fructosamine levels are typically low in canines with an insulinoma [8–10]. Measuring insulin levels may be helpful in making the diagnosis as normal to elevated insulin values present in the face of hypoglycemia are abnormal. An amended insulin:glucose ratio (AIGR) of >30 is supportive of an insulinoma, but other causes such as sepsis and non-pancreatic neoplasia have been shown to produce an elevated AIGR [4,11–13]. Thus an amended AIGR should not be used as a sole diagnostic.

Abdominal imaging via an ultrasound, computed tomography (CT) or scintigraphy has been used to identify a pancreatic mass. However, the accuracy of these imaging modalities varies and may or may not give a definitive diagnosis in cases of suspected insulinoma. Radiographs can be utilized to image the thorax and screen for metastasis, but are not helpful in identifying small pancreatic masses.

Treatment for insulinomas involves either medical or surgical intervention, or a combination of both. In the acute setting, a patient presenting in a hypoglycemic crisis secondary to a suspected insulinoma should be supplemented with 50% dextrose and continued on dextrose-containing intravenous fluids. The administration of dextrose may stimulate additional insulin release,

Box 111.1 Causes of hypoglycemia in dogs and cats [16,43].**Excess secretion of insulin or insulin-like factors**

Insulinoma
 Islet cell hyperplasia
 Paraneoplastic syndrome
 Hepatocellular carcinoma
 Hepatoma
 Leiomyosarcoma
 Leiomyoma
 Oral melanoma
 Hemangiosarcoma
 Lymphoma
 Pulmonary, mammary and salivary carcinoma

Decreased glucose production

Hypoadrenocorticism
 Hypopituitarism
 Growth hormone deficiency
 Hepatic disease
 Acute hepatic failure
 Portosystemic shunt
 Chronic fibrosis
 Cirrhosis
 Glycogen storage disease
 Renal failure*
 Neonates and toy breeds
 Fasting

Excess glucose consumption

Sepsis
 Babesia
 Hunting dog hypoglycemia
 Pregnancy

Drug-associated causes

Insulin
 Beta-receptor antagonists
 Xylitol
 Sulfonylurea

Spurious

Manual error
 Equipment error
 Polycythemia
 Leukocytosis

* Has not been reported in cats and dogs.

causing a rebound hypoglycemia. The emergency clinician should remember that the goal of treatment is to administer enough dextrose to alleviate any clinical signs but not necessarily normalize the blood glucose level. Glucocorticoids will antagonize the effects of insulin and a constant-rate infusion of glucagon to promote gluconeogenesis and glycogenolysis may also prove beneficial. Long-term management involves the use of glucocorticoids and diet modifications; frequent, low simple sugar-containing meals are recommended.

Other possible therapies include diazoxide (benzothiadiazine diuretic, potassium channel activator), octreotide (synthetic somatostatin analogue) and streptomycin as a chemotherapeutic agent. Surgical removal of the tumor is not usually curative as metastatic disease is suspected at the time of diagnosis in most cases of canine insulinoma [4].

Prognosis and survival time vary with each patient and the extent of disease. Survival times were reported as 12–14 months in dogs that underwent partial pancreatectomy [14,15]. A study comparing surgical versus medical management reported a median survival time of 381 days in dogs undergoing partial pancreatectomy

and 74 days in dogs with medical management only [14]. Another recent study reported a median survival time of 785 days with partial pancreatectomy, 196 with only medical management and 1316 with a combination of both [15]. Postoperative hypoglycemia was found to be a negative prognostic indicator [16].

Paraneoplastic Syndrome

Neoplastic tumors may produce hormones, growth factors, and cytokines, causing various effects in the body. Hepatomas, hepatocellular carcinoma, leiomyoma, leiomyosarcoma, and hemangiosarcoma are some of the most common tumors associated with the production of insulin-like growth factors or peptides causing paraneoplastic hypoglycemia [17] (see Chapters 72 and 73).

Decreased Glucose Production**Hypoadrenocorticism** (see Chapter 115)

Hypoadrenocorticism, also known as Addison's disease, is a common endocrine disease found in young to middle-aged dogs. Often called "the great pretender" for its broad spectrum of general clinical signs, Addison's

disease involves a deficiency of cortisol and mineralocorticoids. Atypical cases have been seen in which only cortisol deficiency is detected. Patients may present with waxing and waning lethargy, diarrhea, inappetence, weight loss or in an Addisonian crisis with severe hypovolemic shock. Hypoglycemia occurs due to decreased cortisol production causing a decrease in gluconeogenesis. Although classic electrolyte changes are suggestive of the disease (Na:K ratio < 27:1), an ACTH stimulation test remains the gold standard for diagnosis. A resting cortisol level has also been shown to be diagnostic, with one study reporting a basal cortisol concentration of < 1 mg/dL having a 100% sensitivity and 98.2% specificity for diagnosing hypoadrenocorticism in dogs [18]. Treatment involves mineralocorticoid and glucocorticoid supplementation and generally carries an excellent prognosis.

Hepatic Disease (see Chapter 90)

Various etiologies can lead to hepatic dysfunction, including portosystemic shunts, chronic fibrosis, cirrhosis or hepatopathy (e.g. glycogen storage disease). Signs secondary to hepatic dysfunction vary but may include lethargy, inappetence, fever, weight loss, jaundice, increased or decreased thirst, and abnormal bowel movements. Hepatic dysfunction is characterized by hypoalbuminemia, hypoglycemia, hypocholesteremia, and low blood urea nitrogen (BUN). Liver function testing often reveals hyperammonemia and elevated postprandial bile acids.

Neonates and Toy Breeds (see Chapter 120)

Neonates have been shown to have a decreased liver glycogen content and limited body fat reserves, thus predisposing them to developing hypoglycemia. Toy and miniature-breed dogs may also have hypoglycemic episodes associated with an alanine deficiency [19]. Due to their small size and fragility, adequate nutrition must be provided to neonates and small-breed puppies.

Excess Glucose Consumption

Sepsis

Sepsis, defined as the clinical syndrome caused by infection and the host's systemic inflammatory response to it, can cause severe hemodynamic compromise and vasodilatory shock in critically ill patients. While hyperglycemia is noted in some septic patients, contributing factors to hypoglycemia include depleted glycogen stores, impaired gluconeogenesis, and increased peripheral glucose utilization [20]. Patients suspected of or diagnosed with sepsis should have immediate stabilization and treatment protocols started (see Chapter 159).

Canine pregnancy-associated hypoglycemia is caused by blunting of the normal counterregulatory responses to hypoglycemia [21,22]. Hypoglycemia is also a common complication of canine babesiosis and is a poor prognostic indicator on admission [23].

Drug-Associated Causes

Insulin

Exogenous insulin therapy is most commonly used in animals with diabetes mellitus. Insulin overdose resulting in hypoglycemia is more common in obese cats than in dogs, and in cats receiving insulin doses greater than 6 units per injection [24]. The duration of severity of hypoglycemia does not correlate with the dose and type of insulin used [24]. Animals with inappetence or inconsistent meals and regular insulin administration often develop hypoglycemia. Insulin therapy may need to be temporarily discontinued and restarted at a 25–50% reduced dose until the patient's glucose is stabilized [25]. Other medications such as sulfonylureas and beta-blockers have also been demonstrated to induce hypoglycemia [26,27].

Xylitol

Xylitol is a 5-carbon sugar-alcohol sweetener that is most commonly associated with chewing gum. However, it is found in many other products such as toothpaste and “low carb” snacks like syrups, candies, and cookies. In contrast to humans, xylitol causes stimulation of insulin release from the pancreas in dogs [28]. Hypoglycemia has been associated with a 100 mg/kg exposure and hepatotoxicity with greater than a 500 mg/kg exposure [29].

Spurious

Besides operator and machine error in processing samples, polycythemia and leukocytosis have both been associated with artifactual hypoglycemia via increased cellular metabolism [30,31].

Diagnosis

Hypoglycemia is defined as a blood glucose concentration of less than 60 mg/dL. Whipple's triad was originally developed in 1935 as criteria for the diagnosis of insulinomas, but its lack of specificity allows it to be applied to numerous causes of hypoglycemia [4]. The triad consists of hypoglycemia, clinical signs consistent with hypoglycemia, and resolution of clinical signs with correction of hypoglycemia.

Point-of-care glucometers (POCGs) are routinely used in veterinary medicine as they provide a quick and cost-effective method of evaluating blood glucose concentrations in dogs and cats. Variable degrees of accuracy have been noted when using POCGs designated for humans [32–34]. AlphaTRAK 2 is a POCG marketed for veterinary patients which takes into account species differences between free and hemoglobin-bound glucose [34]. The measurement of glucose using serum and plasma, as opposed to whole blood, by POCGs has been shown to more accurately reflect the serum glucose concentration when compared to biochemical analyzers [35].

Depending on the underlying etiology, continuous glucose monitoring may be required. Repeated venipuncture is not desirable for the patient, so the placement of a sampling line is recommended. The use of a continuous interstitial glucose monitoring system (CGMS), which measures the interstitial glucose concentration as an estimation of blood glucose, may also be an option for some patients. This technology was recently validated for use in dogs and cats, and studies have shown it to be useful and accurate in rats, rabbits, dogs, cats, and humans [36,37]. Additional diagnostics, including a complete cell count, chemistry, urinalysis, and imaging, should be performed to determine the underlying etiology of the hypoglycemia. Further bloodwork such as ammonia levels, pre- and postprandial bile acids, insulin levels, and cortisol levels should be performed when appropriate.

Treatment of a Hypoglycemic Crisis

Historically, it has been recommended for owners at home to administer karosyrup, honey or maple syrup to the gums of pets suspected of suffering from hypoglycemic episodes. However, studies show the limited effect of buccal absorption which renders these methods ineffective unless the syrups are actually swallowed by the patient [38–40]. Thus a veterinarian should evaluate any pet suspected of suffering from a suspected hypoglycemic episode.

In hospital, the goal of stabilization is not necessarily to correct the blood glucose to a normal range but rather to eliminate clinical signs. Dextrose is given at 0.25–0.5 g/kg diluted 1:3 with sterile water for injection

Table 111.1 Treatment of hypoglycemia.

Dextrose 50%	Adults: 0.5 g/kg IV diluted 1:3 in 0.9% NaCl Neonates: Dextrose 1.0 ml/kg of 12.5% dextrose (50% dextrose diluted 1:3 in 0.9% NaCl)
Glucagon	50 ng/kg IV, followed by CRI of 5–40 ng/kg/min IV to effect
Dexamethasone	0.1–0.2 mg/kg IV followed by 0.05–0.1 mg/kg IV q12
Prednisone/ Prednisolone	HA: 1–2 mg/kg IV followed by 0.5–1 mg/kg IV q8 Insulinoma: 0.25–0.5 mg/kg PO q12

or 0.9% NaCl as a slow intravenous bolus. In cases of suspected insulinoma, large boluses of dextrose up to 1 g/kg should be avoided as they can stimulate insulin release. Instead, small boluses should be administered and repeated as needed. Neonates require a more dilute bolus of dextrose (see Box 111.1). The patient should subsequently be placed on a constant-rate infusion of 2.5–5% dextrose-containing fluids. The concentration may be increased based on individual need. Dextrose concentrations greater than 5–7% should be administered through a central line as phlebitis due to high tonicity can occur if given via peripheral catheter administration. D5W should be avoided as the sole intravenous fluid choice for glucose supplementation as it can cause severe to life-threatening hyponatremia [41].

Adjunctive therapy involving glucocorticoids to stimulate gluconeogenesis and antagonize insulin release can be used. A constant-rate infusion of glucagon to stimulate glycogenolysis and increase hepatic glucose production has also been utilized in cases of insulin or insulin-like peptide-secreting tumors [42]. Table 111.1 presents information on dosing. When the patient is conscious and alert, small frequent meals should be provided as an additional source of simple sugars. Blood glucose levels should be monitored and treatments modified to avoid iatrogenic hyperglycemia. Animals with suspected cerebral edema should be treated with 0.25–0.5 g/kg of 25% mannitol intravenously over 10–20 minutes (an in-line filter is recommended).

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Hyperglycemia

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Introduction

Hyperglycemia is frequently encountered in dogs and cats presented for emergency care (Box 112.1). Animals may be presented for signs directly associated with hyperglycemia (e.g. polyuria/polydipsia) or it may be stumbled upon incidentally. Stress-induced hyperglycemia and diabetes mellitus are the most common reasons for hyperglycemia in animals [1]. Diabetes mellitus occurs associated with an absolute or relative insulin insufficiency. Alternative explanations for insulin deficiency include animals with exocrine pancreatic insufficiency and those that have undergone partial pancreatectomy. Severely systemically compromised animals may also develop hyperglycemia associated with massive catecholamine release (e.g. after severe traumatic brain injury) [2]. A careful drug history is important in the emergency setting to ensure that there is no iatrogenic explanation for hyperglycemia (e.g. glucocorticoids, progestins) [1]. Hyperglycemia may also develop in a smaller

proportion of hospitalized animals that were initially normoglycemic with potential negative impact on morbidity and mortality [3].

Stress Hyperglycemia

A transient period of hyperglycemia is common in cats in the hospital setting associated with catecholamine release. This may also be noted in dogs, albeit less frequently. Hyperlactatemia may also have an additive effect on the degree of hyperglycemia noted in animals associated with increased hepatic glucose production. In this setting, blood glucose concentrations are typically in the range of 200–400 mg/dL [1].

It is important to consider the influence that stress may be playing on the severity of hyperglycemia in diabetic animals being examined in the hospital. Disparate results may be seen in the hospital compared to those achieved from obtaining blood glucose measurements at home by owners. More profound hyperglycemia (associated with catecholamine excess) may mislead the clinician into assuming worse overall glycemic control than is likely present. Reflex changes in insulin prescription (e.g. increasing dose or frequency) should be avoided based on these data alone. It can be clinically challenging to separate stress-associated hyperglycemia from other disease-associated causes of hyperglycemia. The clinician should use historical clues (e.g. presence or absence of polyuria and polydipsia, weight loss despite polyphagia) along with other pieces of clinicopathological data (e.g. ketonuria, ketonemia) to reasonably distinguish incidentally identified stress hyperglycemia from other causes.

The hyperglycemia associated with traumatic brain injury is likely associated with catecholamine discharge. The severity of brain injury is associated with the degree of hyperglycemia [2]. The requirement for specific

Box 112.1 Causes of hyperglycemia in dogs and cats.

- Diabetes mellitus
- Stress
- Postprandial
- Traumatic brain injury
- Hyperadrenocorticism
- Hypersomatotropism
- Diestrus
- Drug therapy (glucocorticoids, progestins)
- Parenteral nutrition
- Glucose-containing fluid administration

management of hyperglycemia (e.g. via insulin) is seldom necessary.

Diabetes Mellitus

Animals with diabetes mellitus are commonly seen in the emergency setting. Animals may be presented for assessment of signs associated with previously unrecognized diabetes mellitus. Alternatively, previously diagnosed diabetics may be examined for new issues that could be considered a recognized complication in diabetics (e.g. bacterial cystitis) or be apparently coincidental (e.g. heart failure). For animals without a prior diagnosis of diabetes mellitus, identification of the hallmarks of the disease (i.e. PU/PD, polyphagia, weight loss) along with persistent fasting hyperglycemia with concurrent glucosuria is usually straightforward.

Glucose undergoes filtration by the kidney, with almost all the glucose in the glomerular filtrate being reabsorbed in the proximal tubules. It is therefore not usual to identify glucose in the urine of dogs and cats. Glucosuria is seen if blood glucose concentration exceeds the renal threshold (approximately 180 mg/dL in dogs and 300 mg/dL in cats) [4]. Most dipstick tests use a colorimetric test based on an enzymatic reaction (glucose oxidase). Diabetes mellitus is the most common cause of glucosuria but other conditions may occasionally be recognized (e.g. stress, excitement, administration of glucose-containing fluids, primary renal glucosuria, Fanconi syndrome) [4].

Longer term glycemic control can be gauged via serum fructosamine assessment. An increased fructosamine supports sustained hyperglycemia. This is typically a send-out test, limiting its utility in the emergency setting and lending itself more to the chronic monitoring of diabetic animals receiving insulin.

The emergency clinician should be aware that previously unrecognized diabetic animals may present severely compromised with collapse, severe dehydration, acid–base disturbances, and electrolyte derangements. In some cases, this may be the first overt clinical manifestation of issues. In such cases, the classic historical clues of diabetes outlined above may have been overlooked or their significance underappreciated. This is especially relevant for cats where urinating and drinking habits may be less obvious to owners.

For the systemically compromised diabetic animal, two major scenarios are encountered: the ketotic animal with or without metabolic acidosis, and the non- (or minimally) ketotic hyperosmolar pet. The ability to estimate blood ketones in urine or serum is therefore helpful in the emergency setting. The nitroprusside reagent present in dipstick tests reacts with acetone and acetoacetate, but not beta-hydroxybutyrate. False-negative results from urine

ketone measurements and whole-blood or plasma ketone measurements are more accurate in detection of ketonemia in diabetic animals [5,6]. Ketosis implies an absolute or relative insulin deficiency promoting lipolysis. Ketosis is very common in newly diagnosed diabetic animals. Many of these cases will be only mildly systemically compromised, with retention of their appetite and thirst. Other animals with evidence of ketosis will have concurrent metabolic acidosis (i.e. diabetic ketoacidosis) and benefit from intensive hospitalized care. In these cases, it is important to search for concurrent conditions that may trigger insulin resistance (see below). Fundamentally, exogenous insulin administration is necessary to reverse ketosis and is a major component of the treatment for DKA.

Animals that develop hyperglycemic hyperosmolar diabetes mellitus, on the other hand, have sustained an insult leading to a marked reduction in glomerular filtration rate. In this setting, the ability to excrete glucose in urine is compromised, leading to abnormal retention of glucose in the blood and subsequent hyperosmolality. Profound hyperglycemia is usually present but without ketosis. In this scenario, restoration of glomerular filtration is high priority compared to the provision of insulin. In these animals, careful fluid resuscitation with the judicious use of insulin to slowly reduce hyperglycemia and correct hyperosmolality is necessary. For further information on management of diabetes mellitus see Chapter 113.

Insulin Deficiency and Insulin Resistance

Absolute insulin deficiency (analogous to type 1 diabetes mellitus) is likely present in most dogs with diabetes mellitus. Genetic predisposition with immune-mediated destruction of pancreatic islet cells leads to significantly reduced insulin production. Exogenous insulin supplementation will enable maintenance of normoglycemia, especially when combined with appropriate diet and exercise in the long term. Other situations where insulin insufficiency may be noted include dogs with exocrine pancreatic insufficiency and animals that have undergone a partial pancreatectomy. Partial pancreatectomy is most commonly performed in dogs with insulinoma. Following surgery, exogenous insulin administration may be necessary, depending on the beta-cell mass remaining in the dog. In this situation, appreciation of a reduced insulin requirement over time may be misinterpreted as a positive development. In reality, it may be an indication of increased endogenous insulin production associated with tumor recurrence or metastasis.

It is also important to consider if insulin resistance may have an additive effect in diabetic dogs.

Insulin resistance may occur in situations where counterregulatory hormones like cortisol, epinephrine, growth

hormone or progesterone are elevated [1,4]. Clinical situations where this may occur include hyperadrenocorticism, hypersomatotropism, diestrus, hyperlipidemia, and hypothyroidism. The use of diabetogenic drugs (e.g. glucocorticoids, progestins) may also induce insulin resistance. Insulin resistance exerts a negative influence on insulin sensitivity at the level of the insulin receptor or insulin signaling cascade [4]. This response results in a number of alterations in carbohydrate metabolism, including insulin resistance, increased hepatic glucose production, impaired peripheral glucose utilization, and relative insulin deficiency. Epinephrine stimulates glucagon secretion and inhibits insulin release by pancreatic beta-cells. High cortisol levels increase hepatic glucose production and stimulate protein catabolism and increased gluconeogenesis.

Any sick diabetic dog should be screened for concurrent diseases, especially pancreatitis and occult sources of sepsis, despite the genetic and immune-mediated components of their disease. Diabetes mellitus in cats has increased similarities with type 2 diabetes in people. This typically is characterized by insulin resistance rather than immune-mediated beta-cell destruction. Dietary changes and oral antihyperglycemic drugs have been investigated in the management of diabetic cats. Exogenous insulin administration is the mainstay of therapy however, with evidence that intensified insulin therapy early in the disease course may lead to clinical diabetic remission [7]. Concurrent endocrinopathies should be considered plausible in all diabetic pets, especially those proving to be difficult to control. In dogs, hyperadrenocorticism is the most likely culprit, while hypersomatotropism and hyperadrenocorticism may be present in cats.

The development of hyperglycemia leads to generation of reactive oxygen species and elevated inflammatory markers. The release of proinflammatory cytokines

(TNF-alpha, IL-6, and IL-1-beta) contributes to the insulin-resistant state. Increasing evidence suggests that TNF-alpha interferes with insulin receptor signaling, as well as the synthesis and/or translocation of the glucose transport GLUT-4 to the plasma membrane [8]. Hyperglycemia has been shown to impair leukocyte function and limit phagocytosis, chemotaxis, and bacterial destruction. Hyperglycemia limits neovascularization and collagen synthesis, restricting the body's ability to generate new and healthy tissue at the surgical site. The presence of inflammatory cytokines and state of relative insulin resistance promote lipolysis, increasing the release of free fatty acids (FFAs). Elevated FFAs have detrimental effects on the cardiovascular system by increasing catecholamine concentrations and mean arterial blood pressure. They are also associated with malignant cardiac dysrhythmia, increased myocardial oxygen consumption and presence of ischemic stroke [8]. Hyperglycemia also results in increased platelet aggregation and prothrombotic state. An overproduction of reactive oxygen species can result in direct cellular damage, vascular and immune dysfunction. NF-kappa-B activation and the production of inflammatory cytokines like TNF-alpha, IL-6, and plasminogen activator inhibitor-1 (PAI-1) increase vascular permeability and activate both leukocytes and platelets.

Specific guidelines are instituted for hyperglycemic patients recovering from surgery or critical illness in people. These are typically a combination of basal (long-acting such as glargine) insulin and fast-acting insulin (such as lispro, aspart or glulisine) [8]. These negative effects of hyperglycemia appear to occur in small animal patients also with respect to hospitalization and certain complications (e.g. sepsis) [3]. These patient should be closely monitored during their hospitalization. With increased recognition, similar guidelines for treatment can be established for veterinary patients as well.

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Complicated Diabetes Mellitus

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Introduction

Complicated diabetes mellitus takes one of two forms: diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar syndrome (HHS). Criteria for diagnosing diabetic ketoacidosis include presence of hyperglycemia, glucosuria, and ketonemia or ketonuria with a metabolic acidosis. HHS criteria include severe hyperglycemia (>600 mg/dL), minimal or absent serum or urine ketones, and severe hyperosmolality (>350 mOsm/kg).

Pathogenesis

In both forms of diabetic crisis, insulin deficiency promotes gluconeogenesis and glycogenolysis and reduces cellular utilization of glucose, all of which cause hyperglycemia. Activity of hormone-sensitive lipase is stimulated and free fatty acids (FFA) are released from adipocytes to be used as an energy source. FFA are metabolized to triglycerides, carbon dioxide (CO_2) and water, or the ketone bodies: acetoacetate, beta-hydroxybutyrate, and acetone. In the uncomplicated diabetic, triglyceride production predominates and the small amounts of ketones that are produced are completely metabolized for energy [1]. Counterregulatory hormones (glucagon, epinephrine, cortisol, and growth hormone) are released in response to a concurrent physiological stressor, and this contributes to glucose production, insulin resistance, and protein catabolism. The counterregulatory hormones also stimulate lipolysis, which increases the amount of circulating FFA available for ketone formation [1].

Diabetic ketoacidosis occurs once the quantity of ketoacids overwhelms the metabolic pathways that normally convert ketones to energy, as well as the buffering systems that normally mitigate the effects of ketones on acid–base status. In HHS, ketosis is

prevented by small quantities of circulating insulin and hepatic glucagon resistance that inhibit lipolysis [2,3]. The primary result is hyperglycemia, progressive osmotic diuresis, dehydration, and subsequent decrease in GFR, which is required to achieve the massive blood glucose increase associated with HHS [4,5]. Therefore, the lower the GFR, the higher the blood glucose concentration [4].

History and Physical Examination

Animals with DKA and HHS can present with various historical and clinical findings, since any concurrent disease can stimulate stress hormone release and progression to diabetic crisis. Classic historical findings in diabetic patients include polyuria, polydipsia (PU/PD), polyphagia, and weight loss. Dehydration is seen in both disease processes due to osmotic diuresis, lack of intake, and additional losses via the gastrointestinal tract. Dogs and cats with DKA typically manifest lethargy, mental depression, anorexia, vomiting, diarrhea, weakness, and ketone breath. HHS patients manifest hyporexia, lethargy, vomiting, and weakness. Some animals with HHS also have neurological signs such as circling, pacing, mentation changes (from depression to coma), abnormal pupillary light reflexes, or seizures, which are thought to develop due to hyperosmolality-induced cerebral dehydration [6–10].

Signs of hypovolemia (see Chapter 153) can accompany both crises; findings may include tachycardia, bradycardia (cats), tachypnea, hypothermia, pallor, prolonged capillary refill time, poor pulse quality, and hypotension. Tachypnea and increased respiratory effort may be consistent with hyperosmolality, acidosis, infection, primary respiratory disease or heart failure, which commonly accompany HHS [7]. Many dogs with HHS have a history of recent steroid administration [8].

Diagnostic Evaluation in the Emergency Room

Triage Panel

The first indication that a patient is in a diabetic crisis may be discovered on an emergency blood panel which includes a minimum of “the big 4” (PCV/TP, glucose, azostix) or, preferentially, a more comprehensive panel including a (venous) blood gas, glucose, electrolytes, lactate, and BUN/creatinine. Sick animals with a previous history of DM, those with hyperglycemia identified on the emergency panel, or patients with a metabolic acidosis of undetermined cause should be screened for HHS and DKA.

Measure Blood Glucose Concentration

Extremely high blood glucose concentrations may surpass the upper limit of glucose analyzers. Obtaining a definitive glucose measurement is important for developing a therapeutic plan that reduces risk of an overly rapid decrease in blood glucose. If glucose concentration is too high to measure, the sample can be diluted, reanalyzed, and the glucose concentration calculated. If diluting samples and using a whole-blood point-of-care glucometer, packed cell volume must be taken into account when interpreting these measurements, as hemodilute or anemic blood can result in falsely elevated plasma glucose readings [11,12].

Measure Ketones and Assess Degree of Acidemia

Ketones can be identified using a ketone meter or urine dipstick [13–17]. Ketone meters are more sensitive than urine dipsticks [15], but presence of ketones on either would support a diagnosis of DKA. If urine is unavailable at admission, another highly sensitive way to identify ketonemia is by placing serum or plasma from a spun hematocrit tube on the urine dipstick ketone pad [16,17].

Blood gas analysis can clarify the magnitude of acidemia arising from ketoacidosis, lactic acidosis, uremia, and possibly hyperchloremia; however, acid–base abnormalities cannot be used to differentiate between the two crises.

Quantify Degree of Hyperosmolality

Normal serum osmolality is 290–310 mOsm/kg and neurological signs have been documented in animals when osmolality exceeds 340 mOsm/kg [18]. There are many ways to estimate serum osmolality [19,20]. BUN is an ineffective osmole and effects of potassium on osmolality are minimal, so using a modified equation may better

reflect the effects of osmolality on the patient: $\text{Effective osm} = 2(\text{Na}^+) + (\text{glucose} \div 18)$. Glucose is measured in mg/dL and Na^+ in mEq/L.

Assess Electrolyte Abnormalities

Profound electrolyte abnormalities often develop in patients with DKA and HHS. While the initial measured blood concentrations of these electrolytes can be normal, decreased, or increased, the total body content is typically reduced and deficiencies become evident with the onset of insulin therapy. It is important to obtain baseline electrolyte concentrations in order to develop the optimal therapeutic plan. Failure to address electrolyte deficiencies prior to initiating insulin therapy can lead to complications that can be life threatening.

Sodium

Hyperglycemia and hyperosmolality exert an osmotic force that pulls water into the extracellular (includes vascular space) space. This increase in plasma water dilutes sodium and causes a pseudohyponatremia, a falsely decreased sodium measurement [21]. As the blood glucose level decreases, the osmotic gradient is also diminished, and the excess water leaves the vasculature and interstitium and returns to the intracellular space, causing the measured serum sodium level to rise. An estimate of the actual sodium level can be calculated using the equation:

$$\begin{aligned} \text{Na}^+_{(\text{corrected})} &= 1.6 \times [(\text{measured glucose} - \text{normal glucose}) / 100] \\ &+ \text{Na}^+_{(\text{measured})} \end{aligned}$$

Potassium, Magnesium, and Phosphorus (see Chapter 110)

Multiple mechanisms influence the initial measured potassium concentration in patients with DKA and HHS. Glucosuria and ketonuria induce osmotic diuresis, and electrolytes are excreted along with the ketoacids to maintain electroneutrality [1]. Potassium concentrations are further influenced by insulin deficiency, which decreases the amount of potassium co-transported into cells; acidemia, which causes potassium to shift out of cells in exchange for hydrogen ions; severe hyperosmolality [22], which leads to a shift of potassium out of cells; hypovolemia-induced hyperaldosteronism [23], which increases renal potassium loss; poor renal perfusion or renal dysfunction, which can increase potassium; and decreased intake and gastrointestinal losses which contribute to a decrease in potassium concentration [1]. Regardless of the initial measurement, serum potassium concentration will decrease with therapy as insulin induces transport of glucose and potassium into cells and, as the

acidemia improves, shifting potassium into cells in exchange for hydrogen.

Magnesium and phosphorus concentrations are influenced by similar mechanisms. With insulin therapy, magnesium and phosphorus levels will also decrease as they shift back into cells and are utilized for ATP production. The decline in phosphorus and magnesium has been shown to directly correlate with decline in blood glucose and hydrogen ions [24].

Stabilization and Emergency Treatment

Therapeutic goals for HHS and DKA are to restore effective circulating volume, provide rehydration and maintenance fluids, supplement electrolytes to correct and prevent deficiencies, initiate insulin therapy to help reduce glucose levels and reverse ketone production, and identify and treat underlying diseases.

Restore Effective Circulating Volume (see Chapter 153)

Hypovolemia and severe dehydration are consequences of osmotic diuresis, gastrointestinal and renal water losses, and lack of water intake. In humans, the fluid deficit for an HHS patient is estimated to be twice that of DKA patients and as much as 12–15% of body weight [25–28]. Failure to normalize vascular volume can lead to cardiovascular collapse and contributes to a high mortality rate [25–31]. As long as the patient is not in congestive heart failure, restoration of vascular volume should begin with an intravenous fluid bolus of approximately 15 mL/kg (cat) to 20–30 mL/kg (dog) of an isotonic replacement crystalloid (such as lactated Ringer's solution, Plasmalyte A, Normosol R, or 0.9% NaCl) over 15–20 minutes (see Chapter 167). This dose can be repeated if resuscitation endpoints have not been met (see Chapter 153).

Provide Ongoing Fluid Therapy

Once the patient is volume resuscitated, fluids should then address the patient's dehydration, ongoing losses, and maintenance needs (see Chapters 167 and 172). The patient must frequently be reassessed to ensure the plan is optimal and that rapid changes in body weight and other signs of fluid deficit or overload are not developing. Ongoing losses should be recalculated, typically every 4–6 hours, and fluid rate adjusted accordingly. In patients with heart disease, rehydration must be done carefully, as parenteral fluids can exacerbate pulmonary congestion and subsequent edema. Nasoesophageal (NE) tubes can be effectively used to provide enteral fluids while minimizing risk of fluid overload.

For most patients, a buffered balanced isotonic replacement crystalloid (e.g. lactated Ringer's, Normosol-R, Plasmalyte-A) or 0.9% NaCl is a good initial choice for replacing fluid deficits and ongoing losses (see Chapter 167). Maintenance (half-strength) solutions can be used to provide the maintenance fluid needs or extra free water for treating hypernatremia. Compared to DKA patients receiving a balanced buffered replacement crystalloid, those receiving 0.9% NaCl solution have been shown to have higher chloride and lower bicarbonate concentrations, which can delay resolution of acidemia [32,33]. Improved urine output and blood pressure have also been identified in DKA patients receiving a balanced replacement crystalloid compared to saline [33]. Ultimate fluid composition is based on patient electrolytes. In severely hypernatremic patients, care should be taken to correct serum sodium slowly, with a decrease of no more than 1 mEq/L/h to prevent cerebral edema [34] (see Chapter 108). Fluid therapy reduces blood glucose and ketone concentrations via dilution, an increase in urinary excretion, and decrease in circulating catecholamines [30,35,36]. Acidemia is also improved as enhanced tissue blood flow decreases lactate production and improves GFR.

Treat Electrolyte Abnormalities

Regardless of the measured blood concentrations, whole-body deficits in potassium, magnesium, and phosphorus are usually present and insulin administration will further decrease these electrolyte concentrations (see Chapter 110). Failure to address electrolyte deficiencies before and during insulin administration can precipitate life-threatening complications. Electrolytes are usually added to the fluids used for rehydration and maintenance (Table 113.1). Once electrolytes increase to within reference range and potassium is at least 3.5 mEq/L, insulin therapy should commence. Electrolytes should be monitored frequently (q4–6 h, initially) and fluids and electrolyte content should be altered as necessary. As the patient normalizes, intervals between electrolyte measurements can be extended. If electrolytes cannot be tested on site, referral to a practice with in-hospital electrolyte measuring capability should be considered.

Patients initially manifesting hyperkalemia should be monitored closely and potassium supplementation should begin once the concentration drops within the reference range.

Bicarbonate therapy is rarely indicated in the treatment of diabetic crises (see Chapter 174). Sodium bicarbonate can worsen hypokalemia, ionized hypocalcemia, and hyperosmolality, cause hypernatremia, or induce paradoxical central nervous system acidosis. In patients with DKA, bicarbonate may increase acetoacetate levels,

Table 113.1 Electrolyte supplementation guide for diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome.

Electrolyte	Form	Dose for supplementation		Consequence of severe deficiency
Potassium	Potassium chloride (KCl) (can also use potassium phosphate, see below)	Serum potassium (mEq/L)	Potassium added to bag (mEq/L)*	Hypotension, arrhythmias, weakness, cervical ventroflexion, hypoventilation, respiratory paralysis, and death
		3.5–5	20	
		3.0–3.4	30	
		2.5–2.9	40	
		2–2.4	60	
		<2	80–100	
		Not to exceed 0.5 mEq K+/kg/h		
Phosphorus	Potassium phosphate (KPhos)	0.01–0.2 mmol/kg/h OR give 25–50% of potassium as KPhos and 50–75% as KCl		Hemolysis, weakness, obtundation, myocardial depression, arrhythmias, seizures
Magnesium	Magnesium sulfate (MgSO ₄)	0.5–1 mEq/kg given as constant-rate infusion over 24 hours		Refractory hypokalemia, hypotension, obtundation, seizures, weakness, arrhythmias, possible insulin resistance

*Recommended amounts of potassium are recommended for fluids running at a maintenance fluid rate. Caution should be exercised when using higher fluid rates.

delay resolution of ketoacidosis [37], and worsen cerebral edema [38]. Dogs with DKA administered bicarbonate had a poorer outcome than those that did not, although it was unclear whether the outcome was due to the bicarbonate or the severity of disease prompting bicarbonate therapy [6]. Bicarbonate is generally reserved for patients with ongoing severe acidemia (pH < 7.1, bicarbonate < 8 mmol/L) with refractory hypotension, arrhythmias, insulin resistance or presence of stupor or coma despite adequate and appropriate fluid and electrolyte therapy.

Initiate Insulin Therapy

Prior to starting insulin, it is imperative that the patient is fluid resuscitated and electrolyte deficiencies are corrected. Early insulin therapy can worsen hypovolemia by

rapidly decreasing blood glucose and osmolality, which causes water to move out of the vascular space. A rapid decrease in the blood glucose concentration can also contribute to cerebral edema formation [39,40]. Insulin therapy will also worsen deficiencies of potassium, magnesium, and phosphorus, which can cause life-threatening complications or death.

The primary goal of insulin therapy for DKA is reversal of ketogenesis, and the secondary goal is reduction of blood glucose concentration. Most commonly, successful treatment is obtained with a short-acting regular insulin administered using either an intermittent intramuscular (IM) or intravenous (IV) continuous-rate infusion (CRI) protocol (Table 113.2) [41,42]. Absorption of subcutaneous (SC) insulin injections may be poor or unpredictable in a dehydrated or hypotensive DKA or HHS patient. Newer insulin products, such as glargine, aspart

Table 113.2 Regular insulin protocols for treating diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS).

Insulin protocol type	Initial dose for DKA	Initial dose for HHS	Subsequent management
IV regular insulin CRI	Dilute 1.1–2.2 U/kg of regular insulin in 250 mL 0.9% NaCl. Start this solution at 5–10 mL/h	Dilute 0.5–1.0 U/kg of regular insulin in 250 mL 0.9% NaCl. Start this solution at 5–10 mL/h	Check blood glucose q2h and adjust CRI rate as necessary (see Table 113.3). Goal is to reduce blood glucose by 50–70 mg/dL/h
Intermittent IM regular insulin	0.2–0.25 U/kg of regular insulin, then 0.1 U/kg q2–4h	0.1 U/kg of regular insulin, then 0.05 U/kg q2–4h	Check blood glucose q4h. Goal is to reduce blood glucose by 50–70 mg/dL/h. Subsequent insulin doses are increased or decreased by ~25% to meet this goal. Add dextrose to fluids when glucose < 250 mg/dL

CRI, continuous rate infusion; IM, intramuscular; IV, intravenous.

and lispro, have prompted evaluation of other protocols [43–46], some of which show promise and may be used more commonly after additional study and refinement.

The primary goal for treating HHS patients is steady reduction of glucose concentration. Compared to DKA, in which insulin is critical for reversing ketogenesis, insulin is less critical for resolution of HHS because most of the syndrome is improved by replacing fluid deficit. In the non-ketotic HHS patient, insulin can be withheld until the patient is volume resuscitated and better hydrated, and the glucose concentrations are no longer adequately declining (<50 mg/dL/h) with appropriate fluid therapy alone [36]. The optimal treatment protocol for HHS has not been identified for humans or animals [47]. Compared to DKA protocols, insulin doses are usually decreased by 50% to facilitate a slow decline in blood glucose and reduce the risk of cerebral edema and development of neurological signs [36]. The recommended rate for an IV CRI of regular insulin is 0.025–0.05 U/kg/h [36,48]. For the IM protocol, 0.1 U/kg of regular insulin is administered, followed by 0.05 U/kg q2h until the glucose is less than 300 mg/dL, then q4–6 h.

With both DKA and HHS protocols, the goal is to decrease glucose by 50–75 mg/dL/h [36,39,48]. Blood glucose should be measured every 1–2 hours and the insulin dose adjusted to achieve the desired rate of decline (Table 113.3). If the glucose is dropping too rapidly, the insulin dosage should be decreased by 25–50%.

Identify and Treat Concurrent Diseases

Once cardiovascularly stable, diabetics experiencing DKA or HHS warrant a comprehensive battery of diagnostic tests looking for other conditions that may have contributed to the development of the diabetic crisis. Concurrent treatment of these co-morbidities is necessary for successful outcome of DKA and HHS patients.

A complete blood count (CBC), comprehensive biochemical profile, and urinalysis with culture are indi-

cated for all patients. Other diagnostic tests, such as radiographs of the chest and abdomen, abdominal ultrasound, echocardiography, electrocardiogram, FeLV/FIV screening, endocrine testing (most often of the thyroid or adrenal glands), heartworm testing, and pancreatic lipase measurement may be indicated based on historical, clinical, or physical examination findings.

Abnormalities identified by clinicopathological data are not specific for DKA or HHS and will vary with concurrent disease processes. CBC may reveal anemia or hemoconcentration. Stress or inflammatory leukograms are common in response to physiological stress, infection, or inflammation. Azotemia and hyperphosphatemia may reflect hypovolemia, dehydration, or concurrent primary renal dysfunction. Elevated liver enzyme activities and cholesterol occur commonly with diabetes mellitus, but may also reflect shock, concurrent pancreatitis or hepatobiliary disease, or concurrent endocrine dysfunction, such as hyperadrenocorticism. Hyperbilirubinemia, hypercholesterolemia, and hypertriglyceridemia are more commonly identified in cats with DKA than those with HHS [7].

Urinalysis assesses for presence of ketones and infection. Diabetics have impaired migration of white blood cells to sites of infection, so failure to find an inflammatory sediment does not preclude infection. Urine culture should always be submitted since urinary tract infection was reported in 20% of dogs with DKA [6].

Post-crisis Therapy for Diabetes Mellitus

Regular insulin protocols should be continued until the animal is eating, at which time the patient is transitioned to a long-acting insulin regimen. The recovered DKA/HHS patient is then managed as a “new” diabetic with special attention given to vigilant monitoring, insulin titration, and diagnosis and treatment of any concurrent problems as a means of preventing recurrence of DKA and HHS.

Outcome

Death and euthanasia rate for veterinary DKA patients has been reported to be 7–30% [6,9,42]. In one study, azotemia, metabolic acidosis, and hyperosmolality were more severe in cats that died [9]. In dogs, non-survivors had lower ionized calcium concentration, hematocrit and venous pH; base deficit was associated with outcome such that each 1 mEq/L increase in base deficit yielded a 9% increase in likelihood of discharge from the hospital [6]. Recurrence rate for DKA in cats has been reported to be as high as 42% [9].

Table 113.3 Insulin constant-rate infusion (CRI) adjustment chart for diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome.

Blood glucose (mg/dL)	Insulin CRI rate (mL/h) (see Table 113.2 for details)	Maintenance/replacement fluid composition
>250	10	As is
200–250	7	plus 2.5% dextrose
150–199	5	plus 2.5% dextrose
100–149	5	plus 5% dextrose
<100	0	plus 5% dextrose

Mortality rate for HHS in people is consistently 15–17% [49–51] and has been documented as high as 72% in children [52]. In animals, mortality rate for HHS is also high: 65% of cats and 38% of dogs died or were euthanized prior to discharge and only 12% of cats sur-

vived > 2 months [7,8]. There are no consistent predictors of survival for dogs and cats, although long-term feline survivors had curable concurrent diseases [6] and dogs with abnormal mental status and low venous pH had a poorer outcome [7].

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Adrenal Gland Disorders

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Introduction

The adrenal glands are paired endocrine organs adjacent to the kidneys within the retroperitoneum. The adrenal cortex is composed of three distinct layers: the zona glomerulosa, zona fasciculata, and zona reticularis. These zones produce and secrete mineralocorticoids, glucocorticoids, and sex hormones, respectively, and are under the control of the juxtaglomerular apparatus (JGA) (as part of the renin-angiotensin-aldosterone system (RAAS) for mineralocorticoids) and the pituitary gland (for glucocorticoid regulation). The adrenal medulla secretes and produces catecholamines and is regulated by the autonomic nervous system. Disease can arise from either excess or deficiency of the hormones produced by the adrenal gland.

Pheochromocytoma

Pheochromocytomas are catecholamine-producing tumors predominantly arising from the adrenal medulla. Similarly, extra-adrenal pheochromocytomas, or paragangliomas, are neuroendocrine chromaffin cells tumors that oversecrete catecholamines. In humans, paragangliomas account for 10% of pheochromocytomas [1]. It has only been reported in two canine patients [2,3]. Since paragangliomas are rare, the rest of this section will focus on pheochromocytoma.

Incidence

In canine patients with an adrenal mass undergoing surgical treatment, 13–31% had a confirmed diagnosis of pheochromocytoma [4–8]. In dogs with non-traumatic adrenal gland rupture and associated hemoabdomen, 2/4 dogs suffered from a pheochromocytoma [9]. In larger reports of canine acute non-traumatic hemoabdomen, in the subgroup of dogs with hemorrhage due to malignant

neoplasia, the incidence of pheochromocytoma ranged from 0% to 4% [10,11].

Pathophysiology

Intermittent production of supraphysiological levels of catecholamines results in clinical signs associated with high sympathetic tone (tachycardia, tachyarrhythmias, and/or hypertension). While tachyarrhythmias are most common, there are reports of pheochromocytoma-associated atrioventricular blocks [12]. While rare, decreased conduction abnormalities can be attributed to chronic myocardial injury [13] (see Chapter 53). Chronic severe hypertension can lead to target organ damage such as renal, ocular, or brain injury (see Chapter 63).

Tumor progression can be associated with intravascular invasion or thrombus formation and ascites. Caval thrombus formation is a common co-morbidity in patients with pheochromocytoma, leading to thrombectomy in 35–55% of patients undergoing adrenalectomy [4,6,14]. Approximately 50–66% of those tumors are locally invasive or have metastasized at the time of diagnosis [14,15].

Clinical Signs and Physical Examination

Middle-aged to older dogs are overrepresented [15]. Presenting complaint and clinical signs can be attributed to catecholamine secretion, vascular invasion, metastasis, or tumor rupture. In one canine report, owners reported weakness (62%), polyuria-polydipsia (PU/PD) (29%), collapse (29%), vomiting (24%), panting/dyspnea (19%), anorexia (19%), weight loss (14%), and seizures (5%) [15]. With intravascular tumor invasion or thrombus formation, patients might develop a Budd-Chiari-like syndrome marked by ascites accumulation [16]. Upon physical examination, patients may present signs of hypovolemic shock, along with abdominal enlargement and pain, especially if significant abdominal hemorrhage is present (see Chapter 84).

Diagnostic Results

If pheochromocytoma is suspected, an electrocardiogram should be performed in order to rule out the presence of tachyarrhythmias. Blood pressure should also be measured in order to rule out a hypertensive crisis, as this was reported in 43–86% of patients [14,15]. In patients with confirmed or suspected hemoabdomen, a packed cell volume along with a serum total protein measurement will help guide resuscitative efforts.

Abdominal ultrasound allows for evaluation for the presence of a mass, detection of potential caval thrombi, peritoneal fluid accumulation, local invasion or metastasis. Three-dimensional imaging such as computed tomography (CT) provides additional information of benefit for surgical planning: local invasion, metastasis, vascular invasion, and thrombus formation [8,17]. Thoracic imaging (radiographs or CT) should be performed in order to rule out metastasis.

Fine needle aspiration of adrenal masses for cytological examination allowed for reliable differentiation between medullar and cortical tumor origin in dogs and cats but was associated with serious complications such as hemorrhage or massive catecholamine release [18,19]. However, impression of surgical specimen following mass resection can be used for cytology.

Numerous studies have investigated the use of catecholamines' and their metabolites' concentrations in plasma and urine in order to diagnose pheochromocytomas [20–25]. Urinary normetanephrine-to-creatinine ratio proved to be superior to epinephrine-, norepinephrine-, or metanephrine-to-creatinine ratios [22]. Dogs with hypercortisolism may also have elevated circulating levels of catecholamines and their metabolites. The urinary normetanephrine-to-creatinine ratio outperformed plasma normetanephrine in differentiating pheochromocytoma patients from those with hypercortisolism [25]. It is prudent to recommend standardizing sampling conditions for those tests and allow the patients to have 30 minutes of rest prior to sampling [26] or consider collecting urine at home (which can be impractical due to the need for sample acidification shortly after collection) [27]. The utility of the clonidine suppression test remains unknown in canine patients [28]. Definitive diagnosis requires histopathology.

Treatment

Patients in need of emergent therapy should be stabilized, in particular those with clinical signs of hypovolemic shock due to abdominal hemorrhage (see Chapters 84 and 170). Patients with serious tachyarrhythmias should receive appropriate antiarrhythmic therapy (see Chapter 53). Hypertensive crisis should be addressed if present (see Chapter 63).

Medical therapy in stable patients aims at controlling the effect of excessive catecholamine secretion. Phenoxybenzamine, an alpha-adrenergic antagonist, at a median dose of 0.6 mg/kg PO q12h for a median period of 20 days prior to surgical removal, lowered the mortality rate from 48% to 13% in patients undergoing adrenalectomy [29]. This finding was not repeated in a more recent but smaller study [7]. The use of beta-blockers has not been reported in veterinary pheochromocytoma patients and should be initiated only after proper alpha-blockade is achieved.

Definitive treatment is obtained by surgery either via an open celiotomy or, for non-invasive masses in stable patients, laparoscopy [30,31].

Surgical Outcome and Prognostic Factors

The immediate postoperative period can be accompanied with significant morbidity and mortality; 18–31% of canine patients that underwent adrenalectomy for pheochromocytoma removal did not survive to the postoperative period [4,29]. Of interest to the emergency clinician, 50% of dogs with acute hemoabdomen due to adrenal tumor rupture died in the perioperative period [5]. Patients with pheochromocytoma had worse short- and long-term survival when compared to those with adrenocortical carcinoma (48% versus 79%). Reported median survival time for those patients was 364 days [32]. Another study presented 1-, 2-, and 3-year survival rates of 83%, 60%, and 60% in dogs with pheochromocytoma undergoing adrenalectomy. Negative prognostic indicators include vena cava invasion and extent of invasion (short but not long term) [7], older age, intraoperative arrhythmias, and prolonged surgical time [29].

Hyperaldosteronism

Aldosterone is a steroid hormone with mineralocorticoid activity produced mainly from the zona glomerulosa of the adrenal cortex. In physiological conditions, aldosterone is secreted in response to angiotensin II release following activation of the RAAS as a consequence of decreased renal arterial perfusion or hyperkalemia. Aldosterone acts within the nephron and vascular endothelial cells to restore fluid volume and increase systemic vascular resistance to maintain systemic arterial blood pressure [33].

Secondary hyperaldosteronism can result from decreased renal perfusion or, rarely, due to excessive renin production from the JGA due to neoplasia or decreased JGA blood flow. Primary hyperaldosteronism (PHA) refers to autonomous secretion of aldosterone from the adrenal cortex and is the most commonly

diagnosed form of the disease. The remainder of this section will focus on this condition.

Incidence

Primary hyperaldosteronism is more frequently diagnosed in cats, but there have been case reports of dogs with the disease [34]. Historically, the prevalence in humans was estimated between 0.01% to 3% of hypertensive patients, but more recent studies have shown the true prevalence to be 5.9% of all hypertensive patients [35] and up to 11.3% of patients with refractory hypertension [36].

Pathophysiology

Primary hyperaldosteronism is caused by autonomous secretion of aldosterone due to adrenocortical adenomas, carcinomas or bilateral adrenocortical hyperplasia. Approximately 63% of the documented cases in cats due to adrenal masses have been attributed to malignant neoplasia. Since definitive diagnosis relies on histopathological evaluation, which rarely occurs in patients without an adrenal mass, the incidence of hyperplastic change is likely underreported [37].

In cases of neoplastic PHA, hyperaldosteronism occurs in the presence of hyporeninism. Due to the effects of aldosterone, the nephron retains both sodium and, consequently, free water, resulting in an increased intravascular volume and systemic hypertension. Despite an absolute increase in total body sodium, these patients generally appear to be normonatremic due to the dilutional effect of the retained water. The potassium-wasting properties of mineralocorticoids often lead to hypokalemia, though 10–12% of feline patients with PHA may remain normokalemic [33,38].

Clinical Signs and Physical Examination

The most common clinical sign is muscle weakness associated with a hypokalemic polymyopathy (including plantigrade stance, cervical ventroflexion, and flaccid paralysis) although severity of clinical signs does not always correlate with severity of electrolyte disturbances. Cats with severe hypertension may present for mydriasis or apparent blindness [39,40]. Cats with PHA and concurrent adrenocortical hormone excess (progesterone or other sex hormones) may present clinical signs as a result of diabetes mellitus or hyperadrenocorticism [41,42].

Diagnostic Results

Most cats with PHA will have normal sodium concentrations but are typically hypokalemic. Complete blood

counts and routine biochemical analysis are generally unrewarding other than for evaluation of serum potassium concentration. There is an increasing reported incidence of adrenal hyperplasia and these cats tend to have normo- to mild hypokalemia. Cats with bilateral hyperplasia are more likely to be azotemic but often remain normophosphatemic [37]. Measurement of systemic arterial blood pressure reveals hypertension in the majority of patients.

Abdominal imaging plays a central role in the investigation of any cat with unexplained hypertension or hypokalemia and ultrasonography is a reliable, quick, and non-invasive technique to document the size and architecture of both adrenal glands and kidneys [43]. Sonography should also be used to evaluate for metastatic disease, tumor invasion or evidence of thrombus formation.

Definitive diagnosis is achieved by documentation of elevated plasma aldosterone concentration or aldosterone:renin ratio. The lack of suppression of aldosterone in a fludrocortisone suppression test can be used to confirm hyperaldosteronism [44].

Treatment and Prognosis

Definitive treatment relies on adrenalectomy, which can be performed by either laparotomy or laparoscopy [39,46]. Intraoperative complications include hemorrhage and hypotension, while postoperative complications include pancreatitis, hypoadrenocorticism, and acute kidney injury. Survival rates range from 70% to 77%, with highest mortality in the perioperative period [39,40].

Prior to surgery, medical management should be instituted in order to manage the effects of PHA (hypokalemia and hypertension). Amlodipine besylate should be started at 0.625 mg/cat PO once daily. Its dose should be escalated to achieve a systolic or mean arterial blood pressure less than 150 or 130 mmHg, respectively [45]. To address hypokalemia, both oral potassium supplementation (potassium gluconate 2 mEq/cat twice daily) and mineralocorticoid antagonists (spironolactone, initially 2 mg/kg twice daily) can be combined. Although resolution of the hypokalemia may not occur, its severity generally improves and associated myopathy resolves [40].

Hyperadrenocorticism

Hyperadrenocorticism suggests excessive production of hormones from the adrenal cortex, but in most cases specifically refers to glucocorticoid excess (iatrogenic, pituitary dependent or adrenal dependent). Glucocorticoids

are produced by the zona fasciculata and reticularis under the control of the anterior pituitary; their release is regulated by secretion of adrenocorticotrophic hormone (ACTH), which is under negative feedback control.

Pathophysiology

Hypercortisolism can occur due to either exogenous administration of glucocorticoids or endogenous overproduction of glucocorticoids. In dogs and cats, approximately 80–85% of the cases are due to pituitary adenoma (either micro- or macroadenomas), leading to hypersecretion of ACTH [47]. Most cases of neurological signs relating to a pituitary tumor are caused by macroadenomas [48]. Approximately 15% of cases of naturally occurring hypercortisolism are caused by functional adrenal tumors, which are malignant roughly half of the time [49]. Rarely, concurrent pituitary and adrenal pathologies are identified [50].

Regardless of the etiopathogenesis, clinical signs primarily relate to glucocorticoid excess. A small population of dogs with functional adrenal tumors will develop clinical signs referable to the presence of an abdominal mass (hemoabdomen or Budd-Chiari-like syndrome).

The mechanisms of thromboembolic disease (such as a pulmonary thromboembolism) in patients with hypercortisolism are not well understood [51] (see Chapter 62).

Clinical Signs and Physical Examination

The clinical signs displayed by animals with Cushing's syndrome are a consequence of the immunosuppressive, catabolic, and anti-inflammatory effects of glucocorticoids. The most common clinical signs include PU/PD, polyphagia, and exercise intolerance or muscle weakness. Other clinical signs in the dog include panting, a pot belly or dermatological manifestations (truncal alopecia, pyoderma, and cutaneous atrophy). In the cat, dermatological abnormalities are the most frequent reason for presentation; cutaneous atrophy can be more severe and patients may present with severe skin lacerations and degloving injuries. Often, cats with Cushing's syndrome have previously been diagnosed with diabetes mellitus and are presented for poorly controlled disease [52].

Most clinical signs of hypercortisolism in the dog are slowly progressive, but rarely they might present in acute respiratory distress due to pulmonary thromboembolic disease. Similarly, thromboemboli can affect other critical systems such as the brain, kidneys, pancreas, or gut [53] (see Chapter 62).

Dogs with moderate to severe disease may present with marked muscle atrophy, abdominal distension, changes to the coat, including bilateral, symmetrical

truncal alopecia, as well as evidence of chronic pyoderma, bruising, or calcinosis cutis.

Diagnostic Results

Diagnosis of hypercortisolism is dependent on the presence of appropriate clinical signs and documentation of inappropriate glucocorticoid secretion. Routine laboratory tests may reveal thrombocytosis, elevated alkaline phosphatase activity, hypercholesterolemia, hyperglycemia, or low urine specific gravity, but none of these findings alone confirms its diagnosis. The low-dose dexamethasone suppression test (LDDST) is considered the optimal screening test for Cushing's disease in dogs [54]. In many cases, the clinician may choose to perform a urine cortisol:creatinine ratio (UC:Cr) initially as this test only requires a single urine sample (as opposed to three blood samples, 4 hours apart). These tests rely on a systemically well, calm dog since stress and excitation can lead to false-positive results. As a consequence, neither the LDDST nor UC:Cr should generally be performed in the emergency room setting.

The finding of bilateral adrenomegaly or a solitary adrenal tumor via diagnostic imaging is supportive of the presence of adrenal disease, but should not be the sole criterion upon which a search for endocrine disease is based. Adrenal "incidentalomas" are a common finding in dogs and human meta-analyses suggest that they are unlikely to be a significant finding in patients lacking clinical signs [55], although size greater than 20 mm in a canine study was associated with malignant disease [56].

Thromboelastography, PFA-100 closure times, and fibrinogen activity have been shown to be affected in dogs with Cushing's syndrome [57,58]. Unfortunately, none of these parameters appears to normalize with treatment, even though well-controlled dogs appear to be at lower risk for thromboembolic disease [51].

Treatment and Prognosis

Treatment for the stable dog with hypercortisolism relies on suppression of glucocorticoid synthesis (trilostane, mitotane), adrenalectomy (for patients with functional adrenal tumors) or, potentially, hypophysectomy. Treated dogs generally respond well and have an improved quality of life. In cases of functional adrenal masses, laparoscopic adrenalectomy has been shown to carry a low risk of complications with shorter hospitalization when compared to open approaches [59].

Prognosis for dogs with thromboembolic disease is guarded to grave and treatment is usually empiric (see Chapter 42).

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115

Hypoadrenocorticism

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Etiology and Pathogenesis

Anatomy and Pathophysiology

The adrenal glands are located at the craniomedial poles of the kidneys. They are composed of an outer cortex (90%) surrounding the inner medulla (10%). The cortex consists of three distinct layers, which from the serosal surface inward include the zona glomerulosa, zona fasciculata, and zona reticularis. The cortex secretes mineralocorticoids (aldosterone) from the zona glomerulosa, glucocorticoids (cortisol) from the zona fasciculata, and androgens (e.g. androstenedione, dehydroepiandrosterone) from the zona reticularis. Hypoadrenocorticism involves all three zones of the adrenal cortex, with clinical signs most attributable to loss of mineralocorticoid and glucocorticoid activity. It is reported that up to 90% of the adrenal cortex must be destroyed before clinical signs become evident (Web Figure 115.1a and 115.1b) [1,2].

There are two general categories of hypoadrenocorticism: primary and secondary. Primary hypoadrenocorticism is much more common in dogs than cats (>95% of cases). In dogs, it is believed to result from immune-mediated damage to all three layers of the adrenal cortex (Table 115.1) [1]. Nova Scotia duck tolling retrievers, standard poodles, bearded collies, and Portuguese water dogs have been identified as having a genetic predisposition [3–5]. Primary hypoadrenocorticism is also over-represented in the Great Dane, West Highland white terrier, St Bernard, wheaten terrier, leonberger, basset hound, Airedale terrier, springer spaniel, and rottweiler [1,6,7]. Females tend to be more commonly affected (70% of cases) and the median age of onset in dogs is 4 years (range 4 months to 14 years) [1]. Dogs and cats with primary hypoadrenocorticism (70–90%) will have both glucocorticoid and mineralocorticoid deficiencies and will present with electrolyte abnormalities [1,2]. Primary

Table 115.1 Causes of hypoadrenocorticism in dogs.

Primary causes	Secondary causes
Most common:	Most common:
Immune mediated	Iatrogenic secondary to withdrawal of exogenous corticosteroid administration (rarely causes clinical signs)
Uncommon:	Uncommon:
Iatrogenic drug induced (e.g. mitotane or trilostane)	Idiopathic
Rare causes:	Rare causes:
Granulomatous destruction (e.g. blastomycosis, histoplasmosis, cryptococcosis)	Surgical induced
Amyloidosis	Head trauma
Hemorrhagic infarction (secondary to trauma, infection, necrosis, or coagulopathy)	
Metastatic neoplasia (lymphoma and bilateral anaplastic neoplasia)	
Bilateral abscessing adrenalitis	
Adrenal suppressors (e.g. ketoconazole, etomidate)	

hypoadrenocorticism resulting in only glucocorticoid deficiency and the absence of electrolyte imbalances is uncommon, but has been reported in dogs [6].

Secondary hypoadrenocorticism is much less common (<5% of canine and feline cases) and results from abnormal pituitary gland (a lack of ACTH secretion) or hypothalamic function (a lack of corticotropin-releasing hormone (CRH) secretion). Examples of secondary hypoadrenocorticism include trauma and neoplasia of the pituitary gland or hypothalamus (see Table 115.1). Secondary hypoadrenocorticism tends to result in a lack

of cortisol production while mineralocorticoid levels are preserved (due to atrophy of the zona fasciculata and zona reticularis, with the zona glomerulosa remaining unaffected) [1,2,8]. Therapy differs between primary and secondary causes so it is important to differentiate the two conditions (see Table 115.1).

Mineralocorticoid Deficiency

Aldosterone is vital to maintaining normal sodium, potassium, and water homeostasis through sodium, chloride, and water reabsorption and potassium excretion. The primary site of action is the renal tubule, although aldosterone also plays a role in regulating the gastrointestinal (GI) tract as well as the salivary and sweat glands.

Sodium, Chloride, and Water Homeostasis

Aldosterone deficiency causes increased loss of sodium, chloride, and water via the urine. This contributes to dehydration, prerenal azotemia, unconcentrated urine, hypovolemia, weakness, and shock. Specifically, aldosterone acts on the principal cells of the collecting tubules of the kidney to increase the absorption of sodium. When sodium is reabsorbed via tubular epithelial cells, negative ions such as chloride move with sodium due to electrical potentials. Water is reabsorbed passively as it follows the concentration gradients between the tubular lumen and renal interstitium created by the reabsorption of sodium and chloride [9]. Aldosterone also plays an important role in sodium absorption in the GI tract, particularly in the colon [10,11]. Aldosterone deficiency impairs GI sodium absorption, which also leads to a decrease in chloride and water absorption from the GI lumen. Decreased absorption of GI electrolytes and water contributes to diarrhea, which is often accompanied by vomiting, both of which can further exacerbate extracellular fluid losses and hypovolemia.

With ongoing extracellular fluid loss, intravascular volume can eventually become depleted, leading to hypoperfusion and shock. Death occurs in the untreated patient 4 days to 2 weeks following a complete cessation of mineralocorticoid secretion [9].

Potassium Homeostasis

Aldosterone deficiency can lead to marked hyperkalemia, which is further exaggerated by hypovolemia and decreased glomerular filtration rate (GFR). Plasma potassium concentration is primarily regulated by the action of aldosterone on the renal excretion of potassium and the movement of potassium between extracellular and intracellular compartments [9]. Acidosis is also common in patients with hypoadrenocorticism, which will shift potassium out of cells, contributing to hyperkalemia [12]. One of the more serious sequelae of

hyperkalemia is abnormal cardiac conduction leading to prolonged refractory periods of the cardiac action potential, which can lead to clinically significant bradycardia, atrial standstill, decreased cardiac output, and in severe cases ventricular fibrillation and death (see Chapter 109) [13,14].

Acid-Base Homeostasis

Aldosterone plays a role in the secretion of hydrogen ions (in exchange for sodium) by the intercalated cells of the cortical collecting tubules of the kidneys [9]. In the absence of confounding factors, a mild acidosis develops secondary to aldosterone deficiency. However, during an adrenal crisis in a patient with hypoadrenocorticism, the absence of aldosterone in conjunction with lactic acidosis and decreased GFR (secondary to hypoperfusion) can lead to a marked acidosis (see Chapter 107).

Glucocorticoid Deficiency

Cortisol plays an important role in numerous homeostatic processes. The role of cortisol in regulating blood pressure, blood volume, and blood glucose concentration contributes to some of the more serious complications in patients with hypoadrenocorticism. Cortisol stimulates the release of vasoactive substances, sensitizes blood vessels to the effects of catecholamine, and decreases blood vessel permeability [9]. Cortisol also plays an important role in gluconeogenesis. In the absence of cortisol, intravascular volume decreases, blood pressure falls, and hypoglycemia can develop [9]. Cortisol deficiency may also contribute to GI ileus, further exacerbating diarrhea and vomiting [10].

Cortisol also contributes to sodium homeostasis along with aldosterone [13]. There are reports of hypoadrenocorticism being associated with hyponatremia when mineralocorticoid activity is normal [15]. Cortisol inhibits the release of antidiuretic hormone (ADH). In the absence of cortisol, ADH levels are elevated, causing increased water resorption at the kidneys, which subsequently dilutes the plasma sodium concentration [13].

Patient Evaluation

History and Physical Examination Findings

The history in patients with hypoadrenocorticism can be non-specific and may include vomiting, diarrhea, melena, polyuria/polydipsia, ataxia, tremors or seizures, lethargy, anorexia, weight loss, and inactivity (Tables 115.2 and 115.3). These clinical signs may wax and wane over time. Many dogs will have a history of primary GI signs that may have previously responded to fluid and/or

Table 115.2 Most common findings in canine patients with hypoadrenocorticism.

History	Physical exam findings	Laboratory/diagnostic findings
Lethargy 95%	Depression 95%	Complete blood count:
Inappetence 90%	Weakness 75%	Lack of stress leukogram 92%
Weakness 75%	Dehydration 45%	Neutrophilia 32%
Vomiting 75%	Bradycardia%	Non-regenerative anemia 25–27%
Diarrhea 40%	Hypothermia 35%	Eosinophilia 20%
Weight loss 50%	Collapse 35%	Lymphocytosis 10%
Waxing and waning course 40%	Prolonged capillary refill time 30%	Chemistry:
Prior response to therapy 35%	Melena 20%	Sodium:potassium ratio <27 95%
Shivering and/or muscle stiffness 25%	Weak pulses 20%	Hyperkalemia 85–95%
Polyuria 25%	Bradycardia 18%	Azotemia 85–88%
Polydipsia 25%	Painful abdomen 8%	Hyponatremia 81–82%
		Hypochloremia 40–68%
		Hyperphosphataemia 68%
		Acidosis (low bicarbonate) 40–57%
		Elevated liver enzymes 30–50%
		Hypercalcemia 18–40%
		Hypoalbuminemia 6–39%
		Hypoglycemia 10–30%
		Hypocalcemia 25%
		Hyperglycemia 18%
		Elevated lactate 14%
		Hypocholesterolemia 7%
		Urine specific gravity <1.030 60%

Source: Adapted from Feldman et al. [48], Peterson et al. [7], Adler et al. [16], Kintzer and Peterson [2].

Table 115.3 Most common findings in feline patients with primary hypoadrenocorticism.

History	Physical exam findings	Laboratory/diagnostic findings
Lethargy 100%	Dehydration 86%	Complete blood count:
Anorexia/decreased appetite 95%	Weakness 73%	Anemia 27%
Weight loss 77%	Hypothermia 68%	Lymphocytosis 27%
Vomiting 55%	Weak pulse 45%	Eosinophilia 9%
Waxing-waning course 32%	Slow capillary refill time 41%	Chemistry:
Prior response to therapy 27%	Bradycardia 23%	Sodium-to-potassium ration <27 100%
Polyuria and polydipsia 27%	Collapse/inability to rise 23%	Hyponatremia 95%
Dysphagia 4%	Constipation 9%	Hyperkalemia 91%
	Painful abdomen 4%	Azotaemia 82%
		Hypochloremia 73%
		Hyperphosphatemia 68%
		Low total CO ₂ (metabolic acidosis) 26%
		Elevated liver enzymes 25%
		Hypercalcemia 23%
		*Hypoglycemia: 7%
		Urine specific gravity <1.030 74%

* Low normal glucose concentrations are often reported in cats with hypoadrenocorticism.

Source: Adapted from Peterson et al. [43], Kasabalis et al. [44], Sicken and Neiger [45], Spalla et al. [46], and Woolcock and Ward [47].

glucocorticoid therapy. A precipitating stressful event may also be evident in some cases. The duration of illness is reportedly longer (average 4 months) in dogs with only glucocorticoid deficiency compared to those with both mineralocorticoid and glucocorticoid deficiency (average 1 month) [6]. Hypothermia, bradycardia, weak pulses, dehydration, ataxia, collapse, and abnormal respiratory pattern may be noted in some cases (see Tables 115.2 and 115.3). Clinical signs tend to be milder in dogs with only glucocorticoid deficiency that maintain normal electrolytes (secondary hypoadrenocorticism or a small number of cases with primary hypoadrenocorticism) [6].

Shock is more likely in dogs with both glucocorticoid and mineralocorticoid deficiency than cases with just glucocorticoid deficiency [6]. Patients presenting in shock with concurrent bradycardia should prompt consideration of diseases leading to hyperkalemia, including hypoadrenocorticism.

Feline Hypoadrenocorticism

Hypoadrenocorticism is extremely rare in cats, with fewer than 50 cases having been reported in the literature. Clinical findings in cats are similar to those in dogs and humans, with lethargy, anorexia, and weight loss being the most common signs reported by owners and depression, dehydration, weakness, and hypothermia being the most common physical exam findings (see Table 115.3).

Diagnosis

Emergency Cage-Side Tests and Imaging

An emergency minimum database should be collected in patients presenting with an acute adrenal crisis and shock. This may vary by patient but typically includes blood pressure measurement, biochemistry (glucose, urea, creatinine, lactate, electrolytes, total solids, packed cell volume), acid–base status, electrocardiogram (ECG), and abdominal and thoracic focused assessment with sonography to detect free fluid in the abdominal and thoracic cavities, respectively. Imaging is often undertaken in patients with GI signs or undifferentiated shock. Patients with hypoadrenocorticism may have bilateral adrenal atrophy noted on abdominal sonography (in cases of primary hypoadrenocorticism), but a finding of normal-sized adrenal glands on ultrasound should not preclude a diagnosis of hypoadrenocorticism [16,17]. Radiographs are often unremarkable or may show evidence of hypovolemia, including microcardia, decreased pulmonary vessel vasculature, and a narrowed caudal vena cava (Figure 115.1). Rarely, megasophagus will be

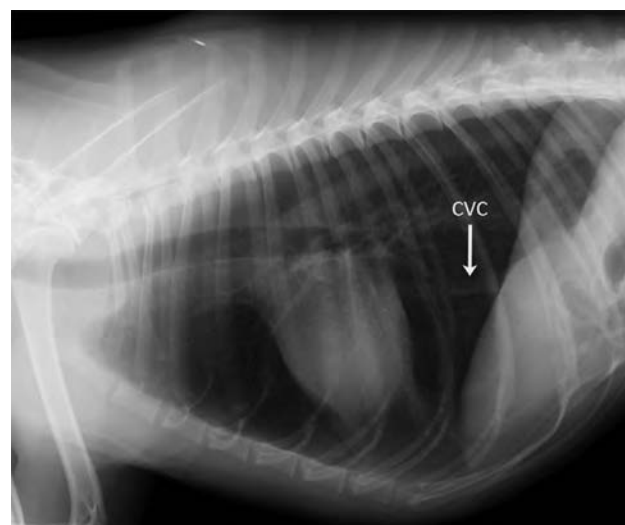


Figure 115.1 Left lateral thoracic radiograph of a collie cross dog with hypoadrenocorticism. Note the marked microcardia and narrowing of the caudal vena cava (CVC, white arrow), consistent with marked hypovolemia.

noted on thoracic radiographs, which is reversible with medical therapy of hypoadrenocorticism.

Complete Blood Count (CBC)

The absence of a stress leukogram (neutrophilia, lymphopenia, monocytosis, and eosinopenia) in a sick patient should prompt consideration of hypoadrenocorticism, but most dogs and cats with hypoadrenocorticism will have variable leukocyte counts [1,6–8,18]. It has been reported that the lymphocyte count is the most reliable CBC parameter in dogs with hypoadrenocorticism and the presence of lymphocytosis in the sick dog should prompt consideration of hypoadrenocorticism [18]. Similarly, eosinophilia or lymphocytosis in a sick cat should prompt consideration of hypoadrenocorticism in the absence of another explanation.

Serum Chemistry Panel

The most frequent findings on the serum chemistry profile in dogs and cats with hypoadrenocorticism include hyperkalemia, hyponatremia, and azotemia (see Tables 115.2 and 115.3) [2,6,16]. Although the sodium:potassium ratio of <27 is considered very sensitive and specific for hypoadrenocorticism, some dogs with hypoadrenocorticism will have ratios >27 , particularly in rare cases of glucocorticoid deficiency without concurrent mineralocorticoid deficiency [16,18]. Other conditions including GI disease, parasitic infection (e.g. *Trichuris vulpus*), third space losses, congestive heart failure, and diabetes mellitus can also result in sodium:potassium ratios <27 in both dogs and cats. However, a ratio <27 should raise suspicion

for hypoadrenocorticism and ratios of ≤ 20 are very suggestive of hypoadrenocorticism, warranting strong consideration of ACTH stimulation testing [16,18].

Azotemia is most likely prerenal in origin as a result of hypovolemia, hypoperfusion, and decreased renal perfusion. Patients should be monitored during fluid resuscitation and rehydration to ensure that azotemia is resolving and that renal insufficiency is not present. Urine specific gravity cannot be relied on to differentiate prerenal from renal causes of azotemia as many patients with hypoadrenocorticism will have medullary washout secondary to hyponatremia, which results in an inappropriately low USG in the face of azotemia (see Tables 115.2 and 115.3).

Hypoproteinemia and hypoalbuminemia are relatively common in dogs as a result of increased GI protein losses and decreased hepatic synthesis. Hypercalcemia is also relatively common in dogs and cats, and although the exact cause of hypercalcemia is uncertain, it tends to resolve quickly following glucocorticoid therapy [2]. In very rare cases, hypoglycemia associated with hypoadrenocorticism may result in seizures in both dogs and cats but tends to resolve quickly following IV dextrose and glucocorticoid therapy. Hypcholesterolemia, increased liver enzymes, and metabolic acidosis have also been reported (see Tables 115.2 and 115.3). Non-specific biochemical changes including anemia, hypocholesterolemia, hypercalcemia, hypoglycemia, and hypoalbuminemia in patients with vague clinical signs should prompt consideration of glucocorticoid deficiency.

Resting or Basal Serum Cortisol Levels

Measurement of resting cortisol level is rapid and inexpensive to perform. Only 1% of dogs with hypoadrenocorticism have values $>2 \mu\text{g/dL}$, which makes the diagnosis very unlikely when the resting cortisol is $>2 \mu\text{g/dL}$. However, 21% of dogs with non-adrenal disease may have values $<2 \mu\text{g/dL}$ [19,20], so an ACTH stimulation test should be performed to confirm the diagnosis in patients with resting cortisol $<2 \mu\text{g/dL}$.

ACTH Stimulation Testing

Adrenocorticotropin hormone (ACTH) stimulation testing is the definitive test for hypoadrenocorticism. A serum cortisol concentration $\leq 2 \mu\text{g/dL}$ pre- and 1 hour post ACTH administration in dogs (30 minutes post for cats) is considered diagnostic of hypoadrenocorticism in the absence of exposure to exogenous corticosteroids or mitotane [6].

Protocols for ACTH administration vary between product manufacturers and it is important to read manufacturer directions when performing ACTH stimulation testing. Liquid formulations and sterile powders requiring

reconstitution with sterile saline have been used with equivocal results [21–23]. Several authors have recommended avoiding ACTH gel preparations as they do not produce reliable ACTH stimulation test results [24,25]. Numerous studies have demonstrated that $5 \mu\text{g/kg}$ (or lower) doses given IV (check product routes of administration) produce reliable adrenal stimulation in dogs, and current recommendations are to administer ACTH at $5 \mu\text{g/kg}$ IV (up to a maximum dose of $250 \mu\text{g}$) [21,24,26]. Current recommendations in cats are to use a single $125 \mu\text{g}$ dose IV.

Most exogenous glucocorticoids falsely elevate cortisol assays so administration of these medications should be avoided until after ACTH stimulation testing is performed. The exception is dexamethasone, which does not interfere with cortisol assays and should be used if emergency glucocorticoid therapy is required prior to ACTH stimulation testing. It has been suggested to wait 24–48 hours before performing an ACTH stimulation test if short-acting glucocorticoids (with the exception of dexamethasone) have been administered, or longer (up to several weeks) if glucocorticoids have been used chronically [1,24].

It may be helpful to perform ACTH stimulation testing in dogs and cats with vague non-specific symptoms in which another cause cannot be found, particularly if GI signs are present. Particularly in dogs, it is reasonable to perform ACTH stimulation testing to rule out hypoadrenocorticism before more invasive testing such as endoscopy and exploratory laparotomy is undertaken.

Cortisol-to-Adrenocorticotrophic Hormone Ratio

Recent studies suggest that the cortisol-to-adrenocorticotrophic hormone ratio (CAR) could potentially be used in place of the ACTH stimulation test for diagnosis of hypoadrenocorticism [27,28]. The advantage of the CAR compared to ACTH stimulation testing is the need for only a single blood sample from which both serum cortisol and plasma ACTH concentrations can be measured. However, differentiation between dogs with hypoadrenocorticism and those with diseases mimicking hypoadrenocorticism is not 100% [28]. In addition, the reliability of the CAR in diagnosing secondary hypoadrenocorticism requires further investigation.

Primary Versus Secondary Hypoadrenocorticism

Primary and secondary causes of hypoadrenocorticism cannot be differentiated based on results of ACTH stimulation testing. When electrolyte imbalances are present, it is highly probable that the patient has primary hypoadrenocorticism, indicating that mineralocorticoid therapy will be required for chronic management. In cases

where there are no electrolyte imbalances, it is difficult to determine whether the cause is primary or secondary and whether the patient is likely to require mineralocorticoid therapy in the future. Secondary causes are unlikely to develop electrolyte imbalances and therefore unlikely to require mineralocorticoid therapy, while many primary cases will progress to develop electrolyte imbalances and eventually need mineralocorticoid therapy.

To differentiate primary from secondary causes, endogenous plasma ACTH concentrations must be evaluated; plasma endogenous ACTH concentration is high in primary hypoadrenocorticism due to loss of feedback inhibition from cortisol on pituitary function, while plasma endogenous ACTH concentration is low in secondary hypoadrenocorticism due to decreased release of ACTH from the pituitary gland.

Consultation with the local reference laboratory is recommended regarding the best way to collect and handle sampling for endogenous plasma ACTH concentration.

Treatment

The most life-threatening presentation in animals with hypoadrenocorticism is shock. Initial therapy should involve improving tissue perfusion via restoration of intravascular volume, correction of life-threatening arrhythmias, correcting electrolyte imbalances, correcting hypoglycemia, and administering rapid-acting intravenous glucocorticoids (see Chapter 153). Once the patient is stable, differentiating primary from secondary hypoadrenocorticism and correcting any underlying causes should be undertaken. It should be noted that although dogs generally tend to respond quickly to therapy for acute adrenal crisis, cats may take 3–5 days before they show improvement despite appropriate therapy.

Fluid Therapy

Intravenous fluid resuscitation should be initiated when shock is first identified and should not be delayed until a definitive diagnosis of hypoadrenocorticism is confirmed (see Chapter 153 for treatment of hypovolemic shock). Early aggressive fluid therapy in patients with hypoadrenocorticism helps to address hypovolemic shock and can help rapidly correct hyperkalemia through plasma dilution and increased renal excretion of potassium. A small proportion of dogs [29] that develop gastrointestinal hemorrhage (present in roughly 15% of dogs with hypoadrenocorticism) [7] will have severe anemia, which may require a blood transfusion depending on the hematocrit and response to fluid therapy (see Chapter 176).

Isotonic crystalloids are a reasonable initial fluid choice in patients with hypoadrenocorticism (see Chapter 167).

There are no studies in veterinary medicine that demonstrate a benefit of one particular isotonic crystalloid over another for treating hypoadrenocorticism. Any commercially available balanced isotonic crystalloid solution will decrease potassium levels through dilution, help correct acid–base imbalances, and improve renal perfusion. Historically, normal saline was the fluid of choice to correct hypovolemia, hyperkalemia, and hyponatremia in veterinary patients with hypoadrenocorticism because it restores intravascular volume, does not contain potassium, and is relatively high in sodium compared to other isotonic crystalloids [12,14]. However, due to the risk of central pontine myelinolysis, which has been reported in dogs that are markedly hyponatremic [30–33], isotonic crystalloids that are lower in sodium concentration (e.g. lactated Ringer's solution or Plasma-Lyte 148) may be a better alternative in the initial management of patients with hypoadrenocorticism. An initial bolus of normal saline followed by boluses of another isotonic crystalloid can also be used if the patient has marked hyperkalemia.

Strong evidence to support a maximal rate of increase in sodium concentration to prevent central pontine myelinolysis is lacking, but it has been suggested that the rate of increase in sodium should not be faster than 0.5 mEq/L/h. To ensure sodium levels do not increase too rapidly, electrolytes should be monitored frequently and fluid therapy adjusted in accordance with the rate of change in electrolytes.

Hyperkalemia

Fluid resuscitation is essential in correcting hyperkalemia through dilution of serum potassium concentration, increased GFR, and correction of acidosis. The vast majority of hyperkalemic patients with hypoadrenocorticism will respond well to fluid therapy alone, and do not require additional therapy to address the hyperkalemia. However, in patients with relevant ECG changes consistent with hyperkalemia (absent P-wave, spiked T-waves, prolonged QRS complexes, bradycardia, atrial standstill, and sinoventricular complexes) [13,14] to the point where cardiac output is decreased and contributing to hypoperfusion, additional therapy for hyperkalemia is warranted (see Chapter 109). This consists of antagonizing the effects of hyperkalemia on myocardial cells concurrent with efforts to reduce the serum potassium concentration.

Calcium gluconate (10% solution) given IV (0.5–1.0 mL/kg to effect over 5–10 min) does not decrease serum potassium levels but will antagonize the cardiotoxic effects of hyperkalemia for 30–60 minutes. The advantage of calcium gluconate is that its cardioprotective effects occur very rapidly and much sooner than other therapies can decrease serum potassium levels.

Patients should be monitored closely with an ECG during administration of calcium gluconate, and calcium gluconate administration should be discontinued if the heart rate falls or if other significant ECG findings (ST segment elevation or arrhythmias) develop. Restarting the infusion at a slower rate once the ECG changes resolve can be attempted [34]. The goal of calcium gluconate therapy is to stabilize cardiac function long enough to allow other therapies to decrease the serum potassium concentration [35].

A dextrose bolus alone (0.5–1.0 mL/kg 50% dextrose dilute to <25% with isotonic crystalloids) or in combination with insulin (regular crystalline insulin 0.1–0.2 U/kg IV) can be administered to decrease serum potassium levels. Intravenous dextrose administration increases endogenous insulin secretion from the pancreas and will shift potassium intracellularly, decreasing serum potassium concentrations up to 0.5–1 mEq/L within an hour [13,14]. The effects can last up to 6 hours. Administering IV insulin along with dextrose produces a more pronounced and rapid decrease in serum potassium levels. Insulin should only be given with an accompanying IV dextrose bolus and an IV CRI of dextrose (add 50% dextrose to IV fluids to make a 2.5–5% solution) for at least 6 hours to prevent iatrogenic hypoglycemia. Ideally, the serum glucose concentration should be measured hourly for at least 6 hours following IV insulin administration.

Alternatively, sodium bicarbonate (1–2 mEq/L) IV can be used to decrease serum potassium by shifting potassium intracellularly in exchange for hydrogen ions (see Chapter 174). The disadvantage of sodium bicarbonate is that it takes longer to decrease serum potassium concentrations compared to the administration of dextrose and regular insulin. It is also important to ensure patients have sufficient ventilation when giving sodium bicarbonate to avoid development of paradoxical central nervous system acidosis. Other concerns associated with administration of sodium bicarbonate include a transient decline in mean arterial pressure after rapid intravenous administration, decreased ionized calcium concentration (which may affect left ventricular contractility), and decreased oxygen delivery caused by decreased unloading of oxygen from hemoglobin at the tissue level (e.g. Bohr effect) [36–39]. In addition, overshoot alkalosis may occur when lactate is metabolized (which results in bicarbonate production) following other resuscitative efforts. There is also evidence to suggest sodium bicarbonate is less effective at decreasing serum potassium concentration in human patients with hyperkalemia when compared to other treatment modalities [40]. For this reason, it is becoming less common in human ICUs as a monotherapy or as part of a combination therapy to treat hyperkalemia [40].

Nebulized albuterol has been prescribed in people for therapy of hyperkalemia, particularly in renal failure

patients receiving hemodialysis (10–20 mg monotherapy can reduce K^+ by 0.6–1.0 mEq/L [41] or 1.2 mEq/L when a 20 mg dose is combined with insulin) [42]. Studies investigating the use of inhaled or IV albuterol in hyperkalemic veterinary patients are lacking although the use of terbutaline has been described in a cat.

In most cases, the combination of IV fluid boluses, calcium gluconate, and IV dextrose with regular insulin will be sufficient to decrease hyperkalemia without the need for sodium bicarbonate or albuterol.

Acidosis

The acidosis seen with an acute adrenal crisis tends to be the result of hypoperfusion (causing decreased renal perfusion and lactic acidosis) rather than the direct effect of aldosterone deficiency on hydrogen excretion by the kidney. Therefore, most cases of acidosis will resolve following initial fluid resuscitation and rarely require treatment with sodium bicarbonate.

Glucocorticoids

Patients presenting in an acute adrenal crisis should have rapid-acting IV glucocorticoids administered as soon as possible. In veterinary medicine, dexamethasone (0.2–0.25 mg/kg IV q12–24h) is probably the most commonly used glucocorticoid as it can be given IV, is fast acting, and does not interfere with ACTH stimulation testing. Dexamethasone should be started concurrent with or as soon as possible following IV catheter placement and fluid resuscitation in patients with an acute adrenal crisis. Other glucocorticoids including prednisone, prednisolone, and hydrocortisone interfere with ACTH stimulation testing and should therefore be avoided until after a diagnosis is confirmed or stimulation testing has been performed.

There is no rapid-acting IV mineralocorticoid for treatment of an adrenal crisis and most animals in an adrenal crisis respond well to fluid therapy, correction of hyperkalemia, and IV dexamethasone. Mineralocorticoid therapy is not generally required until electrolytes have been corrected and the animal is stable following initial therapy. Mineralocorticoid administration should generally be avoided early in the course of treatment while serum sodium concentrations are still low, because they may increase sodium concentrations more quickly and predispose the patient to central pontine myelinolysis.

Chronic Management

Patients diagnosed with hypoadrenocorticism and classic electrolyte imbalances require lifelong glucocorticoid

and mineralocorticoid therapy. Patients with normal electrolytes diagnosed with primary hypoadrenocorticism require glucocorticoid therapy and close electrolyte monitoring as they are very likely to progress and require mineralocorticoid therapy. Patients with secondary hypoadrenocorticism will require lifelong glucocorticoid therapy but are very unlikely to need mineralocorticoid therapy.

Long-term mineralocorticoid supplementation in dogs can be provided by oral administration of fludrocortisone (0.02 mg/kg PO q24h or divided and given twice daily with a daily increase of 0.05–0.1 mg increments until serum electrolyte concentrations are stable). Fludrocortisone does have some glucocorticoid activity but some dogs may still need additional prednisone supplementation, particularly in stressful situations [14]. Alternatively, mineralocorticoid supplementation can be provided to dogs with an injection of deoxycorticosterone pivalate (DOCP; 2 mg/kg SC or IM q25 days) [35]. DOCP does not possess any glucocorticoid activity so prednisone (0.22 mg/kg PO SID) is often required concurrently. Cats are generally treated with DOCP (2.2 mg/kg or 12.5 mg/cat) SQ q3–4 weeks) and daily oral prednisone (0.22 mg/kg q24h) [43]. If cat owners are having difficulty with oral medications then methylprednisolone acetate (Depo-Medrol; 10 mg/cat SC every 3–4 weeks) has been suggested by some authors to replace oral prednisone therapy [14,43].

Complications

Major complications of an acute adrenal crisis are rare, but central pontine myelinolysis and acute renal failure have been reported [24,30,31]. Central pontine myelinolysis

results in neurological signs and is more likely in cases of severe chronic hyponatremia (>48 h) that is corrected too rapidly. Neurological signs may not occur until days to weeks after the crisis. Diagnosis of central pontine myelinolysis can be difficult, because it requires MRI and lesions may not be detectable with MRI for up to 4 weeks after an adrenal crisis.

There is no specific treatment for the condition and neurological abnormalities may be irreversible. There is evidence in humans that dexamethasone may be protective against the development of central pontine myelinolysis if administered early (within 3 hours of starting fluid therapy). Correcting sodium, no faster than 0.5 mEq/L/h, may also decrease the chances of occurrence. Acute renal failure is likely the result of hypoperfusion secondary to hypovolemia and decreased cardiac function leading to renal ischemia. Early aggressive therapy to improve hypoperfusion and close monitoring of renal parameters are recommended to decrease the likelihood of developing acute renal failure and to help differentiate the condition from prerenal azotemia that often accompanies an acute adrenal crisis.

Outcome

Prognosis for patients with hypoadrenocorticism is good to excellent following successful management of an acute adrenal crisis. Most dogs with hypoadrenocorticism die from unrelated diseases and a normal quality of life and life expectancy have been reported [24,43]. However, lifelong therapy is required and an increase in glucocorticoid therapy is often necessary during periods of stress (e.g. travel, surgery, etc.).

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Thyroid Disorders

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Introduction

Thyroid hormones are critical to the regulation of physiological homeostasis. Their activities directly affect the cellular functions of the entire body, including regulation of the basal metabolic rate, as well as the cardiopulmonary, musculoskeletal, nervous, and reproductive systems. Thyroid dysfunctions are the most commonly diagnosed endocrinopathies of small animals and their clinical sequelae vary widely from mild to severe disease.

Thyroid Physiology

The thyroid is a paired endocrine gland adjacent to the trachea and larynx. A set of parathyroid glands are closely associated with each thyroid within the cranial and caudal poles. Thyroid hormones are made within thyroid follicles where thyroid peroxidase iodine iodates thyroglobulin molecules to produce biologically active iodothyronines: tri-iodothyronine (T3) and tetraiodothyronine (T4). Inactive reverse tri-iodothyronine is produced in smaller amounts within the thyroid follicles. Thyroid hormone secretion relies on thyroid-stimulating hormone (TSH), which is released by the posterior pituitary under the negative feedback of T3 and T4. Disease states and drugs, such as glucocorticoids, can also cause negative feedback on the posterior pituitary (reducing secretion of TSH).

Thyroid hormones act by crossing into the cell and increasing synthesis of proteins involved with cellular metabolism. Despite being the biologically active form, T3 is only produced in small amounts (roughly 10%) by the thyroid. Most T3 is formed within target cells or through peripheral conversion of T4 by organs (liver, kidneys, and skeletal muscle). Tyrosine-specific deiodinases cleave iodine moieties from T4 to produce active T3. T4 is the major thyroid hormone in plasma and can

be measured as either free, unbound T4 (fT4) or total (free and protein bound) T4 (tT4).

Once formed, iodothyronines are stored within the lumen of the follicle in a substance known as colloid. Following release from the thyroid, most hormones remain protein bound within peripheral circulation. The high affinity for protein binding buffers concentrations of these hormones that can result from acute change in thyroid function. This binding also helps to prevent urinary loss.

Thyroid-stimulating hormone affects all aspects of thyroid production and regulation. In normal states, thyroid hormones have little diurnal fluctuation. However, illness can cause reduced production of thyroid hormones due to the increased plasma glucocorticoid concentrations. This can also serve to retain resources in times of disease when the catabolic effects of thyroid hormones could be detrimental.

Non-thyroidal conditions can affect thyroid production and measurement. Breed and age variations are well documented; geriatric dogs and sighthounds have been shown to have lower thyroid hormone concentrations than control populations. Euthyroid sick syndrome refers to a condition in which thyroid hormone production is reduced due to concurrent non-thyroidal illness. The degree of inhibition is often related to the severity of disease. Non-thyroidal illness including renal, hepatic, endocrine, cardiac, neurological, neoplastic, and inflammatory diseases have all been documented as causes of euthyroid sick syndrome. Euthyroid sick syndrome has been well documented in many species, including both dog and human [1–4].

Thyroid Testing

The diagnosis of thyroid dysfunction can be challenging due to the effect of non-thyroidal illness on circulating thyroid hormone concentrations. There are many

hormones involved with thyroid function and commercial assays are available for most. Despite not being the most biologically active, T4 remains the most sensitive indicator of thyroid dysfunction. This is because roughly 90% of the extracellular pool of thyroid hormones is stored as T4. T4 can be measured as either total T4 or free T4. Testing of total T4 tends to be more cost-effective and rapid in turnaround, although it is also more affected by non-thyroidal illness as decreases in thyroid-binding proteins often reflect systemic disease rather than endocrine dysfunction.

Thyroid-stimulating hormone can be measured in both dogs and cats, although its utility in the diagnosis of feline hyperthyroidism remains questionable [4]. T3 is an unreliable indicator of thyroid function as it is mostly an intracellular hormone and is degraded rapidly in circulation.

Hyperthyroidism

Hyperthyroidism refers to the excessive release of thyroid hormones. In most cases this is a result of primary disease (autonomous secretion) due to hyperplasia or neoplasia. Hyperthyroidism is the most common endocrinopathy of geriatric cats and is generally caused by either a single adenoma or, more often, bilateral hyperplasia or adenomatous hyperplasia. The pathogenesis leading to feline hyperthyroidism is not well understood and studies investigating nutritional and environmental risk factors have yet to find compelling evidence of its etiology [5–7]. Canine hyperthyroidism is rare and usually the result of thyroid carcinoma, excessive iatrogenic supplementation or dietary intake [8,9].

Hypothyroidism

Hypothyroidism refers to an insufficient production of thyroid hormones and may result from decreased TSH stimulation (secondary hypothyroidism) or decreased production of thyroxine within the thyroid gland due to destructive or infiltrative disease (primary hypothyroidism). Naturally occurring hypothyroidism is most often a result of immune-mediated destruction of the thyroid (lymphoplasmacytic thyroiditis). Hypothyroidism is the most frequently diagnosed endocrinopathy of dogs though it is quite rare in cats.

Clinical Presentations

Hyperthyroidism

Clinical Signs

The clinical signs common to hyperthyroidism reflect the increased metabolic demands of excessive thyroid

hormone concentrations. These include polyphagia with weight loss, polyuria/polydipsia, restlessness or altered behavior, vomiting, and diarrhea. Hyperthyroid cats may appear to seek out cool areas, be less interactive with others, and groom sporadically.

Diagnosis

Diagnosis of hyperthyroidism is established by suspicion of disease along with documentation of elevated thyroid values. fT4 and tT4 measurements both have good sensitivity for disease, although tT4 appears to be more specific. TSH is not generally measured in cats with hyperthyroidism since its concentration might fall below the limit of detection [4].

All cats with hyperactive thyroid tissue will have an enlarged thyroid, although it is not always palpable in cases of ectopic disease, metastatic disease or in large adenomas, which sink into the thoracic inlet.

Treatment

Treatment of hyperthyroidism is aimed at restoration of normal thyroid hormone production either by mitigation or destruction of the overactive thyroid tissue. Medical, surgical, and radiation therapies have been shown to be effective in restoration of this balance [10].

Methimazole, a reversible inhibitor of thyroid peroxidase, has been demonstrated to be effective in the control of both hyperthyroid dogs and cats and can be administered by mouth or topically (usually on the ear pinna) [11]. The starting dose is typically 1.25–2.5 mg per cat once to twice daily. Dosing should be adjusted based on clinical response and follow-up measurement of tT4. Although it is highly effective, side-effects are encountered in up to 44% of cats who receive this medication [12]. Most side-effects relate to the gastrointestinal tract and may be transient in nature, but more severe sequelae such as hepatotoxicity, myelotoxicity, dermatitis, and neuromuscular blockade have been reported [12–14]. These effects are idiosyncratic and do not appear to be dose dependent [14].

A diet deficient in dietary iodide (Hill's Prescription y/d Diet) has been approved and marketed for the treatment of hyperthyroidism in cats. By eliminating dietary intake of iodide, the hyperfunctional thyroid gland is unable to produce excessive thyroid hormones which allows for restoration of more normal values [15]. Unfortunately, ingestion of even a small amount of iodine-containing food can undermine this treatment, so appropriate case selection and client education are critical to the success of this therapy.

Permanent resolution of hyperthyroidism can be achieved via surgical thyroidectomy or administration of radioactive iodine¹³¹.

Hypertensive Retinopathy

Acute blindness is a common opthalmic reason for presentation of cats and dogs to the general practitioner or emergency clinician. Hypertensive retinopathy is the most common reason for acute blindness in the geriatric cat. Upon diagnosis of systemic hypertension, rapid diagnosis of the underlying pathology and pharmacological intervention to control hypertension should be initiated as vision loss is often irreversible and likely inevitable beyond 10–14 days. See Chapters 12 and Chapter 63 for further information.

Physical Examination

Patients with hypertensive retinopathy typically present with mydriasis, although the anterior chamber is generally unaffected. Fundic examination reveals retinal separation, hemorrhage or tortuous vasculature. Some patients might present with hyphema.

Diagnosis

The combination of systemic hypertension and retinal changes described above confirms the diagnosis of hypertensive retinopathy. The practitioner should focus on the diagnosis of the cause of systemic hypertension (Table 116.1).

Treatment

Rapid initiation of antihypertensive medications is indicated. Most often, amlodipine (0.625 mg/cat or 0.1–0.3 mg/kg PO once daily) is effective in controlling systemic hypertension. In refractory cases, acepromazine or hydralazine can be considered.

Thyroid Storm

Thyroid storm or thyrotoxicosis is a rare consequence of uncontrolled hyperthyroidism in human patients that has not been well described in cats. Clinical signs of thyroid storm reflect an acute exacerbation of hyperthyroidism, including fever and perturbations of the cardiovascular, gastrointestinal, and central nervous systems. Although the pathogenesis of thyrotoxicosis is unknown,

there is evidence to suggest that its incidence is more closely correlated to rapid increases in thyroid hormone concentrations rather than absolute values [16,17].

Thyroid storm may occur due to either thyroidal or non-thyroidal disease. Thyroidal causes include I-131 administration, thyroid surgery or abrupt withdrawal of antithyroid medication. Non-thyroidal causes include non-thyroidal surgery, infection, stress or trauma.

Clinical Signs

The clinical signs associated with a thyroid storm are similar to those seen with hyperthyroidism although, as a consequence of thyrotoxicosis, are likely more severe. Cats may become profoundly tachycardic and tachypneic, resulting in decreased systolic function and respiratory fatigue. Fever has also been reported in cats suspected of having a thyroid storm [18].

Diagnosis

No guidelines exist for the diagnosis of feline thyroid storm; its diagnosis is based on the presence of compelling clinical signs, documentation of elevated thyroid hormone concentrations, and evidence of an event or events leading to its occurrence. Hormone levels cannot be used to determine its severity as evidence in human medical literature suggests a lack of correlation between hormone concentration and severity of clinical signs.

Treatment

The goals of treatment are to reduce thyroid hormone production, decrease the effects of systemic thyroid hormones, and identify (or preferably eliminate) the factor leading to its occurrence.

Methimazole is a highly effective drug; its activity inhibits the iodination of tyrosine into thyroid hormones. It can be administered by mouth, transdermal or per rectum. Beta-blockers and antihypertensives (such as amlodipine or hydralazine) can be effective in reducing sympathetic tone and restoring normal blood pressure (see Chapter 63). Crystalloids should be administered judiciously to patients who appear volume depleted; close monitoring is essential to avoid fluid overload as the cardiotoxic effects of thyroid hormone predispose to hypertrophic changes and may result in cardiomyopathy (see Chapter 167).

Iatrogenic Hyperthyroidism

Hyperthyroidism can result from inadvertent oversupplementation of thyroid hormone either by supplementation of thyroid hormones or ingestion of thyroid-containing offal [8,9]. In many instances, patients with iatrogenic hyperthyroidism lack clinical signs of the disease. Diagnosis of this condition stems from identification and

Table 116.1 Common differentials for systemic hypertension.

Dog	Dog or cat	Cat
Hyperadrenocorticism	Diabetes mellitus	Hyperaldosteronism
Pheochromocytoma	Renal insufficiency	Hyperthyroidism
	Idiopathic	

withdrawal of the causative agent, leading to resolution of the thyroid hormone imbalance.

Hypothyroidism

Clinical Signs

Clinical signs of hypothyroidism are often mild and non-specific and include lethargy, weight gain, decreased appetite or stamina. Dermatological findings such as endocrine (bilateral, truncal, and non-pruritic) alopecia or rat tail are common. Intact animals may lack libido or have increased rates of reproductive failure. Less common signs include neurological disease such as seizures, vestibular disease, stupor or coma.

Diagnosis

Diagnosis of true hypothyroidism can be challenging due to the influence of other systemic disorders on the pituitary-thyroid axis. Since the common clinical signs of hypothyroidism mimic those of other metabolic diseases which cause euthyroid sick syndrome, the clinician must be careful to not overinterpret a single low thyroid hormone concentration [2]. In order to raise the suspicion of disease, the clinician must initially identify compatible clinical signs. Only these patients should have thyroid testing as routine testing of healthy animals will lower the predictive value of these tests. Identification of other clinicopathological features such as a mild, non-regenerative anemia or hyperlipidemia may also provoke evaluation of thyroid function.

Total T4 is the most commonly measured thyroid hormone used in the diagnosis of hypothyroidism and remains the most sensitive indicator of disease. Unfortunately, due to the effects of protein binding related to systemic disease, it lacks specificity. However, a low tT4 in a dog with compelling clinical signs, physical examination findings and clinicopathological changes might be sufficient for diagnosis [19]. In other patients with co-morbidities that could affect thyroid function or

hormone concentration, measurement of fT4, TSH, and thyroglobulin autoantibodies can be helpful in the diagnosis of true hypothyroidism [20].

Treatment

Treatment of hypothyroidism, whether primary or secondary, involves thyroid hormone replacement therapy. Levothyroxine is administered by mouth at a dose of 0.01–0.02 mg/kg twice daily. Dosing should be adjusted based on response to therapy and recheck measurement of tT4. Side-effects of levothyroxine are rare, although there are anecdotal reports of brand names being more effective than generic formulations. Thyro-tabs (Lloyd Inc, Shenandoah, IA) are the only FDA-approved oral thyroid supplementation for use in dogs.

Myxedema Coma

Myxedema, or cutaneous mucinosis, is a severe consequence of protracted, untreated hypothyroidism that leads to hyaluronic acid accumulation within the dermis. This leads to accumulation of extracellular fluid and skin thickening. Dogs with myxedema are described as having a “tragic facial expression” characterized by ectropion and a puffy face. When left untreated, this condition may progress to generalized weakness, bradycardia, hypothermia, and, eventually, coma or death. Myxedema may be triggered by the development of concurrent disease [21].

Treatment

Treatment of myxedema relies on parenteral supplementation of thyroid hormone, stabilization of the patient including fluid resuscitation, controlled warming and, in some cases, mechanical ventilation [21]. Since myxedema is often precipitated by concurrent non-thyroidal illness, quick identification and diagnosis of co-morbidities is essential in its treatment. Unfortunately, many dogs with myxedema die due to lack of diagnosis or severity of concurrent disease precluding their stabilization and resuscitation.

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Diabetes Insipidus

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Introduction

Diabetes insipidus (DI) causes polyuria (PU) due to inadequate free water reabsorption in the kidney in dogs and cats. It is an uncommon disease in small animals, and is rarely the primary diagnosis in a dog or cat seen on an emergency basis. Occasionally, a patient may present for an unrelated problem, and pre-existing, undiagnosed DI may be uncovered during a hospital stay. Alternatively, newly acquired DI may develop as a result of another condition. The purpose of this chapter is to help the clinician recognize DI in emergency patients and treat it appropriately in the short term.

Pathophysiology

Arginine vasopressin (AVP), also called antidiuretic hormone (ADH), is produced by the supraoptic and paraventricular nuclei of the hypothalamus and released from the posterior pituitary gland. It acts on the principal cells of the renal collecting tubules to allow electrolyte-free water reabsorption in this normally water-impermeable region of the nephron. Arginine vasopressin is released due to either plasma hyperosmolality or ineffective circulating volume. A plasma osmolality as little as 1–2% above an individual's set-point stimulates central chemoreceptors and leads to AVP secretion [1].

After AVP is released, it binds vasopressin 2 (V_2) receptors on the basolateral membrane of the renal collecting tubule's principal cells. Stimulation of the V_2 receptor activates a G-protein coupled to adenylyl cyclase, which is stimulated to increase intracellular cyclic AMP, leading to protein kinase A activation and resultant insertion of specialized water channels into the collecting tubule cell's luminal membrane. These water channels are composed of aquaporin-2 molecules, which are stored in cytosolic vesicles until this AVP-dependent cascade

leads to their translocation to the luminal membrane. Aquaporin-2 water channels allow electrolyte-free water to be reabsorbed from the ultrafiltrate in the nephron's tubular lumen into the relatively hypertonic medulla, which decreases plasma osmolality back toward normal.

When AVP is produced in inadequate amounts or not at all, or when AVP is ineffective at its target cell, the patient is unable to reabsorb water adequately in the kidney. As a result, a large volume of very dilute urine is produced and the animal drinks excessively to compensate for the water loss. This problem is called diabetes insipidus. Diabetes insipidus may be due to pituitary disease, in which case it is called "central," or due to disease at the level of the collecting tubule cell, in which case it is called "nephrogenic." Nephrogenic DI is usually due to a problem with the V_2 receptor or aquaporin-2 water channel [2]. Both central and nephrogenic DI can be either congenital ("primary") or acquired ("secondary"), although congenital nephrogenic DI has not been reported in the cat [3]. Reported causes of acquired DI in dogs and cats, many of which are seen in the emergency room, are listed in Table 117.1. Finally, DI may be "complete," which implies a complete lack of AVP production or responsiveness, or "partial," which indicates that AVP production or responsiveness is present but inadequate. Animals with complete DI are more severely clinically affected than those with partial DI.

Recognizing Diabetes Insipidus in the Emergency Patient

Diabetes insipidus is rarely seen in the emergency room. In this author's experience, when DI is seen in this setting, it is most often an incidental or secondary finding. Diabetes insipidus may have been a pre-existing condition that the client did not recognize, particularly if the pet lives outdoors or is largely unattended. In such

Table 117.1 Causes of acquired diabetes insipidus.

Central	Nephrogenic
Traumatic brain injury [4–9]	Paraneoplastic – intestinal leiomyosarcoma in the dog [2,10]
Neoplasia [11–14]	Hypercalcemia [2,3]
Pituitary surgery [15,16]	Hypokalemia [2,3]
Post cardiopulmonary arrest [17]	Leptospirosis [18]
Inflammation [19,20]	Ureteral obstruction [2]
Idiopathic	Kidney failure [2]
Drugs [3]:	Drugs [3]:
Alpha-adrenergics	Alpha-adrenergics
Glucocorticoids	Barbiturates
Ethanol	Glucocorticoids
Phenytoin	Tetracyclines
	Vinca alkaloids
Parasite migration	<i>E. coli</i> endotoxin [3]

cases, DI may be uncovered once PU, polydipsia (PD), or hypernatremia is noted during hospitalization. Alternatively, newly acquired DI may appear secondary to a separate, new condition such as traumatic brain injury, intracranial neoplasia, electrolyte imbalance, or medication (see Table 117.1).

History

Polyuria is the most prominent and reliable clinical sign in patients with DI. The PU is generally profound, although its degree depends on whether the DI is complete or partial and, if partial, how severe. Patients with access to water and able to drink will also be polydipsic. Clients may not appreciate that their pet’s urination and drinking habits are abnormal, or the DI may be acquired due to a new problem; thus, lack of reported historical PU/PD does not rule out the diagnosis. Dogs with DI often also have urinary incontinence [14].

As shown in Table 117.1, there are many causes of acquired DI seen in emergency room patients. Therefore, DI should be considered in the patient with any of these conditions that develops PU, PD, inappropriately low urine specific gravity (USG), or hypernatremia. Figure 117.1 provides a diagnostic algorithm for the recognition of DI.

Physical Examination

Compensated DI does not produce physical examination abnormalities because patients drink water to offset their excessive urinary losses. However, if water intake is inadequate, marked hypernatremia can develop and cause central nervous system signs such as obtundation, head pressing, or seizures. Clinical interstitial dehydration

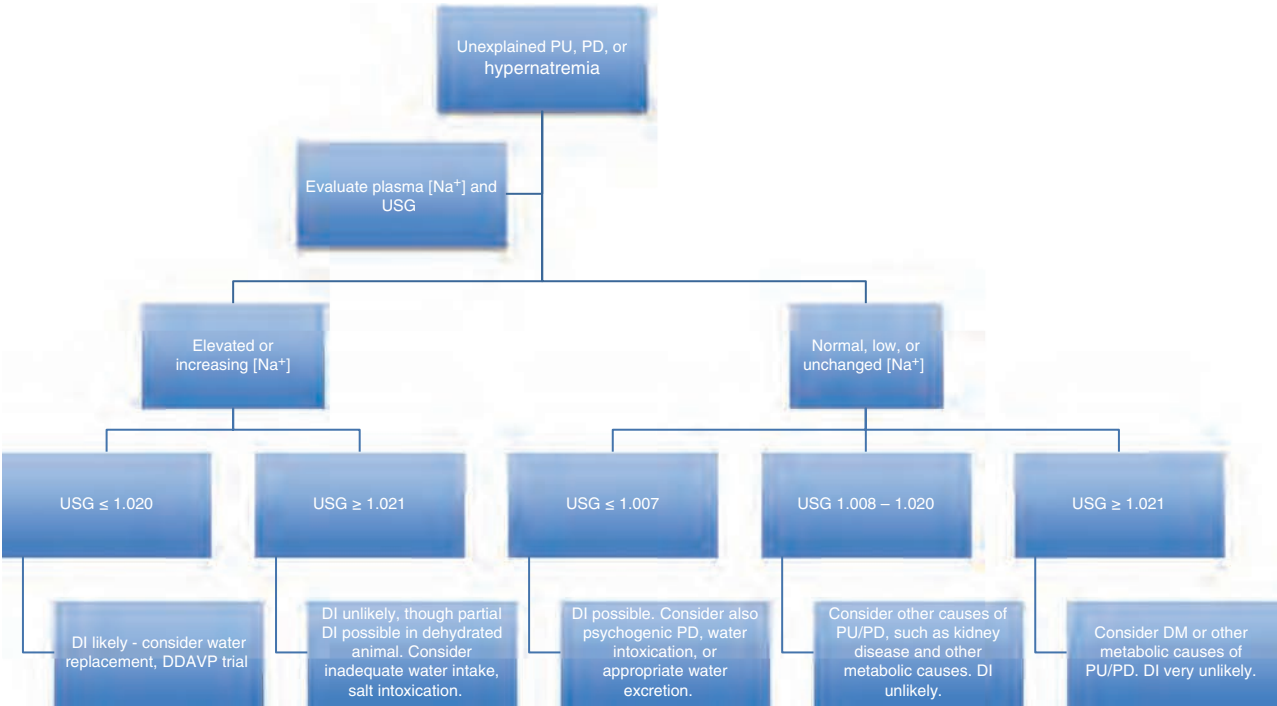


Figure 117.1 Schematic representation of one approach to the clinical evaluation of unexplained PU, PD, or hypernatremia in the acutely ill animal.

may be seen in decompensated patients. However, most patients with DI have no specific physical examination abnormalities attributable to the disease.

Clinicopathological Abnormalities

The patient with DI generally has hyposthenuric to isosthenuric USG due to excessive free water in the urine, although partial DI patients that are $\geq 5\%$ dehydrated may have a USG as high as 1.020 or greater. [3]. Urine osmolality is generally iso-osmolar to plasma (280–310 mOsm/kg), although dehydrated patients with partial DI may be able to achieve urine osmolalities ≥ 600 mOsm/kg [3]. Patients with DI that do not take in enough water to compensate for their urinary water loss develop hypernatremia, although normally compensated individuals allowed to drink water freely may be normo- or even hyponatremic [14]. Emergency room and hospitalized patients with DI can develop clinically important hypernatremia in just a few hours, particularly if their DI is severe, because they are often either unable or disallowed to drink water. This hypernatremia can occur regardless of physical examination hydration findings or blood volume status, and thus must be found by blood electrolyte monitoring. Electrolytes should be evaluated in any animal with unexplained PU, and hypernatremia should increase the suspicion for DI.

One investigation found that 24% of dogs with central DI whose urine was cultured had bacterial cystitis [14].

Definitive Diagnosis

When DI occurs in an emergency setting, a formal definitive diagnosis often cannot be made. The two most common methods for diagnosis, response to exogenous AVP and the modified water deprivation test, often require more time than is practical in the emergency room.

Response to Exogenous AVP

Patients with central DI show improvement in polyuria and hypernatremia with administration of exogenous AVP, usually in the form of desmopressin acetate (DDAVP). Thus, a DDAVP trial may help in diagnosis. Injectable DDAVP can be given at 5 μ g SC and the urine evaluated 2 and 4 hours later. Injectable synthetic aqueous vasopressin can be given at 0.2–0.4 U/kg up to a maximum of 5 U/kg IM; urine is evaluated 30, 60, and 120 minutes following injection [3].

Another option is the intranasal desmopressin acetate preparation, which can be administered subconjunctivally to dogs and cats at a dose of 1–2 drops OU every 12–24 hours.

An increase in USG of $\geq 50\%$ after exogenous AVP administration is consistent with a diagnosis of central DI

[3]. Although it may take patients with decreased renal medullary tonicity (“medullary washout”) many days to respond to exogenous AVP, a subconjunctival DDAVP trial has been described as a fairly quick diagnostic method for central DI in a critically ill dog [17]. Patients with nephrogenic DI generally do not respond to AVP, so response to exogenous AVP cannot be used to rule out that disease.

Modified Water Deprivation Test

The traditional test for DI is the modified water deprivation test, in which a pet is not allowed any intake (oral, intravenous, or otherwise) until it loses 3% of its body weight in urine, at which time USG is measured and the animal is administered exogenous vasopressin to evaluate for response with injectable AVP as described above. The test can be used to distinguish partial from complete and central from nephrogenic DI. Full details of this test are available elsewhere [3].

For obvious reasons, the modified water deprivation test is not appropriate for emergency room patients. Additionally, it can be dangerous even in stable animals, and can lead to misdiagnoses [21].

Although a formal, definitive diagnosis often cannot be made in this setting, recognition and supportive care for DI in the emergency room are critical. In the sick, hospitalized patient, DI is strongly suspected when a combination of polyuria with lower than expected USG (generally ≤ 1.020 , commonly < 1.008) [3] and hypernatremia is present. In this author's experience, it is usually progressive hypernatremia on routine, serial blood work that initially suggests DI. The patient is then treated for hypernatremia and polyuria.

Treatment

Emergency room patients with DI usually have hypernatremia because they have an obligate urinary free water loss and are not drinking enough water to compensate for it, either because of their illness or because water is being withheld.

Water Replacement

Hypernatremia should be treated, even if it is not causing obvious clinical signs. Treatment involves free water administration, usually in the form of intravenous 5% dextrose in water or oral water intake. The dose and rate of water administration need to be carefully determined. A full discussion of the treatment of hypernatremia is provided in Chapter 108. During treatment, plasma $[\text{Na}^+]$ should be measured no less often than every 4 hours and the fluid administration rate adjusted accordingly, to ensure an appropriate rate of correction.

AVP Administration

Once the plasma $[Na^+]$ reaches a safe value (probably the high end of the reference interval), initiation of subconjunctival DDAVP at 1–2 drops OU every 12–24 hours is reasonable. Starting DDAVP when the patient is still hypernatremic can be done, but this method risks an overly rapid drop in plasma $[Na^+]$, which can cause cerebral edema. Oral DDAVP can also be used; reported doses are 0.1–0.2 mg in dogs [3] and 0.025–0.05 mg in cats [4] every 8–12 hours.

Complications of Treatment – Cerebral Edema

Overly rapid correction of plasma $[Na^+]$ can cause cerebral edema due to water shifting into comparatively hyperosmolar brain tissue. Patients with hypernatremia should be monitored for obtundation, head pressing, seizures, or other central nervous system abnormalities. If the patient develops such signs, plasma $[Na^+]$ should be measured to confirm that it is less than when treatment was initiated. This step is important because the clinical signs of progressive hypernatremia can be similar to signs of overzealous correction. If plasma $[Na^+]$ has dropped, the patient should be treated with mannitol 0.5–1 g/kg IV or 7.2% NaCl at 3–5 mL/kg over 20–30 minutes. Administration should ideally be through a central vein, and if the first dose is ineffective, a second dose or other

medication may be tried. Hypertonic saline should not be administered rapidly because it can cause vasodilation and hypotension when given as a rapid bolus.

Patient Discharge

If signs persist beyond hospital discharge, the pet should be referred to its general practitioner or an internal medicine specialist for definitive testing for DI. In the meantime, free access to ample fresh water must be provided once the pet returns home, and the client should be warned about expected polyuria.

Prognosis

The prognosis for DI varies by etiology. Patients with congenital central DI are often successfully treated with DDAVP. Patients with congenital nephrogenic DI can be treated with sodium restriction and thiazide diuretics [3,22], but marked PU/PD usually persists and so these patients generally require lifelong ample free water access and tolerant owners. Patients with acquired DI may see resolution if the underlying cause can be eliminated. However, one study found that dogs with acquired central DI often have underlying brain neoplasia, which commonly leads to euthanasia or death within months of diagnosis [14].

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H. Reproductive Disorders

Dystocia

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Female Reproductive Anatomy and the Physiology of Parturition

Anatomy

The genital organs of the bitch and queen consist of two ovaries, two fallopian (ovarian) tubes, a bicornuate uterus, a single cervix, the vagina, the vulva, and the mammary glands [1].

The bitch and the queen have a long vagina, short uterine body, and long uterine horns. The ovaries and ovarian tubes receive blood supply from the ovarian arteries, whereas the vagina receives blood supply via the vaginal artery. The major blood supply of the uterus is via the uterine artery, but the cranial and caudal aspects of the uterus receive some blood supply via the ovarian and vaginal arteries respectively [2].

The female reproductive tract is innervated by both sympathetic and parasympathetic nerve fibers. Sympathetic innervation of the ovary runs concurrently with the ovarian artery, while sympathetic innervation of the uterus and vagina forms plexuses both within the respective organs and within the broad ligament (having arisen from retroperitoneal pelvic tissue) [3]. Parasympathetic nerve fibers arise from the pelvic nerves and innervate via the pelvic plexus [3].

Physiology of Parturition

The progesterone required to maintain pregnancy in the bitch is secreted by the corpus luteum [2]. Progesterone concentration is not markedly different between pregnant bitches and non-pregnant bitches [4,5]. Peak progesterone levels are reached at approximately day 20–30 of pregnancy, ranging between 15 and 80 ng/mL. After this time, progesterone levels steadily decline. In order to

maintain pregnancy, progesterone concentration must be maintained above a minimum concentration of 2 ng/mL [4,5].

The signal for parturition is thought to be fetal. Maturation of the fetal adrenal cortices results in cortisol release from the fetal adrenal gland [5] which in turn results in increased estrogen secretion by ovarian tissue through day 45–60 of pregnancy [6]. Estrogen stimulates the upregulation of genes encoding myometrial contraction-associated proteins, and promotes prostaglandin release from the uteroplacental complex (now thought to be primarily trophoblastic cells) [7,8]. Prostaglandin E2 (PGE2) produced is luteolytic, resulting in corpus luteum regression and a reduction in circulating progesterone [9]. As a result of the luteolytic effect of PGE2, progesterone concentration rapidly drops from a range of 4–10 ng/mL to approximately 2 ng/mL over a 12–24-hour period toward the end of pregnancy [5]. Falling progesterone is believed to cause a rise in circulating prolactin, and subsequently lactation [5]. Parturition occurs 24–48 hours following the rapid decline in circulating progesterone [5].

Prostaglandin F2-alpha plays a key role in increasing the sensitivity of the myometrium to oxytocin. This in turn facilitates smooth muscle contraction, and softening of the cervix [5].

Oxytocin also plays a role in parturition. Oxytocin is secreted via the posterior pituitary gland in response to increased pressure placed upon the cervix. Oxytocin release results in activation of a sensory pathway that ultimately terminates in the paraventricular nucleus of the hypothalamus. Neural impulses are then sent to the posterior pituitary resulting in the release of oxytocin. Oxytocin in turn increases myometrial contractility.

Estimating Expected Date of Parturition

Using mating date as the basis for estimating parturition date in the bitch is unreliable, with parturition possible at any point 57–72 days post mating [10]. Causes for variation in expected parturition date include the variable time at which a bitch may stand to be mated relative to time of ovulation, prolonged life of the oocyte and the length of time spermatozoa can survive in the reproductive tract of the bitch [10,11].

Vaginal cytology and endocrinology can give a better indicator of expected parturition date. Parturition occurs 57+/- 3 days following the onset of cytological diestrus in the bitch [11,12]. Onset of cytological diestrus is indicated through a sudden shift from primarily superficial cornified cells (>90%) (seen throughout estrus) to approx 50% non-cornified parabasal and intermediate cells within 24 hours of onset of diestrus [13]. Serum luteinizing hormone or progesterone can be used as markers to predict parturition. Parturition typically occurs 65 days after a peak in LH [11,12]. At the time of ovulation, progesterone concentration typically measures 4–10 ng/mL. Parturition occurs 63 days (+/-1) following the date of ovulation [12].

Transabdominal ultrasonography can be used to predict parturition date. There is relatively good predictive accuracy when at least two fetal parameters (fetal crown rump length and body diameter) are measured on more than two fetuses between day 30 and 39 of pregnancy [14,15].

There can be large variation in expected parturition date in the queen if date of mating is used as the marker for expected date of parturition. Parturition in the queen can range from 52 to 74 days depending on whether gestation was timed from the first or the last date of breeding.

Stages of Parturition

There are three distinct stages of parturition (Table 118.1). Literature regarding expected duration of each stage of parturition is anecdotal. Whether a clinician should intervene with parturition should be based upon indicators of dystocia and the patient, rather than anecdotal expectations.

Dystocia

Dystocia is defined as an inability to expel the fetus(es) from the uterus or birth canal [17].

Risk Factors

Brachycephalic and chondrodysplastic canine breeds are generally overrepresented with respect to dystocia,

Table 118.1 Stages of parturition.

Stage of parturition	Expected duration	Characterized by
Stage 1	6–12 hours (bitch and queen)	Nesting behavior [10,12,16] Subclinical uterine contractions Dilation of the cervix Uterine contractions
Stage 2	2–12 hours (bitch) Up to 24 hours (queen)	Overt abdominal contractions Expulsion of fetus(es) from vaginal canal
Stage 3	Varies with stage 2 parturition	Placental expulsion [1,2,4] Uterine involution

as are brachycephalic (e.g. Persian and British short-hair) and dolichocephalic (e.g. Siamese and Cornish rex) breeds in cats [18,19]. The underlying cause for the overrepresentation of these breeds is likely the result of congenitally narrowed birth canals and maternal–fetal disproportion [10].

Other risk factors for dystocia include small litter size, excessive litter size, increased age of the bitch, and underlying metabolic disease resulting in uterine inertia [20–22].

Literature is devoid of studies exploring a potential cause for a perceived high probability of dystocia in singleton pregnancies. It is proposed that the fetal signal required to initiate parturition is insufficient, perhaps resulting in a failure of production of luteolytic hormone and subsequently no prepartum drop in progesterone. As such, dams fail to demonstrate some premonitory signs of parturition (for instance, no lactation prior to parturition), have delayed parturition or may fail to enter stage 1 or stage 2 of parturition.

Classifying Dystocia

Dystocia can be classified by the manner of presentation (clinical category), or by underlying etiology.

In divergence from previous literature that is extrapolated from large animal obstetrics studies, we propose a new manner of classifying small animal dystocia based upon the clinical presentation of the patient [23]. The manner of presentation of a patient suffering dystocia can be classified into four clinical categories (Box 118.1).

The aetiology for dystocia is best divided into maternal and fetal causes (Table 118.2). Dystocia has been found to be of maternal origin in 13% of cases, fetal in 37% of

Box 118.1 Clinical categories of small animal dystocia.**Failure to begin stage 2 labor**

Cessation of stage 2 labor before completion
 Prolonged unproductive stage 2 labor
 Apparently normal stage 2 labor with fetal distress

cases, and attributable to small litter size in 17% of cases [18]. Approximately one-third of dystocia cases do not have a clear underlying cause attributed even after surgical intervention [18].

The majority of fetal causes of dystocia are the result of malpresentation [22]. The presentation of the fetus in the birth canal is categorized three ways.

- **Presentation:** anterior, posterior or transverse.
- **Position:** the positioning of the fetal spine in relation to the dam's pelvis.
- **Posture:** how the fetus' limbs and head are positioned in relation to the body.

Up to 40% of canine fetuses are born in a posterior presentation [24]. Causes of malpresentation can include but are not limited to transverse presentations, an anterior presentation with retention of the forelimbs, a posterior presentation with retention of the hindlimbs, or lateral or ventroflexion of the neck.

When is Examination of the Bitch or Queen Warranted?

Owners frequently call with concerns during parturition. The challenge is to determine if there is a reason for

Table 118.2 Attributable causes of dystocia.

Physiological	Anatomical
Maternal	
Primary uterine inertia	Primary:
Secondary uterine inertia	Abnormal pelvic canal size
Stress/environmental factors	Secondary:
Reduced abdominal muscle tone (high body condition score, old age)	Pelvic fracture
Hereditary/genetic	Uterine torsion
Estrogen/progesterone abnormalities	Uterine prolapse
Hypocalcaemia	Vaginal mass
Inadequate oxytocin release	Vaginal stricture
Fetal	
Malpresentation	
Fetal oversize	
Anasarca and other fetal malformation	
Fetal death and subsequent reduced cortisol release	

Box 118.2 Indicators for clinical examination.

- Client concern
- Signs of systemic illness
- Decline in body temperature, followed by return to normal temperature with no progression into labor
- Stage 1 labor extends beyond 12 hours with no evidence of progression
- No puppy within 2 hours of entering stage 2 labor (or no kitten within 1 hour) [10,24]
- Forceful abdominal contractions and no fetus within a 30-minute period [24]
- Intermittent abdominal contractions with no fetus delivered within a 2-hour period
- If pregnancy extends beyond 72 days with no progression into labor
- Stillborn fetuses are passed
- Uteroverdin in vaginal discharge but no puppy or kitten passed within 2 hours

the dam to be transported to the veterinary facility for examination. Unnecessary transport of the dam may be disruptive to normal parturition and should be avoided if possible.

Examination is indicated under specific conditions as outlined in Box 118.2.

Clinical Examination**History**

History should include expected whelping date, previous diagnostics (e.g. endocrinology or vaginal cytology at time of mating), breed of sire, parity, expected litter size, and underlying medical conditions.

Physical Examination

The physical should encompass assessment of vital signs, mucous membrane colour and refill, femoral and metatarsal pulse quality, thoracic auscultation, abdominal palpation, and, mammary, vaginal, and rectal examination.

Diagnostics

Diagnostics should consist of blood biochemistry and hematology, blood gas (including ionized calcium), and electrolytes. Assessing serum progesterone is warranted if the whelping date has been exceeded and the female fails to demonstrate signs of active labor. Radiography is warranted to confirm pregnancy, ensure cessation of parturition, or to assess for abnormalities such as gas in the uterus, or a fetus positioned in transverse presentation.

Sonography is the modality of choice for dystocia. Ultrasound can diagnose fetal distress via assessment of

fetal heart rate. Normal fetal heart rate should be in the range of 200–220 beats per minute. Fetal bradycardia is a sign of fetal distress and warrants intervention. If fetal heart rate is below 180 beats per minute, intervention may be indicated [10,25,26].

Indicators for Intervention

Veterinary intervention is warranted if:

- there is obstruction (diagnosed on vaginal examination, radiography or sonography) (Figure 118.1)
- the bitch/queen has not entered labor, and progesterone is <2 ng/mL
- the bitch/queen is systemically ill
- fetal heart rate is deemed bradycardic (<160 to 180 beats per minute) at term
- there is suspicion of uterine rupture or torsion.

Medical Management of Dystocia

Medical management of dystocia is controversial; the use of ecbolics such as oxytocin is often contraindicated, and can result in poor outcomes. Medical management in the bitch typically results in a parturition success rate of approximately 30% [20]. Finding an appropriate medical candidate in itself is difficult (Box 118.3).

Box 118.3 Prerequisites for a candidate to be treated via medical means [16,25].

Labor has not been prolonged
Cervix is dilated
Fetal size is within limits for vaginal delivery
Obstructive causes of dystocia have been ruled out

If medical management is chosen, electrolyte or acid–base abnormalities should be corrected prior to administering supplemental calcium or glucose. If the bitch is found to have low ionized calcium, 10% calcium gluconate 0.2 mL/kg can be administered IV [27]. Intravenous calcium should be administered as a constant-rate infusion (CRI) over a matter of minutes, while heart rate and rhythm are monitored with ECG and concurrent thoracic auscultation [16,27].

Hypoglycemia can be corrected with dextrose at a dose rate of 0.25–0.5 g/kg, diluted 1:2 with 0.9% NaCl. This should be administered over a 10-minute period as a CRI [28].

If the criteria for medical management are met, oxytocin can be administered at a dose rate of 0.5–2 IU SC or IM [29]. Oxytocin is best used in conjunction with calcium gluconate, with oxytocin stimulating smooth muscle contraction and calcium gluconate increasing the force of smooth muscle contraction [30]. Repeated use of oxytocin is controversial.

If medical management fails to result in parturition, surgical intervention is necessary.

Surgical Management

Prior to surgery, the patient should have an intravenous catheter placed, intravenous fluid administration started, and flow-by oxygen administered [31]. The abdomen should be clipped and scrubbed prior to induction. Pre-medication of the bitch or queen is not warranted [18,31]. Alfaxalone at 2 mg/kg IV to effect or propofol at 2–6 mg/kg IV to effect for induction, and maintenance on low-level isoflurane are widely recommended anaesthetic protocols [18,31,32] (see Section 7). For maintenance of intravenous fluids, balanced crystalloids at 5 mL/kg/h is recommended during the procedure.

A ventral midline approach to the abdomen is made. The incision is extended from slightly cranial to the umbilicus to just cranial to the pubic bone [25]. The linea alba is visualized, and care is taken to lift the linea alba from the underlying abdominal structures before an incision is made. The uterus is easily identifiable; uterine horns are lifted and exteriorized from the abdomen (ensuring that not too much tension is placed on the uterus) and placed on moistened laparotomy sponges overlying the abdominal cavity. A small, single, uterine incision is then made



Figure 118.1 Puppy presenting with anterior positioning and retainment of forelimbs, resulting in obstruction of the birth canal.

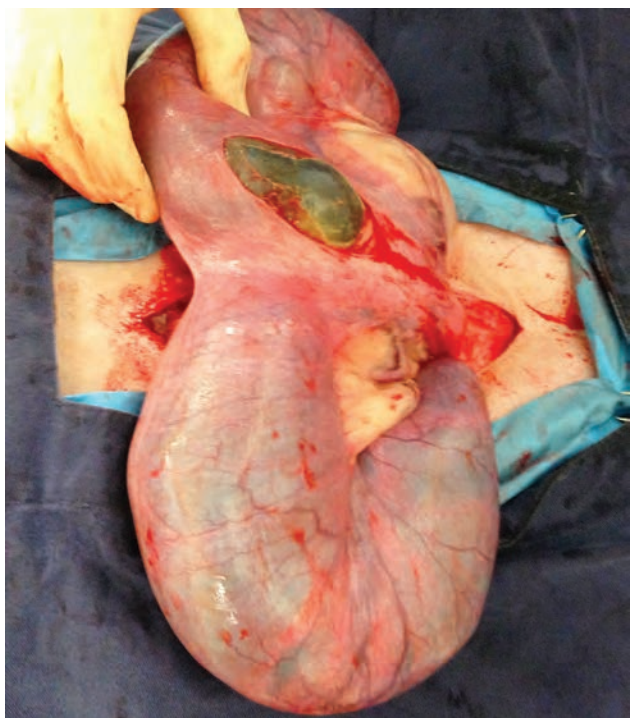


Figure 118.2 Incision through the uterine wall, with subsequent exposure of the chorioallantois.

over the base of one of the uterine horns with a scalpel (Figure 118.2). This is extended with Metzenbaum scissors to a size allowing the passage of the fetus(es) out of the uterine body. Each fetus is manipulated toward the incision site, and on presentation to the site of the uterine incision, the chorioallantois is broken with hemostats to allow delivery of the neonate from the uterus [32]. The amnion is also ruptured and the resultant umbilicus is clamped and tied. If the chorioallantois fails to separate from the uterine wall when the neonate is delivered, it can be gently separated from the endometrium.

Prior to closing the surgical site careful visual and digital examination of the anterior vagina, cervix and both uterine horns must be performed. This is to ensure all neonates have been delivered. The uterine incision is

closed with a single layer of 2-0 or 3-0 absorbable suture in the Utrecht (modified Cushing) pattern [18,33].

Following closure of the uterus, oxytocin is administered at 0.5–1.0 IU/kg SC, the abdomen is lavaged with warm saline, and closed in three layers. Skin should be closed with a simple interrupted pattern (horizontal mattress or cruciate patterns are commonly used), or alternatively, the surgeon may wish to close with intradermal sutures. Postoperative analgesia upon recovery often consists of a single injection of non-steroidal anti-inflammatory drugs (meloxicam 0.2 mg/kg SC for bitches or meloxicam 0.1 mg/kg SC for queens), assuming there is no underlying renal or gastrointestinal compromise.

Postoperative Care and Management

Postoperative care of the bitch or queen and the neonate(s) is vital. Dams, especially maidens, are prone to mismothering after a cesarean. The owner must be made aware of the risk of mismothering, and the importance of monitoring neonatal weights to ensure continued growth in the days after birth. Pups should be weighed every 12 hours for the first 2 weeks of life. Over the initial 24 hours, it is normal for weight to decrease but over the coming fortnight, a growth rate of 2–4 g per day per expected kilogram of adult weight should be expected [34]. The bitch or queen should be fed a concentrated, high-quality food several times daily during lactation to ensure she maintains a healthy body condition score and the puppies/kittens receive adequate nutrition. Calcium supplementation is not recommended unless the bitch or queen demonstrates clinical signs of eclampsia [34]. Neonates should be fed soon after parturition to ensure transfer of maternal antibodies through colostrum. Supervised feeding of the puppies or kittens (with the owner assisting attachment to the teat if needed) should occur every 2–3 hours for the first days. Neonates should be kept separate from the bitch or queen until normal mothering is confirmed.

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Eclampsia*Michelle A. Kutzler, DVM, PhD, DACT**Oregon State University, Corvallis, OR, USA***Introduction**

Eclampsia is a life-threatening condition first described nearly 100 years ago [1]. It results from an acute depletion of ionized calcium in the extracellular compartment during the peripartum period.

Etiopathogenesis

Eclampsia occurs more frequently in bitches than queens with young, primiparous bitches at greatest risk [2]. Eclampsia most frequently occurs 2–4 weeks postpartum (peak time of lactation) but can occur during late pregnancy [3] or parturition [4] or more than 45 days postpartum (time of weaning), which is especially true in cats [5,6]. Although not reported in the literature, the author has managed one case of eclampsia that developed in a small-breed dog with an overt false pregnancy and significant galactorrhea. Bitches with large litters or a large litter size to body weight ratio [7] are at the greatest risk. Although eclampsia can occur in any breed, small- and toy-breed dogs are overrepresented. Eclampsia is very rare in large-breed bitches [8], with the exception of the German short-haired pointer [9]. There does not appear to be a breed predisposition in cats [10].

Mechanistically, eclampsia develops from the inability of calcium homeostatic mechanisms (increased gastrointestinal absorption, decreased renal excretion, increased osteolysis) to compensate for the loss of calcium through lactation, and to a lesser extent from fetal skeletal ossification [11–13]. Therefore, additional predisposing factors include inappropriate prepartum calcium supplementation as well as improper or inadequate perinatal nutrition [7]. Excessive prenatal calcium supplementation or insufficient dietary magnesium inhibits parathyroid hormone release and can promote

parathyroid gland atrophy. In addition, excessive prenatal calcium supplementation stimulates thyroid calcitonin secretion, which then acts to decrease the rate of bone resorption of calcium. Through both of these actions, normal physiological mechanisms to mobilize and conserve adequate calcium stores as well as utilize dietary calcium sources are reduced.

Ionized serum calcium in dogs is normally about 55% of total serum calcium concentration [3]. However, prolonged hyperpnea during labor or dystocia can promote or exacerbate hypocalcemia as the resulting alkalosis favors protein binding of calcium, thereby decreasing ionized calcium (the biologically active form of calcium). It is important to mention that total serum calcium concentration is not affected by changes in pH. However, the equilibrium between ionized calcium and protein-bound calcium is affected by pH and an alkalotic animal may show signs of eclampsia yet have a normal total serum calcium concentration [14]. For this reason, albumin, bicarbonate, and anion gap measurements should be simultaneously interpreted [7,15].

Diagnosis

A presumptive diagnosis of eclampsia is often made based upon history and the presenting clinical signs. The onset of clinical signs of eclampsia in dogs is usually rapid with a predictable progression (Table 119.1) [3,16].

Early clinical signs include anxiety, restlessness, pacing, whining, and lack of interest in offspring. Facial pruritus of variable intensity and biting at the feet have also been reported [3]. Neuromuscular transmission is directly proportional to the calcium to magnesium ion ratio in the extracellular fluid [17,18]. In dogs and cats, decreased extracellular calcium ion levels increase nerve cell membrane permeability to sodium ions, especially in peripheral nerves, which has an excitatory

Table 119.1 Progression of eclampsia stages in dogs with corresponding clinical signs.

Stage	Clinical signs
I	Anxiety, restlessness, pacing, whining, hypersalivation, anorexia, polyuria, polydipsia, vomiting, diarrhea $\pm$ facial pruritus of variable intensity and biting at the feet
II	Ataxia, staggering, muscle tremors, mydriasis with diminished pupillary light reflexes, behavioral changes associated with lack of interest in offspring
III	Muscle stiffness and hyperesthesia, hyperthermia secondary to tetanic muscle contractions, panting, tachycardia, behavior changes associated with aggression
IV	Tonic-clonic muscle spasms in all four limbs (tetany), collapse with opisthotonos, labored respiration, behavior changes associated with disorientation
V	Arrhythmia (premature ventricular complexes) and seizures (musculoskeletal signs are often exaggerated with tactile stimulus); death may ensue

effect [18,19]. This allows for spontaneous discharge of nerve fibers to induce contraction of skeletal muscles and alteration of central nervous system function [3]. As a result, neuromuscular clinical signs quickly progress from generalized muscle fasciculations and stiffness to spasms and tetany [4,8,18–21]. Bitches showing signs of tetany usually have ionized calcium levels <0.6 – 0.8 mmol/L [7,11]. Extreme hypocalcemia can also cause low myocardial contractility and subsequent low cardiac output [21]. As the symptoms worsen, seizures and death may ensue [4,21].

Clinical signs of eclampsia in queens are similar to dogs and include acute lethargy, anorexia, weakness, bradycardia, hypersalivation, tachypnea progressing to dyspnea, and muscle fasciculations progressing to seizures [3,10,22–24].

Because total calcium concentrations fluctuate with serum protein concentration, acid–base status, and other electrolyte alterations, total serum calcium concentrations do not reliably correlate with ionized calcium [25–29]. Clinical manifestations of eclampsia correlate with both the absolute decrease in ionized calcium concentrations (<2.4 – 3.2 mg/dL or <0.6 mmol/L) and the rate and progression of ionized calcium decrease [11,14]. In queens, eclampsia occurs when serum ionized calcium concentrations fall below 1.0 mmol/L [30].

Hypoglycemia is a common sequela of eclampsia and can arise secondarily due to energy demands of tetany. But it is important to remember that severe primary hypoglycemia can also result in seizures [31] and must be ruled out with additional primary seizure causes (e.g. meningoencephalitis and strychnine toxicity) [20].

Treatment (Box 119.1)

In cases of eclampsia, treatment should not be delayed for laboratory confirmation. Response to treatment is dramatic and often a gratifying diagnostic tool.

Treatment is primarily aimed at correcting ionized calcium concentrations. Initial treatment includes slow intravenous administration of organic calcium compounds (20% calcium borogluconate or 10% calcium gluconate) at a rate of 1–1.5 mL/kg for dogs and 2.5 mL/kg for cats over a 10–30-minute period or until resolution of clinical signs [3,4,32]. Calcium chloride should be avoided due to the corrosive perivascular effects if extravasation occurs. Vomiting during intravenous calcium administration has been reported [20]. Careful cardiac monitoring via auscultation or electrocardiography is critical during calcium administration to prevent serious cardiac effects, including asystole [33]. Development of bradycardia, QT shortening, or arrhythmias indicates that the rate of calcium administration is too rapid and it must be temporarily discontinued and then restarted at a slower rate [4].

Response to initial treatment may last for only a short period (2 hours) and the animal must be monitored for signs of relapse. The original dose may be repeated [14]. The IV dose of calcium gluconate (not chloride) required to resolve clinical signs can be diluted 1:1 in a normal (0.9%) saline solution or 5% dextrose for subcutaneous administration divided into three equal doses over 24–48 hours to prevent immediate relapse. A continuous-rate infusion (CRI) of elemental calcium can be delivered at 1–3 mg/kg/h to maintain normal calcium levels in severe cases [14]. To avoid precipitation of calcium salts, solutions containing sulfate, phosphate, or bicarbonate should not be infused with calcium.

Secondary hypoglycemia and seizing must be treated if present. Administration of a 10% dextrose solution is recommended in cases of co-existing hypoglycemia [4]. To control seizure activity, barbiturates or diazepam can be administered [3,5,34]. Because cerebral

Box 119.1 Emergency treatment for eclampsia.

5–15 mg/kg of elemental calcium slow IV
10% calcium gluconate or 20% calcium borogluconate

- Dogs: 1–1.5 mL/kg slow IV
- Cats: 2.5 mL/kg slow IV

Note: if other calcium salts or concentrations are used, the volume of administration will need to be changed accordingly.

Calcium administration should take place over 10–30 minutes with close monitoring via auscultation or ECG.

edema can occur from uncontrolled seizures, mannitol may be indicated for potential cerebral edema [34]. If severe hyperthermia ($>104^{\circ}\text{F}$, $>40^{\circ}\text{C}$) exists, this should be controlled with active cooling. Magnesium deficiency or alkalosis should be corrected if present [14].

Prognosis after treatment is favorable, but relapses can occur through the end of lactation and with a subsequent pregnancy [20]. The offspring should be removed from the dam and hand-fed a milk supplement for 24–36 hours to reduce the risk of a relapse [4,32,35]. The lactating dam which experienced eclampsia should be orally supplemented with calcium carbonate or calcium lactate at 100 mg/kg body weight per day, divided with meals [4,23,32]. Vitamin D metabolites should be started early if hypocalcemia is expected to persist, as it takes several days for intestinal calcium transport to be upregulated. Calcitriol is the preferred active vitamin D metabolite, given its quick onset of action, short plasma half-life, and relatively short biological half-life; thus, discontinuing the drug will rapidly correct iatrogenic hypercalcemia, if it occurs. Calcitriol is administered at a dose of 20–30 ng/kg once daily for 3–4 days for induction, then 5–15 ng/kg once daily for maintenance therapy, titrated to desired serum calcium concentration [14].

If the offspring are 4 weeks old or more, they should be weaned [4]. If puppies are weaned to stop lactation, monitor the dam for self-milking (licking own mammary glands, which can induce milk letdown). Wrapping the mammary glands with a bandage for part of the day and then releasing the bandage an hour or so before replacing it may help in some cases. Alternatively, lactation

cessation can be achieved using an antiprolactinic drug (cabergoline 5 $\mu\text{g/kg}$ orally once daily for 7 days) [36,37]. Historical literature includes the use of glucocorticoids (e.g. prednisolone) to reduce the risk of eclampsia relapse [38]. However, glucocorticoids are contraindicated as they decrease intestinal calcium absorption, enhance renal excretion of calcium, and impair osteoclasia [13,34].

Prevention

A number of authors have speculated that eclampsia is a nutritionally related disorder of pregnancy or lactation resulting from either the overfeeding of high calcium-containing animal protein (egg or meat) or the feeding of dog foods containing cereals with phytate (because phytate binds ionized calcium, making it biologically unavailable) [5,9,39]. As a result, recommendations to prevent eclampsia involve feeding a balanced (puppy or kitten) formula commercial pet food without additional vitamin or mineral supplementation during the second half of gestation. This gestational diet should contain between 1.0% and 1.8% calcium and 0.8% and 1.6% phosphorus. Dietary supplementation with any dairy products during gestation should be avoided as they disrupt normal calcium-phosphorus-magnesium balance in the diet and may promote the development of eclampsia. The postpartum diet should be balanced for all lifestages, including lactation, and contain at least 1.4% calcium, with a calcium:phosphorus ratio of 1:1.3 [34].

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Neonatal Resuscitation

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Physical Examination

The physical examination should be performed quickly and Apgar scores obtained, paying particular attention to keeping the neonate warm and stimulated to breathe at all times.

The neonate should be assessed for the presence of a cleft palate, open fontanelle, umbilical hernia, patent urachus, hair coat and limb conformation, and patency of urogenital openings. The mucous membranes should be pink and moist, the umbilicus should not have surrounding erythema, the hair coat should be complete, and the limbs should have normal conformation with moderate muscle tone. Thoracic auscultation should reveal normal vesicular breath sounds and the lack of a heart murmur, although physiological murmurs may be possible. Normal heart and respiratory rates at birth in neonatal puppies and kittens are 200–220 beats per minute and 10–18 breaths per minute, respectively. The abdomen will be less haired than in an adult and should be pliant and not painful. Many neurological reflexes are not present at this age but the suckling, righting, rooting, and dorsal stimulation reflexes should be present within an hour after birth (Table 120.1). Observation of meconium staining indicates high stress *in utero*.

The Apgar evaluation parameters are assessed, scored, and the sum is taken (Table 120.2). Puppies with scores of 7–10 are classified as no distress, with significantly better survival than those with scores of 4–6 (moderate distress) or 0–3 (severe distress). Using the Apgar score in conjunction with the findings of a complete physical examination, an informed decision can be made as to how aggressive the resuscitation efforts should be [1].

Umbilical cord care should take place after the neonate is resuscitated; clamping is best 2+ cm from the body wall, which reduces traction and iatrogenic umbilical hernia. The umbilicus of the neonate should be treated with 2% tincture of iodine immediately after

Table 120.1 Neonatal reflexes. Assessment of the following four reflexes in a neonate helps to determine vigor.

Reflex	Response
Dorsal stimulation	A neonate is rubbed strongly over the dorsal lumbar area and should move vigorously and/or squeal in response
Righting reflex	The neonate is placed on its back and should then immediately turn itself over into ventral recumbency
Suckling reflex	A finger, bottle or the dam's nipple is offered to the neonate that should then begin suckling
Rooting reflex	The neonate should push its muzzle into a cupped hand or against its mother's mammary in search of milk

birth to reduce contamination and prevent ascent of bacteria into the peritoneal cavity (omphalitis-peritonitis). Alcohol-based tincture of iodine is superior to aqueous povidone-iodine, which does not promote umbilical desiccation as quickly.

Table 120.2 Apgar scores.

Parameter	Score		
	0	1	2
Heart rate (bpm)	<180	180–220	>220
Respiratory effort: breaths per minute	No crying; <6	Mild crying; 6–15	Crying; >15
Reflex irritability	Absent	Grimace	Vigorous
Mobility	Flaccid	Some flexions	Active motion
Mucous membrane color	Cyanotic	Pale	Pink

bpm, beats per minute.

Source: Adapted from Johnson and Casal [1]. Reproduced with permission of John Wiley and Sons.

Respiratory Concerns

Normal respiratory rate in the neonate ranges from 10–18 breaths per minute at 1 day of age to 16–32 breaths per minute by 1 week of age [2]. If respiratory distress is encountered at birth, it may indicate pulmonary hypertension, decreased surfactant levels (prematurity), aspiration of meconium, or excess fluid in the airways. Congenital defects may cause persistent pulmonary hypertension and respiratory distress that is refractory to treatment [3].

Neonates should never be “swung” in a downward arc to remove fluid as this has been documented to cause intracranial trauma [4]. Airways are established by removing fetal membranes from the face followed by gentle suction with a bulb syringe or aspirator, prior to umbilical clamping. Systems capable of generating greater negative pressure than a bulb syringe should be used with caution, as they may cause airway injury and laryngospasm.

Cleaning and drying of the neonate stimulates respiration, crying, and movement. Stimulating genital and umbilical areas induces reflex respiration in neonates [2]. Another method to stimulate respiration is use of the Jen Chung acupuncture point (GV 26), in which a needle is inserted into the nasal philtrum at the base of the nares and rotated when cartilage/bone is contacted. Drying the muzzle and the Jen Chung acupuncture point likely stimulates respiratory neuroreceptors present in the muzzle that are functional at birth [5].

If respiratory distress is evident, oxygen can be supplied via face mask. If no improvement is noted after 1 minute, positive pressure ventilation with a snugly fitting mask should be initiated. Initial ventilation rates should be 40–60 breaths per minute during the first 30 seconds, then the rate should be decreased to 12–20bpm [3]. Endotracheal intubation and use of a rescue breathing bag (using a 2 mm endotracheal tube or a 12–16 gauge intravenous catheter) is feasible but there is more potential for trauma of the upper airway. Administering 30–40 breaths per minute, with FIO₂ less than 40–60% and approximately 10 cmH₂O pressure, is advised [5]. Excessive insufflation using a mask can cause aerophagia, and overventilation is associated with higher mortality. Doxapram acts as a central stimulant and its effect is diminished by brain hypoxemia [6]. The use of doxapram as a respiratory stimulant is unlikely to improve hypoxemia associated with hypoventilation and is not recommended [5].

Cardiac Concerns

The two most common causes of neonatal bradycardia or asystole are hypoxia and hypothermia [1,5]. During the first 4 days of life, bradycardia is not vagally mediated

and is considered to be indicative of hypoxia [2]. When hypothermia (below 96°F/35.5°C) is identified, normal cardiac function is not likely to resume. If not corrected with oxygen and ventilation alone, external chest compression can be initiated [3,5], done with the thumb and forefinger on either side of the thorax with approximately 100–120 compressions per minute.

There are multiple causes of ventricular tachycardia, including hypoxia, pain, ischemia, sepsis, electrolyte changes, trauma, and primary cardiac disease. Treatment of the underlying cause should be attempted first. Cardiopulmonary arrest requires rapid identification and intervention. Positive pressure ventilation and chest compressions should be started immediately. Cardiopulmonary resuscitation of the neonate follows the general CPR guidelines (see Chapter 150). Intravenous drug administration may not be feasible. Intratracheal administration can be considered but the intraosseous route is recommended. Atropine is not indicated, as neonatal bradycardia is not vagally mediated and anticholinergic-induced tachycardia will exacerbate myocardial oxygen deficits [2,5]. ECG evaluation may aid in guiding resuscitation. If ventricular fibrillation is identified, defibrillation is the ideal treatment but providing appropriate defibrillation doses for a neonate may not be possible.

Glucose is the main energy substrate of the neonatal brain and myocardium and should be monitored frequently. Sodium bicarbonate or calcium administration is not recommended [3].

Hypothermia

Newborn puppies and kittens cannot regulate their body temperature until about 4 weeks of age and are thus dependent on outside sources of heat (maternal care, heat lamps, etc.). Normal body temperature in puppies is 96°F (35.5°C) to 97°F (36°C) for the first 1–2 weeks of life. Normal body temperature in kittens is 98°F (36.7°C) at birth and increases to 100°F (37.8°C) by the end of the first week. For orphaned puppies, it has been recommended to maintain an environmental temperature of 80–90°F (26.7–32.2°C).

Hypothermia has been shown to have a negative impact on immunity, nursing, and digestion. In addition, it decreases food intake and exacerbates dehydration, hypoglycemia, bradycardia and ileus, decreasing the willingness to nurse and predisposing tube-fed puppies to aspiration and subsequent pneumonia [2]. Chilled neonates must be rewarmed slowly (minimum 30 minutes), avoiding peripheral vasodilation, to a maximum of 32.7°C (99°F) in neonates up to 7 days old [7]. During resuscitation, placing a chilled neonate's body into a warm water bath (95–99°F) can improve core

temperature. Resuscitation efforts can continue while a neonate is being actively warmed.

Exogenous heat is best supplied in the form of an overhead heat lamp. Heating pads may burn neonates incapable of moving away [5]. Neonates have a behavioral heat-seeking response [2]. Neonates lying separately may be too hot, vocalize loudly when too warm, then quickly fatigue and stop crying. Neonates that are too cold also quit vocalizing and become inactive; kittens are almost always quiet to begin with, making subjective observation of euthermia more difficult [1]. Studies in neonatal kittens have shown that rapid rewarming in the face of hypoxia may result in relative hyperthermia [8]. The response of the respiratory chemoreflex decreases at the same time as the ventilation decreases due to the decrease in metabolism, predisposing to apnea [9].

Dehydration and Fluid Therapy

Dehydration in the neonate is most commonly associated with diarrhea, vomiting, or decreased fluid intake. Low urine specific gravity (1.006–1.0017) is normal, as is the detection of protein, glucose, and amino acids because of immaturity of the proximal tubules during the first 2 weeks of life. The value of skin turgor as an assessment of hydration status is less than ideal in the neonate due to difference in body water content [10]. Checking mucous membranes is a better method of assessing the neonate's hydration state. Tacky mucous membranes indicate 5–7% dehydration and any increase in dehydration beyond that will result in dry mucous membranes and decreased skin elasticity.

Neonates have greater water requirements and greater insensible water loss than adults [11], and because neonatal canine kidneys have minimal capacity to conserve water before 40 days of age [12], dehydration will occur in any instance of decreased milk intake. Therefore, neonates are more prone than older animals to develop water and electrolyte imbalances, either excess or deficit, during fluid therapy [1].

Maintenance fluid requirements are reported to be 80–100 mL/kg/day [6]. When neonates are found to be dehydrated but normovolemic, fluids should be administered for correction over 6–8 hours to decrease the chances of inadvertent overload. In normovolemia, subcutaneous administration is often used to replace the fluid deficit if the patient is not severely compromised, if only a small volume is needed or there are financial concerns. In the face of moderate dehydration, a bolus of 30–40 mL/kg is recommended, followed by a constant-rate infusion of 80–100 mL/kg/day of warmed crystalloids. In cases of hypovolemia or shock, recommended rates are up to 40–45 mL/kg/h [6], with serial monitoring of mucous

membrane color, pulse quality, extremity temperature, lactate levels, and mentation [3]. Lactated Ringer's solution may be ideal, since lactate is the preferred metabolic fuel in the neonate during times of hypoglycemia [3]. Signs of fluid overload include increased respiratory rate or effort, restlessness, serous nasal discharge, subcutaneous edema, ascites, or excessive weight gain within less than 24 hours.

Fluids are administered through the cephalic or jugular vein in these smallest of patients using small (22–25 G) and short (0.5 inch) IV catheters. Fluids may also be administered via the intraosseous (IO) route if IV access is not possible. Options for IO catheter placement include the femur, humerus or tibia, depending on the size of the patient. Typically, 18–22 G spinal needles or 18–25 G hypodermic needles will be used. This portal can be used for fluid boluses, emergency drug administration, and blood transfusions. Sterile preparation is required for IO placement, with the catheter inserted parallel to the long axis and into the marrow space. Gentle aspiration will ensure placement and patency followed by suturing in place for security. Intravenous access should then be established as soon as possible, and the IO catheter should be removed to minimize the possibility of osteitis or sepsis [3].

For quick drug administration but not large volumes of fluids, the umbilical vein may be considered if it has not already thrombosed.

Hypoglycemia

Clinical signs associated with hypoglycemia include weakness, flaccidity, seizure, and coma. The goal is to restore a euglycemic range without causing hyperglycemia. Because the neonatal kidney is ineffective at conserving water in the face of osmotic diuresis, dehydration may result from hyperglycemia [1]. Resolution of clinical signs of hypoglycemia is a poor indicator of treatment response, as there are several similar non-specific clinical signs, such as hypothermia, metabolic errors, and seizures, which may also be seen with hypoglycemia.

Clinical hypoglycemia is characterized by blood glucose levels less than 30–40 mg/dL. It can be treated with a dextrose solution given either IV or IO, at a dose of 0.5–1.0 g/kg body weight using a 5–10% dextrose solution (1 to 2 mL/100g weight). Subcutaneous administration of dextrose is undesirable due to the potential for abscessation at the site [5]. Dextrose at 50% must be diluted for IV administration to avoid phlebitis. However, this concentration may be applied to the mucous membranes but if severe hypovolemia or dehydration is present, the neonate's circulation may not be adequate for absorption, so IO administration is preferable. If the neonate is too weak to nurse, a mixture of warmed 4.5% saline with 2.5% dextrose can be administered via a stomach tube at

0.1–0.5 mL/30 g body weight every 15–30 minutes until suckle capability returns. However, if available, colostrum from the dam is superior to this mixture [5].

There are some cases of neonates with refractory hypoglycemia, which may only respond to hourly boluses of dextrose in addition to IV CRI crystalloid with dextrose supplemented. If no positive responses are noted within 24 hours, the neonate should be assessed for inborn errors of metabolism.

Sepsis

Bacterial sepsis is a common contributor to neonatal mortality. The most commonly cultured organisms associated with sepsis are *Escherichia coli*, streptococci, staphylococci, and *Klebsiella* spp. Sudden death may be the only clinical sign observed; a decrease in weight gain or net loss with failure to suckle may be the first indication of infection. Other clinical signs may include hematuria, decreased urine output, persistent diarrhea, unusual vocalization, abdominal distension and pain, cold limbs or body, possible sloughing of extremities.

Empirical therapy includes use of the antibiotic ceftiofur at a dose of 2.5 mg/kg SC every 12 hours for no longer than 5 days [1,2,13]. It alters normal intestinal flora minimally and is usually effective against the causative

organisms. Alternatively, amoxicillin/clavulanic acid is a safe, broad-spectrum antibiotic that can be given at 20 mg/kg orally twice daily.

Septic patients can have increased capillary permeability and vasodilation and may require aggressive fluid resuscitation. It has been demonstrated that using fresh or frozen plasma from a well-vaccinated adult dog might augment immunity, and may be administered either via CRI or subcutaneously [14]. Because puppies less than 48 hours old have reduced thrombin levels, presumptive therapy with vitamin K1 may be used (0.01–1.0 mg subcutaneously per puppy) [5].

When to Stop Resuscitation Efforts

Deciding when to stop attempts at resuscitation can be difficult. Some helpful guidelines include discontinuing after 30 minutes of effort with no response or continued bradycardia with agonal respirations despite resuscitation attempts. Cessation of attempts should also be considered in the face of a serious congenital defect. This may include but is not limited to a cleft palate, loud murmur, large umbilical hernia, large omphalocele, large open fontanelle, anasarca, anogenital defects, and severe vertebral or limb abnormalities not compatible with a good quality of life.

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Diseases of the Neonate

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Introduction

Neonatal dogs and cats are defined here as being less than 4 weeks of age, prior to weaning, which normally occurs at 5–6 weeks. Orphan puppies and kittens present unique sets of disorders related to their immaturity at birth, dependence on acquisition of colostrum, small size, and fragility. Neonatal patients are most commonly presented to the emergency veterinarian due to failure to thrive or to an acute onset of signs of illness. Clinical signs are most commonly due to historical dystocia, congenital anomalies, infectious disease, and environmental trauma.

Epizootiology

Average reported neonatal mortality rates (greatest during the first week of life) vary, ranging from 9% to 26%. Most puppies and kittens that fail to survive to weaning are stillborn or die within the first 3–7 days of life [1]. Prudent veterinary intervention in the prenatal, parturient, and postpartum periods can increase neonatal survival by controlling or eliminating factors contributing to puppy morbidity and mortality. Poor prepartum condition of the dam, dystocia, prematurity, congenital malformations, genetic defects, injury, environmental exposure, malnutrition, parasitism, and infectious disease all contribute to neonatal morbidity and mortality. Optimal husbandry affects neonatal survival favorably by managing labor and delivery to reduce stillbirths, controlling parasitism and reducing exposure to infectious disease, preventing injury and harmful environmental exposure, and optimizing nutrition of the dam and neonates. Proper genetic screening for selection of breeding animals minimizes inherited congenital defects.

Low birth weight is the most significant risk factor for neonatal puppy and kitten death. Birth weights of

puppies are breed dependent; normal birth weights for the smaller breeds can range from 75 g to 350 g, medium breeds 200–300 g and the larger breeds from 400 g up to 800 g. The average birth weight of surviving kittens is 100 ± 10 g [2]. Morbid puppies and kittens may be smaller at birth, with reduced weight gain or even weight loss. The cause of low birth weight or poor growth is usually difficult to determine but may include prematurity, inborn errors of metabolism, birth defects, infections, nutritional deficiencies, and maternal neglect.

Risk of neonatal loss was also associated with obese dams, singleton litters, and for the first neonate born in a litter. A higher rate of death of the first neonate born could reflect an inexperienced dam. The breeder's level of knowledge about whelping may also play a key role in neonatal survival. Delaying nursing until the entire litter is born or until the dam is awake from anesthesia for a cesarean section subjects neonates to delayed colostrum intake. Neonatal survival is directly related to the quality of labor (avoidance of dystocia). Extended or difficult labor may result in birth trauma, in neonates that are too weak to nurse, or in ill or exhausted dams that are unable to care for their offspring.

Physiology

Post resuscitation, or within the first 24 hours of a natural delivery, a complete physical examination should be performed by a veterinarian, technician, or knowledgeable breeder. Body temperature ranges from 95°F to 99°F (35.5–36.5°C). The oral cavity, hair coat, limbs, umbilicus, and urogenital structures should be visually inspected. Normal hydration is evidenced by normal skin turgor. The mucous membranes should be pink and moist, a suckle reflex present, the coat full and clean, the urethra and anus patent. Urination and defecation are easily elicited by gentle stimulation with a cotton ball

moistened with warm water. A normal umbilicus is dry without surrounding erythema. The thorax should be ausculted; vesicular breath sounds and a lack of murmur are normal. If a murmur is detected, auscultation should be repeated in 48–72 hours; innocent physiological murmurs will disappear. Respiration is regular, 15–35 breaths per minute, and no fluid should be ausculted over the lung fields. Minimal clear nasal discharge can be evident. The heart rate is rapid, usually 180–250 beats per minute. The abdomen should be pliant and not painful. A normal neonate will squirm and vocalize when examined, but will sleep quietly or nurse when returned to the dam. Normal neonates will attempt to right themselves and orient by rooting toward their dam. Daily examination of each neonate for vigor and recording of weight is critical.

The signs of distress or disease in neonates are usually non-specific, most commonly including continuous vocalization, ineffective nursing, and restlessness. Failing neonates can become disoriented, stranded, limp, and hypothermic.

Puppies and kittens lack adult thermoregulatory mechanisms until 3–4 weeks of age, so the ambient temperature must be high enough to facilitate maintenance of a body temperature of at least 97°F (36°C). Typically, the dam and littermates will provide adequate warmth in a draft-free box indoors with an ambient room temperature of 70–75°F, resulting in adequate thermal support to the neonates (Box 121.1). Hypothermia negatively affects immunity, nursing, and digestion. Low-birth weight neonates are most susceptible to chilling. Exogenous heat should be supplied as indicated (i.e. in the absence of the dam), best in the form of an overhead infrared heat lamp. Heating pads run the risk of burning neonates incapable of moving away from excessively hot surfaces. Hyperthermia is to be avoided; dams will avoid the box, resulting in reduced nursing and mothering behavior. Excessive exogenous heat results in vocalization and

restlessness. Neonates typically pile up together in the absence of the dam to maintain body heat.

Chilled neonates must be rewarmed slowly (30 minutes) to avoid peripheral vasodilation and dehydration. Tube feeding should be delayed until the neonate is euthermic, as hypothermia induces ileus and regurgitation, and aspiration can result.

Neonates are inefficient at gluconeogenesis, and have low glycogen storage capabilities. Glycogen stores are depleted shortly after birth, making adequate nourishment from nursing vital. Even minimal fasting can result in hypoglycemia. In addition, neonates have poor glucose absorption from the kidneys.

Incompletely developed immune systems during the first 10 days of life make neonates vulnerable to systemic infection (most commonly bacterial and viral) [2].

Neonatal Disorders in the Immediate Postpartum Period

Disorders of Metabolism

Pathophysiology

Inborn errors of metabolism, lysosomal storage disorders, and mucopolysaccharidoses occur in dogs and cats. Congenital hypoglycemia and intracellular accumulation of deleterious substrates will occur.

Clinical Presentation

Disorders of metabolism are suspected in neonates that appear normal at birth, but display progressive lethargy, poor nursing, persistent vomiting and eventually central nervous system signs. No infectious or traumatic etiology can be identified.

Diagnostics

The history of a related animal having a documented inborn metabolic disorder is of interest. Specific genetic tests are available for some disorders [3,4].

Therapy

The prognosis is usually hopeless for veterinary patients, as gene therapy is indicated.

Anasarca

Pathophysiology

Anasarca, a lethal congenital edema, can occur with or without concurrent cardiovascular abnormalities. Congenital hereditary lymphedema causes edema of the extremities and sometimes head, and is associated with morphological lymphatic abnormalities. The genetics are not known; the trait is thought to be inherited as an autosomal dominant trait.

Box 121.1 Normal neonatal body temperatures by age and ambient room temperature required to maintain this.

Neonatal normal body temperature (rectal)	
Week 1	95–99°F
Week 2–3	97–100°F
At weaning	99–101°F
Environmental warmth required at level of neonates	
Week 1	84–89°F
Week 2–3	80°F
Week 4	69–75°F



Figure 121.1 Anasarca. Stillborn Labrador retriever; obstructive dystocia resulted in emergency cesarean section.

Clinical Presentation

Generalized subcutaneous edema, with intrathoracic and intraperitoneal fluid accumulation, is present. Anasarca puppies are commonly a cause of dystocia due to oversize, and can be stillborn. Anasarca is a problem common in bulldogs, but recognized in other breeds as well. It is suspected to have a heritable component (Figure 121.1).

Diagnostics

Prepartum ultrasonographic evaluation of the fetuses can be used to screen for this disorder, especially in breeds at risk. On radiographic evaluation, the skeleton may appear of appropriate size for natural delivery, but generalized edema often prevents passage through the birth canal.

Therapy

There are multiple anecdotal remedies, none proven or reported in the scientific literature. Diuretic therapy can sometimes slightly normalize affected neonates, but euthanasia is usually indicated if the neonate is not stillborn. Environmental, dietary, and pharmacological contributory factors are not scientifically defined.

Ciliary Dyskinesia

Pathophysiology

Abnormal mucociliary transport and neutrophil function result in chronic rhinitis, tracheobronchitis, and bronchopneumonia. Situs inversus can be present.

Clinical Presentation

Primary ciliary dyskinesia, the extremely rare immotile cilia syndrome, should be suspected in neonates exhibiting persistent mucopurulent nasal discharge, coughing, and abnormal breath sounds without other demonstrable cause (i.e. cleft palate).

Diagnostics

The diagnosis is most easily made if semen can be acquired and evaluated for motility in the postpubertal individual; confirmation of the diagnosis requires pulmonary electron microscopy in prepubertal puppies.

Therapy

The long-term prognosis, even with supportive therapy, is poor.

Hydrocephalus

Pathophysiology

Neonatal neurological disorders can be inherited or can result from intrauterine teratogens or trauma during parturition. Morphological neurological abnormalities occur most frequently. Aqueduct atresia, birth trauma, or meningoencephalitis can also cause the development of (acquired) hydrocephalus [5].

Clinical Presentation

A domed calvarium, open fontanelle, and prominent suture lines are often present. Clinical signs vary from inapparent to progressively debilitating neurological changes. Hydrocephalus has an increased frequency in toy and brachycephalic breeds, and can occur in cats. Early clumsy, weak, or ataxic ambulation can indicate a neurological or musculoskeletal abnormality.

Diagnostics

Neonatal patients with focal, partial, or grand mal seizures for which no metabolic or toxic etiology can be identified can benefit from intracranial ultrasound. Scanning the brain through the fontanelle, usually partially open in pediatric patients, permits non-invasive evaluation of the ventricles. Evaluation of a normal littermate facilitates recognition of excessive cerebral spinal fluid accumulation by serving as a control. CT scanning or MRI can confirm the diagnosis.

Therapy

Omeprazole decreases CSF movement into the ventricles via proton pump inhibition. Corticosteroids and diuretics can offer some relief. Ventriculoperitoneal shunting has been described in puppies [6]. Neurological abnormalities noted on physical exam may be permanent.

Umbilical Herniation

Pathophysiology

A developmental anomaly resulting in extrusion of a portion of the gastrointestinal tract outside of the body wall, occurring within the umbilical canal (omphalocele) or lateral to the umbilical canal (gastroschisis), has been reported in humans and occurs in both dogs and cats.

Clinical Presentation

Umbilical herniation is noted on physical examination of a neonate (Web Figure 121.1).

Diagnostics

The diagnosis is made antepartum in humans with abdominal ultrasound, based on the recognition of fetal gastric wall (rugal) structures or intestinal contents in an abnormal location, and is theoretically possible in veterinary patients.

Therapy

The condition is usually hopeless in small veterinary patients presented to the veterinarian hours after birth; however, a 30–70% survival rate is reported in humans with immediate postpartum surgical intervention. The prognosis for omphalocele is worse than gastroschisis. Earlier surgical intervention before inevitable septic contamination occurs may improve the prognosis in veterinary patients; clients should be educated as to its recognition postpartum and timely presentation to a veterinarian.

Bowel Malformation: Agenesis or Duplication**Pathophysiology**

Agenesis is most common at the terminal colon, but can occur anywhere in the intestinal tract. Duplication is rare, but again can occur anywhere in the intestinal tract.

Clinical Presentation

The clinical signs may be non-specific. Enteric agenesis usually results in severe clinical signs in the neonatal period (failure to defecate, abdominal distension, vomiting).

Diagnostics

Enteric duplication or agenesis can be confirmed ultrasonographically in neonatal patients. A fluid-filled juxtaintestinal formation with variable peristalsis and contents can be seen. Ultrasonographic findings usually include marked fluid and gas distension of bowel proximal to the defect.

Therapy

Surgical repair of rectal agenesis is possible if the defect is diagnosed in a timely manner; fecal incontinence can result.

Patent Urachus**Pathophysiology**

The urachus permits the flow of urine from the bladder into the allantoic sac of the fetus, and normally atrophies at birth.

Clinical Presentation

A persistent patent urachus in the neonate is characterized clinically by urine dribbling from the umbilicus. If an incompletely patent urachus is present, a urachal diverticulum may result. Urachal diverticula can predispose the bladder to recurrent infection because of abnormal urinary flow in the region.

Diagnostics

Patent urachus is apparent on physical examination. The fluid-filled urachus can be identified ultrasonographically, extending cranially from the cranioventral bladder wall. A urachal diverticulum is seen as a divot in the apex of the bladder.

Therapy

Ligation of the urachus is indicated if spontaneous closure does not occur. Surgical excision of a diverticulum can be indicated in the future if urinary tract infection occurs.

Cleft Palate**Pathophysiology**

Congenital palate defects occur in dogs with an incidence of up to 25%. Secondary cleft palate is a congenital oronasal fistula resulting in incomplete closure of the hard and soft palate. Cleft palate occurs alone or in combination with a primary cleft palate involving the lip and premaxilla. Cleft palate results from incomplete fusion of the palatine shelves, most critical at 25–28 days gestation. Palatal defects are attributed to genetic (recessive or incompletely dominant polygenic inheritance), teratogenic (drugs, supplements), nutritional (folic acid deficiency) or infectious (viral) factors [7].

Clinical Presentation

Ineffective nursing and suckling result; these neonates fail to thrive, developing aspiration pneumonia and rhinitis. Milk may be seen coming from the nares during or after nursing.

Diagnostics

Affected neonates are diagnosed by visual inspection of the face and oral cavity (Figure 121.2).

Therapy

Feeding by orogastric tube is indicated until the puppy reaches a size permitting oral surgery, traditionally advised at 8–12 weeks of age. Palatoplasty in such young puppies remains difficult due to patient size and anticipated postoperative orofacial growth, often necessitating multiple operations. Esophagostomy or gastrostomy tube placement can facilitate feeding over time,

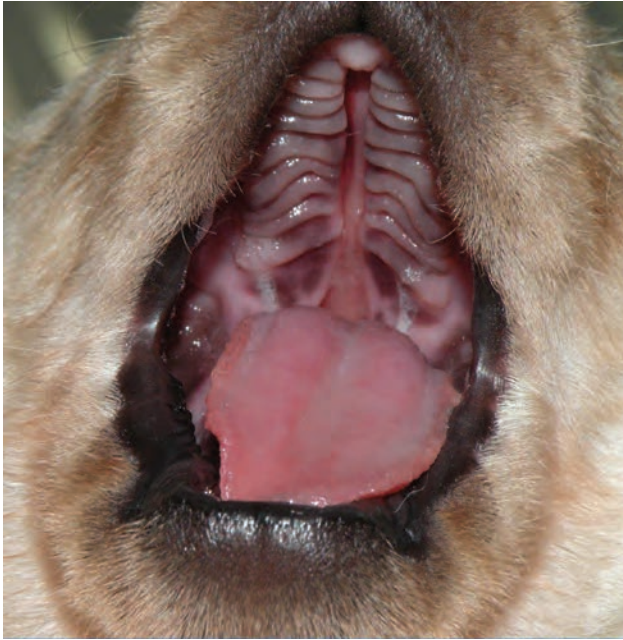


Figure 121.2 Cleft palate in a 3-day-old Labrador retriever puppy; no craniofacial defect is present.

but requires significant client commitment and can still result in aspiration. Palatal prostheses are problematic.

Methods to improve survival of pet puppies with cleft palates are sought by motivated clients. Following the postpartum diagnosis of cleft palate, feeding the dam's colostrum for 24 hours followed by artificial bitch milk replacer by intermittent orogastric tube can be instituted. At 4 weeks of age, transition to a dry (not soft soaked) commercial pediatric dog food should be made, facilitating swallowing without ingesta becoming misplaced into the nasal cavity. Water should be made available through an overhead ballpoint tube cap system. This permits dogs with secondary cleft palate to attain adult size before reconstructive surgery, which may not be necessary due to closure of the defect with maturity.

Neonatal Isoerythrolysis (see Chapter 66)

Pathophysiology

Neonatal isoerythrolysis occurs in kittens after initial colostrum ingestion. The disease occurs as a result of the dam's and kitten's blood types being different, and the kitten ingesting antibodies against its own blood type. Type B cats with type A kittens are the most likely to produce this condition, as type B cats carry strong anti-A antibodies [8].

Clinical Presentation

The most common breeds with high numbers of type B cats include the Cornish rex, Devon rex, and British

short-hair. Kittens show signs of anemia, such as lethargy, tachycardia, tachypnea, and pale mucous membranes, and are often icteric. Extreme presentation may also show necrosis of the tail tips and other extremities due to ischemia.

Diagnostics

The diagnosis is based on the findings of anemia and icterus with no evidence of blood loss or hemoparasites.

Therapy

Treatment depends on severity. All affected kittens should be removed immediately from the dam. Transfusion of cross-matched donor blood or washed type B from the dam may be used. Blood products can be transfused at a rate of 10–20 mL/kg over a 4-hour period via intravenous or intraosseous catheter. The prognosis is poor in kittens showing any degree of clinical signs. Prevention is achieved by avoiding mating type B queens to type A toms. Breeding animals should be blood typed, ideally with A bred to A and B bred to B. Another strategy is to collect umbilical blood from kittens before nursing, and determine if the type is the same as the dam's before nursing is allowed.

Immunodeficiency

Pathophysiology

Neonatal dogs and cats are born immunocompetent but immunodeficient due to minimal transplacental acquisition of maternal antibodies. Adequate ingestion of colostrum must occur promptly postpartum for puppies to acquire passive transfer of immunity. Neonates should be encouraged to suckle promptly after birth once resuscitation is completed; this usually necessitates close monitoring after a cesarean section as the dam is still groggy from anesthesia. The intestinal absorption of IgG generally ceases by 24 hours after parturition.

Clinical Presentation

Neonates which have failed to nurse adequately can present with signs of hypoglycemia, excessive vocalization due to hunger, or lethargy; subsequent signs of infectious disease occur. Orphans should be considered to be colostrum deprived.

Diagnostics

Failing to observe colostrum ingestion is key to the diagnosis. Neonates should show weight gain after nursing in the immediate postpartum period. The diagnosis is usually presumptive. Snap tests for semi-quantitative antibody measurement do not exist for dogs or cats currently.

Therapy

Failure to acquire colostrum within 24 hours of birth should prompt administration of adult conspecific plasma to a neonate; if >24 hours of age, parenteral administration is indicated (SC or IP). Colostrum-deprived kittens given adult cat serum at a dose of 150 mL/kg (0.15 mL/g) developed serum IgG levels comparable with suckling littermates, but colostrum-deprived puppies given 40 mL/kg (0.40 mL/g) adult dog serum orally and parenterally failed to match suckling littermates' IgG levels. Puppies likely require as much as 100 mL/kg (0.10 mL/g). The dose should be divided over several administrations within a 12-hour period due to the volume [9,10].

Neonatal Ophthalmia**Pathophysiology**

Neonatal ophthalmia is an acute, mucopurulent infection of the conjunctiva which occurs before the eyelids separate (~14 days of age). Both gram-positive and gram-negative bacteria have been causal.

Clinical Presentation

Accumulation of fluid associated with ophthalmia produces noticeable swelling over the eye(s).

Diagnostics

The condition is apparent on physical examination and confirmed by intervention (Web Figure 121.2).

Therapy

Opening the eyelid by gentle manipulation with a gauze sponge or sterile mosquito forceps will allow cytology and culture of the fluid. The conjunctival space should be irrigated with sterile saline. Ten to 14 days of topical antibiotic is indicated. Ocular lubrication can be advisable as normal tear production is diminished until 10–14 days of life. Damage to the eye can occur if the condition is not recognized and treated.

Limb Deformities: Amelia, Hemimelia (Absence of a Limb or Distal Portion of a Limb), Pelvic Limb Hyperextension**Pathophysiology**

Limb deformities are commonly idiopathic; in some cases they are suspected to be heritable defects.

Clinical Presentation

Neonates with pelvic limb hyperextension are not as mobile as normal littermates and may not nurse effectively or competitively. The pelvic limbs are hyperextended and commonly rotated laterally.

Diagnostics

The defects are apparent in the physical examination. (Web Figure 121.3).

Therapy

Pelvic limb hyperextension can be corrected if addressed early in the neonatal period. Physical therapy (flexing and rotating medially) and gentle binding of the limbs can correct the defect in 3–4 days (Web Figure 121.4).

Neonatal Disorders in the Later Postpartum Period**Orphans****Pathophysiology**

Kittens and puppies under 3 weeks of age lack voluntary elimination without external stimulation, normally provided by the dam. The lack of nursing can result in hunger-driven suckling of littermates.

Clinical Presentation

Neonates with distended abdomen, vocalization, and restlessness can indicate constipation or urine retention. Focal areas of petechiation can be evident from littermate suckling.

Diagnostics

The diagnosis is made from the history of orphaning and physical examination.

Therapy

The micturition and defecation reflexes are stimulated using a cotton ball with lubrication on the anogenital area after each feeding. Periodic separation of the neonates in an orphaned litter may be necessary until solid food is introduced. Tube feeding is often the easiest and safest option for continued nutritional maintenance in orphan neonates until bottle feeding is well accepted. Neonates should receive multiple small feedings to achieve acceptable daily weight gain, approximately every 2 hours. For any patient receiving meals via tube feeding, care should be taken that the feeding tube is placed into the esophagus, not the trachea. The easiest way to ensure that placement is correct is to witness vocalization while the tube is in place, or to initiate it by pinching a toe or the scruff of the neck. If vocalization is heard, the tube is presently in the esophagus. When bottle feeding or tube feeding, the neonate's body should be sternal in orientation, with the skull planes parallel to the body.

In the first day of life, each puppy or kitten may lose or maintain the birth weight or even lose weight, but subsequently should steadily be gaining 5–10% of their body

weight daily. Neonates should gain weight steadily from the first day after birth (a transient mild loss from birth weight is acceptable on day 1) – puppies gaining 1–3 g per day per kilo (2.2 lb) of anticipated adult weight and kittens 50–100 g weekly.

The neonatal caloric requirement is 133 calories/kg/day during the first week of life, 155 calories/kg/day for the second, 175–198 calories/kg/day for the third, and 220 calories/kg/day for the fourth [2]. Commercially manufactured milk replacement formulae (Esbilac, Pet-Ag Inc., Elgin, IL; Puppy Milk Replacer Formula, Eukanuba, Iams Co., Dayton, OH; Veta-Lac Powder for Puppies, Vet-A-Mix, Shenandoah, IA; KMR, Pet-Ag Inc., Elgin, IL) are usually superior to home-made versions; recent studies have shown that none is equal to a bitch's milk and none is perfect. The use of milk obtained from the dam can be considered if available. An osmotic diarrhea (usually yellow, curdled stool appearance) can result from overfeeding formula, necessitating dilution of the product by 50% with water or a balanced crystalloid such as lactated Ringer's solution.

Aspiration Pneumonia

Pathophysiology

Aspiration pneumonia is a common disease of neonatal puppies and kittens. The disease often presents concurrently with the presence of cleft palate, but can occur spontaneously during nursing, bottle feeding, or tube feeding. Overfeeding causing overdistension of the stomach and placing a feeding tube in the trachea are the most common causes of aspiration.

Clinical Presentation

Aspiration pneumonia can present as an acute respiratory problem, but can also present with a history of the neonate or others in the litter wheezing or coughing, often accompanied with poor weight gain or fever. Other causes of dyspnea include congenital peritoneopericardial diaphragmatic hernias and trauma.

Diagnostics

Mucous membranes may be gray or blue in severely affected neonates. Auscultation of the chest will yield the presence of crackles and/or wheezes which may be distributed in all fields, or may be focal in nature. Puppies or kittens are often febrile due to infectious process. The neonate will often be unthrifty and small in appearance if the disease has been chronic. Thoracic radiographs can be performed if the patient is stable enough to tolerate room air or flow-by oxygen as well as restraint techniques. Radiographs can indicate how extensive the pneumonia is, which can be important in prognosis and monitoring improvement during treatment.

Therapy

Puppies and kittens with marked dyspnea should be immediately transferred to an oxygen cage (see Chapter 181), and handled within that environment until the animal is eupneic on room air. Some neonates that are more mildly dyspneic or tachypneic may tolerate flow-by oxygen during initial evaluation.

Empirical antibiotic therapy should be initiated. Clavulanic acid-potentiated beta-lactam antibiotics are often implemented initially, as they are among those safest to administer to neonates [11]. Initially parenteral administration is advised. Transtracheal washing for culture samples in a tiny neonate is rarely attempted, but may be applicable in neonates that do not respond to empirical treatment. Fluid and nutrient support are indicated.

If the animal becomes stable in oxygen and appears to have improved, slow tapering of the environmental oxygen can be initiated, monitoring for respiratory changes as the environmental oxygen is reduced. The patient should be comfortable breathing room air consistently for at least 12–24 hours prior to release. Oral liquid preparations of the antibiotic are preferable for home administration with proper instruction.

Swimmer Puppies

Pathophysiology

Swimmer puppies fail to develop normal ambulation by 10–14 days of life, moving instead on their ventrum by paddling their limbs laterally and caudally. Obese puppies from small litters, commonly raised on relatively slippery surfaces, are predisposed.

Clinical Presentation

A failure to ambulate normally is evident upon physical examination. Compression and deformation of the sternum and thorax occur concurrently.

Diagnostics

The defect is apparent on physical examination.

Therapy

Treatment should be instituted immediately upon diagnosis, consisting of caloric restriction, physical therapy, and improved traction in the nest box. Refractory cases can require body harnessing to keep the limbs under the trunk (Web Figure 121.5). If diagnosed early (3–5 weeks of age), the condition is reversible.

Juvenile Cellulitis

Pathophysiology

Juvenile cellulitis (puppy strangles) is a progressive, granulomatous, pustular disorder of puppies, most commonly

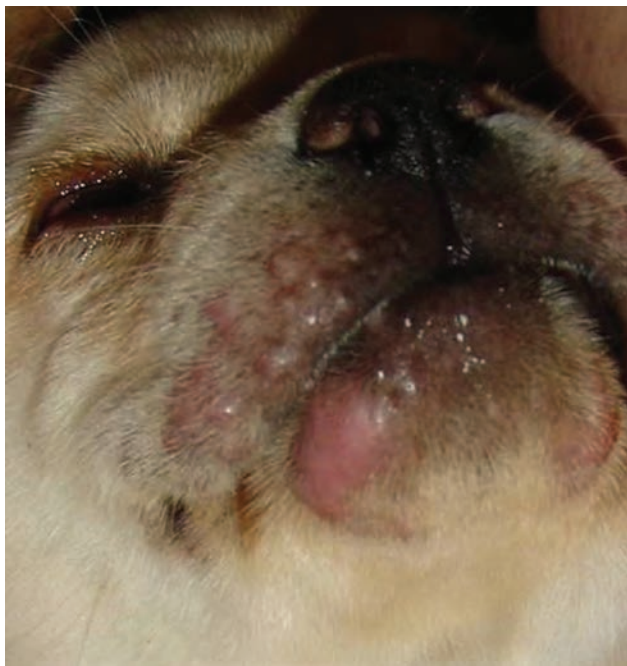


Figure 121.3 Juvenile cellulitis in a 4-week-old Labrador retriever. Pustules at the oral mucocutaneous junction.

in dogs younger than 4 months of age but occasionally reported in dogs up to 4 years of age.

Clinical Presentation

The eyelids, pinnae, lips, chin, muzzle, paws, abdomen, thorax, vulva, prepuce, and anus can be affected with lesions that fistulate, drain, and crust (Figure 121.3). Lymphadenomegaly, most commonly mandibular and superficial cervical, can be distant from the affected skin sites and is often painful. Pyrexia, anorexia, sterile suppurative painful arthritis, and an inflammatory hemogram can occur. Severe pyoderma, necessitating only antibiotic therapy, can have a similar appearance.

Diagnostics

Pustules and lymph nodes are usually sterile when cultured. Superficial cutaneous flora can be cultured from open, draining lesions. The diagnosis is confirmed by histopathological evaluation, but is commonly made on the basis of clinical appearance, especially if no response to antibiotic therapy occurs. The predominant inflammatory cell in juvenile cellulitis, characterized by light and electron microscopy and immunohistochemical staining, is an epithelioid macrophage.

Therapy

Juvenile cellulitis requires aggressive immunosuppressive therapy early in the course of the disease for resolution and to avoid the sequelae of cicatricial lesions.

Traditionally, puppies have been placed on immunosuppressive doses of prednisone (2.2 mg/kg/day), causing concerns with immunization efforts. Griseofulvin therapy offers an apparently effective treatment without the side-effects associated with corticosteroid administration, enabling discontinuation of corticosteroids sooner in the course of the disease. It has been reported to be effective as sole immunomodulatory therapy (14.2–34 mg/kg PO q12h). Griseofulvin is postulated to induce downregulatory signals within the lesions. The use of griseofulvin as sole therapy could be attempted in early cases [12].

Vaccination of puppies undergoing immunosuppressive therapy is not advised and they must be strictly isolated from sources of infectious disease.

Bacterial Overgrowth Syndrome-Associated Diarrhea

Pathophysiology

Persistent diarrhea can occur in otherwise healthy neonates due to bacterial overgrowth associated with overfeeding. Symbiotic colonic bacteria assist digestion. The upper GI tract was once believed to be sterile, but normal colonization of the duodenum, jejunum, and ileum is now appreciated. Bacterial overgrowth syndrome (BOS) occurs when the normally low bacterial colonization in the upper GI tract significantly increases. Neonates lack propulsive peristaltic action; gut motility results only from aboral pressure from nursing. Diminished gut motility promotes bacterial overgrowth. Gastric acid normally reduces the proximal small intestinal bacteria. Neonates have reduced gastric acidity. Malabsorption of bile acids, fats, carbohydrates, proteins, and vitamins causes many of the symptoms of diarrhea and weight loss associated with BOS. Bacteria deconjugate bile acids, promoting further carbohydrate malabsorption and producing an osmotic diarrhea.

Clinical Presentation

Otherwise healthy, vigorous, and often overweight neonates have persistently soft, sometimes malodorous stools.

Diagnostics

Fecal examination for parasites is negative, although prepatency can mask infection. A direct smear can support BOS.

Therapy

Treatment is aimed at reducing the damage caused by malabsorption and restoring nutritional health and normal gut flora. The antimicrobials of choice for therapy of BOS-associated diarrhea are ampicillin, amoxicillin or metronidazole; the latter is less preferable in neonates.

due to the potential for CNS signs with overdosage and the neonatal diminished capacity for hepatic metabolism. Probiotics can be helpful to normalize beneficial gut flora populations. Enterocolitis from intestinal parasites can be severe in pediatric patients with high worm burdens. Prophylactic deworming with a broad-spectrum anthelmintic such as pyrantel pamoate should be instituted at 2, 4, and 6 weeks of age, before identification of infestation is possible with fecal examination.

Urinary Ectopia

Pathophysiology

Urinary ectopia is considered a heritable congenital condition more common in females. Ectopic placement of the distal ureter into the urethra, vestibule or vagina is usually associated with ureteral dilation with or without renal pelvic dilation. A ureterocele is an uncommon congenital dilation of the ureter near the bladder, appearing as a cystic structure within the bladder lumen or wall. The ureterocele occurs most commonly in association with an ectopic ureter. Hydronephrosis can eventually result from an uncorrected ectopic ureter due to flow impedance at the abnormal site of insertion. Urinary tract infection is commonly associated with ectopia, due to accompanying urethral sphincter mechanism anomalies and, if not detected and treated, can progress to pyelonephritis and ureteritis. Infection and its associated inflammation in the tract can cause further damage.

Clinical Presentation

The most common sign of ectopia of the urinary tract is incontinence. Astute breeders can identify incontinence in neonates; ectopia should be ruled out. Urine scalding in the perivulvar area can be evident.

Diagnostics

Abdominal ultrasound offers an excellent initial screening tool. Visualization of a non-vascular fluid-filled structure with a hyperechoic wall passing dorsal to the urinary bladder, or obvious insertion of the structure into the proximal urethra, suggest the diagnosis. Visualization of the ureteral jets in the bladder suggests normalcy, but some ectopic ureters insert initially into the bladder and additionally tunnel distally to terminate in an abnormal site. Visualization of the dilated ureter usually occurs near the urinary bladder. Visualization of the bladder neck and proximal urethra may be obscured by pubic bone, making identification of such termination difficult. Contrast-enhanced computed tomography is the most sensitive and specific modality for the diagnosis of ectopia but, like double contrast radiography, requires anesthesia, making initial evaluation with ultrasound desirable when ectopia is suspected clinically.

Therapy

Repair is delayed until adequate patient size is achieved and can be surgical or by endoscopically facilitated laser technique. Control of infection and urine scalding is advised in the meantime.

Hypoglycemia

Pathophysiology

Previously described neonatal limited gluconeogenesis, glycogenolysis, glycogen reserves and dependence on frequent feeding predispose puppies and kittens to clinical hypoglycemia. Hypoglycemia can also result from endotoxemia, septicemia, portosystemic shunts, and glycogen storage abnormalities. Extreme or prolonged hypoglycemia can result in permanent neurological changes due to brain injury.

Clinical Presentation

A hypoglycemic neonate may be weak and have poor responsiveness to stimulation, but may alternatively be crying and restless.

Diagnostics

Acquisition of blood and evaluation of glucose using table-top testing is most efficient and appropriate given the available blood volume. A value of 70 mg/dL is considered normal in neonatal life, and a value <50 mg/dL is an indication of hypoglycemia [13].

Therapy

If possible, parenteral dextrose is preferred over oral sources. Clinical hypoglycemia can be treated with dextrose solution intravenously or intraosseously, at a dose of 0.5–1.0 g/kg using a 5–10% solution, or a dose of 2–4 mL/kg of a 10% dextrose solution. Single administration of parenteral glucose is adequate if the puppy can then be fed or nurses. Fifty percent dextrose solution should only be applied to the mucous membranes because of the potential for phlebitis if administered intravenously; however, circulation must be adequate for absorption from the mucosa. Neonates administered dextrose should be monitored for hyperglycemia because of immature metabolic regulatory mechanisms. If a neonate is too weak to nurse or suckle, a mixture of a warmed, balanced crystalloid (1/2 strength) saline solution and 5% dextrose may be administered subcutaneously at a dose of 1 mL per 30 g of body weight, until the pup can be fed or nurses. A balanced warmed nutrient-electrolyte solution can be administered orally by stomach tube every 15–30 minutes until the neonate is capable of suckling. Oral fluid and glucose replacement may be preferable if the puppy has an adequate swallowing reflex and is not clinically compromised.

Fading Puppy Syndrome: Neonatal Bacterial Septicemia and Herpes Infection (CHV-1)

Pathophysiology

The fading puppy syndrome refers to neonatal death secondary to systemic infection. *In utero* or postpartum viral infection with canine distemper, canine parvovirus, canine adenovirus, canine and feline herpes, feline infectious peritonitis, feline immunodeficiency virus, panleukopenia, and feline leukemia virus cause neonatal mortality. Bacterial causes of neonatal infection include *Brucella canis* (canine), *Campylobacter*, *Salmonella*, *Klebsiella*, streptococci and staphylococci, and *Leptospira* (canine); *Neospora* (canine) and *Toxoplasma gondii* (canine and feline) are potential protozoal pathogens. Mycotic infection is rare.

Incompletely developed immune systems and inadequate thermoregulatory capacity during the first days of life make neonates vulnerable to systemic infection (both bacterial and viral).

Exposure of a naive bitch to CHV-1 during the last 3 weeks of gestation can result in either late term abortion of a litter or neonatal deaths within their first few weeks of life, because inadequate periparturient maternal antibodies exist to allow passive immunity to be acquired by the neonates. Transmission of CHV-1 to neonates can occur subsequent to contact with infectious vaginal fluids during whelping or with vulvar or oronasal secretions in the postpartum period. Puppies born to a naive bitch may also come into significant, infectious contact with CHV-1 from another dog shedding the organism. The recently infected brood bitch generally has no other clinical signs. Healthy recently infected adult dogs of either gender can show signs of a mild upper respiratory infection (sneezing, serous oculonasal discharge) for a few days, but are otherwise usually unremarkable.

The incubation period of CHV is 6–10 days. The virus replicates in the epithelial cells of the oronasal and pharyngeal mucosa and the regional lymphatics. The lower (<38°C or 100°F) body temperature normal in canine neonates permits the virus to actively replicate and spread.

Clinical Presentation

Factors that reportedly predispose a puppy to septicemia include endometritis in the bitch, a prolonged delivery/dystocia, feeding of replacement formulae, the use of ampicillin, stress, low birth weight (<350 g for a medium-sized breed), and chilling with body temperature <96°F [14]. Commonly, a decrease in weight gain, failure to suckle, hematuria, persistent diarrhea, unusual vocalization, abdominal distension and pain, and sloughing of the extremities indicate bacterial septicemia may be present. Neonatal bacterial septicemia can cause

rapid deterioration resulting in death if not recognized and treated promptly.

In CHV-1, puppies often present as individuals, but the disease often has affected or will later present similarly in the littermates. Although reported to cause fetal loss and resorption, the classic presentation is a high rate of stillborns in a litter, followed by the remaining live puppies dying due to systemic effects of herpesvirus. Classic signs in the neonate are not specific and include incessant vocalization, anorexia (with poor weight gain), dyspnea, abdominal pain, incoordination, diarrhea, serous to hemorrhagic nasal discharge, and petechiation of the mucous membranes. The mortality rate in litters infected *in utero* or during birth can approach 100%, with deaths occurring during the first few days to a week of life [15].

Diagnostics

Premortem diagnosis can be challenging, and clinical signs may not be noted due to sudden death. Necropsy with identification of viral inclusion bodies or positive PCR testing confirm the diagnosis of CHV-1. Gross histopathology of bacterial septicemia and canine herpes infection can be very similar. PCR profiles for abortion and neonatal death are commercially available.

Prevention

The umbilicus of neonates should be treated with tincture of iodine immediately after birth to reduce contamination and prevent ascent of environmental bacteria into the peritoneal cavity (omphalitis-peritonitis).

Minimal transplacental transfer of immunity occurs in the dog. Adequate ingestion of colostrum must occur promptly postpartum for puppies to acquire passive immunity. The transmission of protective immunity (placental or colostrum antibodies) between a bitch and her puppies depends upon the prior existence of adequate serum maternal antibodies. Therefore, breeding bitches with exposure to CHV-1 earlier in life have the best opportunity to seroconvert and develop protective antibodies. This commonly occurs in kennels or at crowded canine events such as dog shows and trials. Documentation of positive CHV-1 serology generally indicates adequate maternal antibodies. Bitches who are naive to CHV-1 during pregnancy must be strictly isolated from potential exposure during gestation and for at least 6 weeks postpartum to prevent transmission of the virus to her fetuses or neonates. Subsequent litters of the infected pregnant or postpartum bitch are usually normal, having acquired resultant maternal antibodies.

A vaccine is available in Europe, but not currently in the United States. Efficacy studies for use of the vaccine are limited. The vaccine is recommended only in female breeding dogs with a perceived risk of CHV-1 infection

(exposure in a pregnant naive bitch) to prevent neonatal disease and mortality.

Therapy

Therapy with broad-spectrum, bactericidal antibiotics, improved nutrition via supported nursing, tube feeding or bottle feeding, maintenance of body temperature, and appropriate fluid replacement are indicated. The third-generation cephalosporin antibiotic ceftiofur sodium (Naxcel; Pharmacia and Upjohn) is an appropriate choice for neonatal bacterial septicemia as it alters normal intestinal flora minimally and is usually effective against the causative organisms. Ceftiofur sodium should be administered at a dose of 2.5 mg/kg SC q12h for no longer than 5 days. Because puppies less than 48 hours old have reduced thrombin levels, presumptive therapy with vitamin K1 may be used (0.01–1.0 mg SC per puppy).

Failure to respond to antibiotic therapy for neonatal septicemia should prompt consideration of CHV-1 infection.

Specific antiviral therapy, if instituted in a timely manner, has been reported to reduce mortality from CHV-1. Aciclovir is an antiviral agent with activity against a variety of viruses, including herpes simplex. Aciclovir is preferentially taken up by susceptible viruses and converted into the active triphosphate form, inhibiting viral DNA replication. Aciclovir is poorly absorbed after oral administration and is primarily hepatically metabolized. It can increase the toxicity of nephrotoxic drugs. The half-life in humans is approximately 3 hours. Its use in veterinary medicine is not well established and it should be used with caution and only in situations where indicated. The safety and effectiveness in humans less than

2 weeks of age are not established. The dose (20 mg/kg PO q6h × 5 days) is currently extrapolated from that for humans. Providing ambient exogenous heat to raise the neonatal body temperature above 101°F can reduce viral replication [16].

Trauma

Pathophysiology

Trauma of a variety of causes can result in emergency presentation. Trauma can result from the dam's manipulation of her litter (Web Figure 121.6). Sometimes trauma can be intentional, and more commonly so in the bitch than the queen. First-time mothers can sometimes become aggressive or cannibalistic towards a litter. Also, trauma may present due to improper handling by the owner or children in the home. Breeders who "swing" puppies to clear fluid from the lungs after delivery can cause intracranial trauma resulting in neurological signs [17].

Clinical Presentation

Pain, dyspnea, abdominal distension, contusions/lacerations, hemorrhage, weakness, and seizures can occur with trauma.

Diagnostics

Physical examination reveals signs of trauma. Ultrasound of the abdomen and whole-body radiography are useful.

Therapy

Therapy is dictated by the nature of the injury. Special aspects of neonatal anesthesia (local or general) should be taken into consideration.

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Metritis and Mastitis

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Metritis

Metritis in the bitch and queen is predominantly a postpartum condition that results from an ascending bacterial infection in association with parturition. It is hormonally distinct from pyometra as it occurs during a time when the serum progesterone concentration is low, and is a primary event rather than secondary to underlying uterine pathology such as cystic endometrial hyperplasia–pyometra complex (see Chapter 123). Predisposing factors for the development of metritis include abortion, dystocia, obstetric manipulation, retained fetal or placental tissue, and uterine prolapse [1]. The bitch is more frequently represented than the queen. A diagnosis of metritis in the postpartum dam may be made with consideration of history, clinical signs, clinical pathology data, and imaging.

Clinical Signs

Clinical signs of metritis vary, and range in severity, depending on the degree of endotoxemia and systemic involvement (Figure 122.1) [1–3]. Vaginal discharge may be considered a key clinical marker for metritis but it is not always easy to objectively define what is normal during the postpartum period.

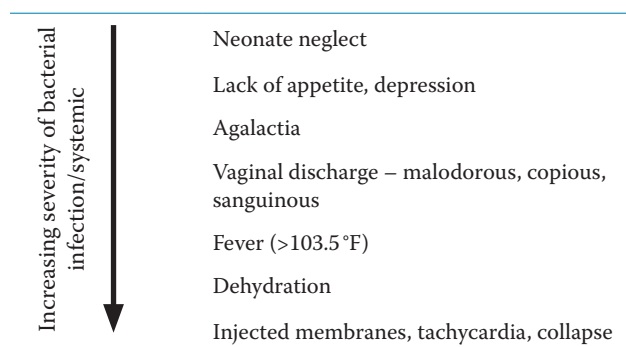


Figure 122.1 Range of clinical signs of metritis in the bitch and queen.

Any sick dam presented within 7 days of parturition should be evaluated for metritis. A malodorous serosanguinous vaginal discharge is not abnormal *per se* for the bitch during the postpartum period. However, as a general rule, the combination of voluminous, hemorrhagic, and/or putrid-smelling postpartum vaginal discharge should raise concern for metritis [4]. Unless postparturition imaging is known to have been completed prior to presentation, the possibility of a dead retained fetus should always be considered. Untreated, a dam with a persistent retained dead fetus(es) may rapidly develop sepsis.

Diagnostics

Initial diagnostics should include a complete blood count, biochemical analysis, and abdominal imaging. Ultrasound-guided cystocentesis is the preferred method for urine collection. Cases presenting with signs of sepsis or peritonitis may benefit from evaluation for disorders of coagulation (see Chapter 70).

Classically, metritis is associated with a leukocytosis and left shift. Biochemical parameters are variable, but may include alterations in serum proteins, renal function consistent with dehydration, and sepsis [1,2]. A single report of hypercalcemia has been described [5]. Coagulation changes may be present in cases with sepsis. The majority of cases are associated with *Escherichia coli* but other pathogens such as *Staphylococcus* and *Streptococcus* are also encountered [1,6]. Guarded culture and sensitivity of the cranial vaginal discharge may be considered to confirm bacterial populations and obtain sensitivity and minimum inhibitory concentration data. If a speculum is not available, an empty 1 or 3 mL sterile syringe case may be introduced into the caudal vaginal canal to act as a guard for the introduction of a sterile cotton tip applicator to the cranial vaginal vault for culture.

Diagnostic imaging is required to identify any retained fetus(es). Radiographs may be helpful for the rapid

identification of a retained fetus, but ultrasound is the diagnostic imaging of choice as it permits evaluation of the uterine contents [2]. The urinary bladder provides an acoustic window for the body of the uterus and predicts the location of the uterine body. The normal postpartum uterus is prominent, and retained fetuses can be readily identified and lack of heart beat confirmed [7]. From days 1 to 4 post partum, the normal canine uterus is enlarged and echogenic with irregular uterine walls that may be difficult to distinguish from uterine contents. Uterine diameter varies and is report to range from 1.1 to 3.8cm at placental sites, and 0.5 to 1.4cm in between [8]. The typical mean uterine diameter in the queen changes from 16.6mm at day 1 to 6.2mm at day 14 post partum [9]. Normal variations in uterine diameter during the period of involution make confirmation of metritis based on a single-timepoint ultrasound evaluation challenging. The most complete clinical evaluation includes serial ultrasonographic evaluation of the uterus and uterine content, in conjunction with clinical pathology data and clinical parameters [7].

As metritis is clinically distinct from pyometra based on the timing of presentation (postpartum), evaluation of serum progesterone is rarely, if ever, indicated.

Treatment

Treatment priorities include rehydration, antimicrobial therapy, and administration of an ecbolic agent. Pending culture and sensitivity, antimicrobial choice should be based on efficacy towards *Escherichia coli* with consideration of whether or not continued nursing of neonates is planned (see Chapter 200). The decision regarding whether or not to remove neonates and hand raise them depends predominantly on the health of the dam. Enrofloxacin, amikacin, and second-generation cephalosporins are good initial choices for *E. coli*; the addition of amoxicillin is of benefit for streptococcal cover [10,11]. While amoxicillin/clavulanic acid is generally considered neonate safe, and a good choice when treating genital *E. coli* infections in the dog and cat, recent data suggests increasing resistance [12,13]. Based on susceptibility changes, trimethoprim-sulfonamides may be the preferred empirical oral treatment however, its use would preclude continued nursing as it is excreted in milk [12].

PGF2-alpha (Lutalyse) is the first choice for an ecbolic agent and may be used at 250 µg/kg SC q24h until uterine evaluation has occurred. More frequent PGF2-alpha administration (q8h) in conjunction with repeated imaging and in-house monitoring may be used to evacuate a single dead fetus in the bitch [4]. Caution is advised if more than one dead fetus is present. An intravaginal PGF2-alpha protocol has been described in the literature but is not routinely used [14]. Due to changes in oxytocin receptor expression that are not well defined for the dog

and cat, the use of oxytocin as an ecbolic agent is not advised more than 24 hours post partum.

For the majority of patients with mild clinical signs, medical treatment can be administered as an outpatient within a few hours. Follow-up treatment can typically be provided within 24 hours by the regular veterinarian. More severe cases requiring intensive supportive care and/or surgery typically require separation of the neonate and dam. As metritis is not associated with an underlying uterine pathology, the prognosis for return to fertility is considered to be good.

Mastitis

Mastitis typically occurs in the postpartum period and covers a wide range of presentations from non-septic galactostasis through gangrenous mastitis and sepsis [2,3]. One or multiple glands may be affected as connective tissue separates each gland sinus system [3]. In the postpartum period, mastitis is typically associated with ascending infection and environmental hygiene may be a factor in its development. As neonates are also susceptible to adverse environmental conditions, basic husbandry should be evaluated.

Mastitis may also occur during pseudopregnancy in the bitch and with inflammatory mammary adenocarcinoma [3]. In the dog, mastitis has also been reported with systemic blastomycosis and *Mycobacterium* [15,16]. In the queen, there is very little mammary tissue in the non-lactating female and clinical cases of mastitis are typically limited to the postpartum period [17].

Clinical Signs

Presentation is generally during the first 2 weeks post partum. Mild cases of mastitis are accompanied by discomfort, pain, and swelling of one or more gland. More severe cases may present with fever (>103.5°F), depression, anorexia, and failure to care for neonates, or failure of neonates to thrive. The most severe cases present with signs of septic shock, mammary abscess formation, or gangrene. Milk from the affected gland(s) is not always grossly abnormal but green, reddish brown, or hemorrhagic discoloration should raise suspicion for mastitis.

Diagnostics

Initial diagnostics should include a complete blood count, biochemical analysis, and urinalysis. Classically, mastitis is associated with a leukocytosis and left shift. Biochemical parameters are variable but are typically normal for mild cases, and consistent with dehydration, and sepsis for severe cases. Color Doppler imaging is described

for evaluation of central lobar vascular supply for cases progressing to gangrene and tissue necrosis, but B-mode ultrasound alone does not appear to predict treatment outcome [18]. Cytology of milk from the affected gland(s) may be helpful to identify abundant bacteria, but it is worth noting that normal milk may contain some bacteria [3]. Milk white blood cells are not an indicator of mastitis and vary greatly from gland to gland [19].

A milk sample should ideally be submitted for bacterial culture and sensitivity and measurement of pH to help guide antimicrobial selection. Typical bacterial isolates associated with bacterial mastitis include *E. coli*, *Streptococcus* and *Staphylococcus* spp [1–3,17].

For those cases presenting outside the postpartum period, thoracic radiographs and fine needle aspirate cytology should be considered for any mass lesions associated with the mammary gland [15].

Treatment

Dams with non-septic milk stasis and mild discomfort are typically not systemically ill and may be treated with warm compress application, analgesia, and monitoring. Nursing of the affected glands should continue as galactostasis will contribute to the disease process. Dams with signs of fever

and peripheral leukocyte changes benefit from antimicrobial therapy and supportive care (see Chapter 200). The degree of intervention will vary depending on the severity of their clinical signs. Whether or not to remove neonates from the dam and hand raise the litter is a decision that should be based on the condition of the bitch, the age of the neonates, and the availability of nursing care. If neonates are to be removed, cabergoline (5 µg/kg PO q24h for 5 days) may be used to decrease milk production [1].

Selection of antimicrobials based on milk pH has been described to improve distribution into the mammary gland [2]. Under normal circumstances, milk is slightly more acidic than serum and antimicrobial agents that are weak bases with good activity against *E. coli* may be advantageous (such as trimethoprim-sulfonamides). However, milk may become more alkaline with bacterial infection and under those circumstances amoxicillin-clavulanic acid or cephalosporins may be preferred. Enrofloxacin may be used regardless of milk pH, and in patients that continue nursing if the benefits outweigh the risk of cartilage abnormalities.

For cases that progress to mammary abscessation or gangrenous mastitis despite treatment, neonates should be removed from the dam and the affected glands removed or surgically debrided.

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Pyometra

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Signalment, Clinical Presentation, and Associated Disease

Pyometra is a reproductive disorder of mature, intact bitches and queens. However, previous exposure to reproductive hormonal therapy and congenital abnormalities of the genital tract, such as vaginal strictures, predispose younger bitches and queens to developing pyometra [1–4]. Dramatic variation in the incidence of pyometra between different breeds suggests a genetic component in both bitches and queens. In bitches, the mean age of pyometra diagnosis is 7.25 years with a range of as early as 4 months to 16 years [5]. Fewer data are available in queens, as the incidence is lower, presumably due to less cumulative uterine exposure to progesterone when compared to the bitch.

The majority of pyometra cases present with a history of recent estrus, and pyometra is preceded by cystic endometrial hyperplasia (CEH). In bitches, the classic time frame is 1–4 months after estrus [6], while queens typically present within 4 weeks (2–5 weeks range) [7]. In any ill intact bitch or queen, pyometra should be considered as a differential and a thorough reproductive history taken (noting parity, last estrus, and any prior hormonal therapy). The most common clinical findings of pyometra in bitches are vaginal discharge (80%), pyrexia (47%), polyuria/polydipsia (<50%), and emesis [8,9]. Non-specific findings include lethargy and anorexia and in more advanced cases, signs of shock such as tachycardia, tachypnea, hypotension, and pale or injected mucous membranes. Careful abdominal palpation may reveal large tubular organ/uterine enlargement and may elicit pain. Queens classically present with milder signs that can include purulent vaginal discharge, anorexia, lethargy, emesis, unkempt appearance, and a palpable uterine enlarge-

ment/abdominal distension [7,10,11]. The cervical patency determines the presence or absence of vaginal discharge and is an important consideration in case management. Open-cervix pyometra typically results in milder systemic signs. In contrast, closed-cervix pyometra cases typically present without overt vaginal discharge and generally marked clinical signs of illness due to sepsis. Vaginal discharge can range from purulent to hemorrhagic to mucoid.

The pathogen predominantly associated with pyometra is *Escherichia coli* (>70% of cases), but other vaginal commensal bacteria (*Staphylococcus aureus*, *Enterobacter*, *Pseudomonas*, *Klebsiella*, *Proteus*, and *Streptococcus* spp) have been recovered [12–15]. The majority *E. coli* strains isolated in pyometra contain specific uropathogenic virulence factors (UVF) that enhance endometrial adherence [16] and may produce lipopolysaccharide (LPS), leading to serious systemic disease in the patient. Pyometra can lead to the development of the systemic inflammatory response syndrome (SIRS) (see Chapter 159). SIRS has been reported in up to 50% of bitches with pyometra and has been associated with a poor prognosis and increased duration of hospitalization [15,17]. In cases of pyometra-induced sepsis, serum concentrations of inflammatory markers such as C-reactive protein (CRP), serum amyloid A (SAA), and prostaglandin F2 metabolites (PGFM) have been shown to significantly increase [15,17,18]. Pyometra can lead to severe sepsis and multiple organ dysfunction syndrome [19].

Diagnostics

Cranial vaginal cytology, culture, and vaginal speculum visualization may aid in the diagnosis of pyometra.

For aerobic culture and susceptibility, a sample of the cranial vaginal discharge is obtained using a guarded swab and speculum. In the majority of pyometra cases, a large number of degenerate neutrophils and intra- or extracellular bacteria are typically seen on cytology. However, the diagnosis of pyometra should not be made on vaginal cytology alone, as large numbers of neutrophils with some bacteria are normal during diestrus.

The diagnosis of pyometra is primarily made by ultrasound. Typical ultrasonographic findings consistent with pyometra include uteromegaly, thickened uterine walls, proliferative endometrial changes, fluid-distended convoluted tubular horns, and anechoic to hyperechoic luminal fluid [20,21]. Uterine fluid in pyometra is usually homogenous, but can be flocculent with slow swirling patterns [22]. Ultrasound can differentiate pyometra from other soft tissue causes of uterine distension, and is imperative for evaluation of the presence of cystic endometrial hyperplasia and integrity of the endometrium. Moderate to advanced CEH can be reliably diagnosed as 1–4 mm anechoic cysts within a thickened endometrium [8]. Severe CEH may be associated with a poorer response to medical therapy [8]. If uterine torsion or rupture is suspected, ultrasound can also be used to evaluate the presence of peritonitis (see Chapter 87).

Pyometra classically presents with a marked leukocytosis characterized by monocytosis and a severe neutrophilia with a left shift and toxic changes. The leukocytosis is typically more severe in closed-cervix pyometra cases [12]. A mild to moderate normocytic, normochromic, non-regenerative anemia of chronic disease may be present. Up to 25% of pyometra cases can have a normal complete blood cell count (CBC), especially if pyometra is detected early in its course on ultrasonographic examination [9].

Patients with pyometra may have variable changes in their serum chemistry values. The most common abnormalities include azotemia, increased liver enzymes, hyperbilirubinemia, hypercholesterolemia, hyperglobulinemia, hypoalbuminemia, and hyperproteinemia [12]. Azotemia may be present (12–37%) in affected bitches and can be due to prerenal dehydration and/or endotoxin-induced (*E. coli*) renal tubular damage [23]. These renal changes are typically transient and reversible with treatment. However, a blood urea nitrogen of over 60 mg/dL has been associated with acute kidney injury and a poor prognosis [24] (see Chapter 94). Some strains of *E. coli* produce cytotoxic necrotizing factors, which in conjunction with dehydration can cause reversible hepatocellular damage or hypoxia [24]. Urinalysis may reveal dilute urine, bacteriuria, glucosuria, and/or proteinuria.

Treatment

Stabilization

Due to the insidious onset and non-specific signs of pyometra, many patients present in the advanced stage of the disease and may require stabilization prior to initiating definitive therapy. Full evaluation of cardiovascular, respiratory, and metabolic systems is required and stabilization provided as indicated prior to anesthesia (see Chapter 2). If the patient is stable, surgical and anesthetic risk may be reduced and stability improved by initiating medical therapy to lyse the corpus luteum, dilate the cervix, and facilitate evacuation of the purulent uterine fluid [25].

Antibiotic Therapy

Broad-spectrum antibiotic therapy should be started immediately upon presentation in all pyometra cases (see Chapter 200). Empiric antibiotic selection initially should target *E. coli* and have good uterine penetration. A combination of a fluoroquinolone and extended-spectrum penicillin is preferred [26]. Other appropriate antibiotic choices in pyometra include trimethoprim-sulfonamide and third-generation cephalosporins [27]. Long-term antibiotic therapy should be based on the results of a bacterial culture and sensitivity profile of the purulent exudate, and should be continued for 2 weeks (in surgical cases) to 1 month (with medical management).

Surgical Versus Medical Management

The severity of clinical presentation and breeding potential of the animal direct the decision to pursue medical or surgical management to address the underlying cause of pyometra. Historically, surgical ovariohysterectomy (OHE) was the only treatment for pyometra and still is the treatment of choice in most cases (especially in non-breeding animals). Surgery directly removes the source of the purulent exudate and endotoxin release. With the advances made over the last 20 years, medical management is a viable alternative to surgery in pyometra cases in which the owner wishes to preserve fertility. Medical management should be considered in valuable breeding bitches/queens (<6 years). However, if the patient's condition deteriorates or if significant clinical improvement is not seen within 2 days of initiating medical therapy, surgical management may need to be reconsidered. If peritonitis or uterine torsion is suspected, medical management is contraindicated (see Chapter 87).

Surgical Management

Once the patient has been stabilized, antibiotic therapy instituted, and surgical risk minimized, surgery can be

performed. Pyometra OHE surgery is similar to spay surgery except the uterus is grossly enlarged and can be quite friable. After careful removal of the uterine stump, the remaining small amount of uterine lumen should be lavaged with warm isotonic saline and omentalized. Afterwards, the peritoneal cavity should be copiously lavaged, and a sample of the uterine fluid should be obtained for culture and susceptibility [25]. If peritonitis is present, a closed active suction drainage system should be placed [28]. Surgical management of uterine stump pyometra is similar and requires exploratory laparotomy with surgical excision of all remaining uterine and remnant ovarian tissue.

All surgically managed pyometra cases should be intensively monitored for 24–48 hours postoperatively. Signs of sepsis, hypovolemia, azotemia, anemia, hypoglycemia, hyperproteinemia, liver or renal dysfunction, and acid–base derangement should be immediately addressed [25]. Supportive treatments and intravenous fluids should be continued for at least 24 hours until the patient is eating and drinking on their own. Serum biochemistry and CBC should be followed postoperatively until abnormalities resolve (typically within 5 days). Appropriate surgical treatment of pyometra should cause the marked inflammatory response to subside, so monitoring of serum SAA, CRP, and hepatoglobin may be useful in postoperative detection of complications (ongoing infection) and resolution [29].

Peritonitis is the most common complication followed by anorexia, pyrexia, vomiting, renal insufficiency, and hepatic disease (see Chapter 87). Most complications resolve within 2 weeks [25]. After surgery, 92% of bitches survive, suggesting a good prognosis [23]. Renal status (pre- and postoperatively) is the best prognostic indicator. Other factors that affect prognosis for pyometra include cervical patency, dehydration status, uterine rupture (septic peritonitis), and significant co-morbidities [25].

Medical Management

Medical treatment (Table 123.1) involves the use of prostaglandin F₂-alpha (PGF₂-alpha), dopamine agonists, and progesterone receptor antagonists (antiprogestins), either alone or in combination. Although many protocols have been described for the medical management of pyometra, their goals are essentially the same.

The first goal is to remove the effects of progesterone to facilitate cervical relaxation, myometrial contractions, and improved local uterine immunity. These changes allow natural expulsion of purulent uterine contents and bacteria through an open cervix. This goal can be accomplished by the use of prostaglandins (alone or in combination with dopamine agonists) and/or progesterone

receptor antagonists. The second goal of medical management is prevention of bacterial proliferation through appropriate antibiotic therapy. In animals with advanced CEH, the final goal of medical management is to facilitate endometrial regeneration (thus preserving fertility) by prolonging the anestrus period. This can be accomplished by the use of androgen receptor agonists, such as mibolerone. Owners should be warned of possible future recurrence after treatment and potential reduction in fertility.

Prostaglandin F₂-alpha and Prostaglandin Agonists

Success in the treatment of pyometra has been reported with the use of PGF₂-alpha therapy alone or in combination (off-label). Repeated dosing of PGF₂-alpha induces luteolysis, directly decreasing progesterone levels, which leads to cervical opening and decreased glandular secretions [30,31]. Additionally, prostaglandins directly promote uterine contractions, which with a patent cervix permit expulsion of uterine discharge. Therapeutic PGF₂-alpha is available in a natural form (dinoprost tromethamine) and a synthetic form (cloprostenol or alfaprostol).

Treatment with PGF₂-alpha can have significant dose-dependent side-effects, especially at higher doses. Side-effects include panting, emesis, hypersalivation, hypothermia, diarrhea, urination, anxiety/shivering, ataxia, and abdominal contractions. Additional side-effects seen specifically in queens were vocalization, grooming, kneading, mydriasis, and lordosis [10]. PGF₂-alpha has a narrow therapeutic index and in rare cases (especially with higher doses and a closed cervix), shock and death may result [25]. Therefore, administration of low doses through subcutaneous or intramuscular injections is recommended. Adverse effects typically develop within 20–30 minutes and should abate within another 30 minutes. Tolerance develops quickly and reduction of side-effects generally occurs with each subsequent dose. Hospitalization, at least at the onset of PGF₂-alpha therapy, is recommended due to frequency of side-effects and dosing and potential toxicity. Suggested doses are given in Table 123.1. The use of ecbolics is contraindicated in a closed cervix pyometra in both bitches and queens unless the cervix opens spontaneously or is induced medically [5,9,10,25,30].

Clinical improvement is expected within 48 hours of initiating prostaglandin treatment. Copious vaginal discharge is typically observed for at least 48 hours then gradually diminishes. A rapid reduction in uterine diameter on ultrasound should be evident within 24–48 hours [32]. Following the progression of uterine evacuation by ultrasound every few days is important to determine the duration and efficacy of therapy. Resolution of pyometra is characterized

Table 123.1 Suggested medical management protocols for pyometra.

Protocols	Drug(s) and dosing	Side-effects and indications	References
Low-dose PGF2-alpha	Dinoprost trimethamine (low dose): 20–25 µg/kg SC q2–4 h daily until uterine evacuation/luteolysis	May require hospitalization due to high dosing frequency This dosing regimen minimizes side-effects of PGF2-alpha	[45] [46]
Titration dose PGF2-alpha	Dinoprost trimethamine (titration dose): 10 µg/kg SC for 3–5 doses on day 1; 25 µg/kg SC for 3–5 doses on day 2; 50 µg/kg SC for 3–5 doses on days 3–10 (or until resolution of vaginal discharge)	This dosing regimen minimizes side-effects of PGF2-alpha	[9]
High-dose PGF2-alpha (>0. mg/kg q24h)	Dinoprost trimethamine (high dose): 250–500 µg/kg SC q24h × 3 days	Worse PGF2-alpha side-effects Increased risk of uterine rupture Contraindicated in closed-cervix pyometra (due to risk of peritonitis/rupture)	[30]
Intravaginal infusion of PGF2-alpha	Dinoprost trimethamine (intravaginally): 150 µg/kg topically (as a vaginal infusion at 0.3 mL/kg) q12h × 3–12 days (until resolution)	Better results in treatment of open-cervix pyometra Intravaginal administration helps minimize systemic side-effects of PGF2-alpha	[44]
PGF2-alpha in queens *	Dinoprost trimethamine (medium dose): 100 µg/kg SC q12–24h × 3–5 days OR Dinoprost trimethamine (titration dose): 10–15 µg/kg SC q8h on day 1; 25 µg/kg SC q8h on day 2; 50 mg/kg SC q8h for day 3–10 (or until complete uterine emptying)	Side-effects of PGF2-alpha dosing (especially with first doses) This dosing regimen minimizes side-effects of PGF2-alpha	[10] [25]
PGF2-alpha analogue**	Cloprostenol (synthetic PGF agonist): 1–5 µg/kg SC q24h × until resolution	Treatment may need to be continued for 7–10 days or until complete uterine emptying is observed [17,43,44]	[5] [45]
PGF2-alpha analogue + dopamine agonist	Cloprostenol (PGF2-alpha analogue): 1 µg/kg SC q24h × 7 days WITH Cabergoline (dopamine agonist): 5 µg/kg PO q24h × up to 14 days OR Bromocriptine (dopamine agonist): 10–20 µg/kg PO q8h × up to 14 days	Dosing protocol is similar in both bitches and queens Dopamine agonist should be given for at least 7 days or until resolution when used in combination with PGF2-alpha Bromocriptine is less popular since it must be given TID with food and is associated with emesis	[36] [25]
Antiprogesterin	Aglepristone : 10 mg/kg SC once only on days 1, 2, 8, 15, and 30 (after dosing on day 8, evaluate treatment efficacy weekly prior to additional doses)	Very few adverse effects, but aglepristone is contraindicated with compromised hepatic or renal function Negligible uterotonic effects, so can be used with open- or closed- cervix pyometras Reported resolution rates of 45% by 28 days to 60% by 90 days	[38] [32]

Protocols	Drug(s) and dosing	Side-effects and indications	References
Antiprogesterin + PGF2-alpha analogue	Aglepristone (antiprogesterin): 10 mg/kg SC once on days 1, 3, 8, and 15	100% resolution rates reported when protocol used on open-cervix pyometras	[37]
	WITH Cloprostenol (PGF2-alpha analogue): 1 µg/kg SC once on days 3 and 8 (OR once on days 3, 5, 8, 10, 12, and 15) (after dosing on day 15, then weekly doses until complete resolution on US)	With closed-cervix pyometra, PGF2-alpha therapy should be commenced 24–48 h after initial aglepristone dose (to allow cervical opening by aglepristone prior to PGF2-alpha induction of uterine contractions)	[38]

*In queens, the early corpora lutea are more refractory to PGF2-alpha-induced luteolysis, therefore a higher daily dosing of PGF2-alpha may be required for a longer period in early diestrus [25].

**Synthetic PGF2-alpha analogues have been associated with prolonged activity, enhanced specificity for uterine smooth muscle, and reduced observable side-effects (especially emesis). However, they have reduced ability to stimulate uterine contractions so are not as effective as natural PGF2-alpha for uterine emptying [9].

by complete uterine emptying observed on ultrasound and cessation of vaginal discharge [24].

Future fertility with prostaglandin therapy is reported to be 75–87% in bitches [33,34]. Variable recurrence of pyometra after PGF2-alpha treatment has been reported: between 5% recurrence for bitches that became pregnant on their next heat to as high as 70% recurrence in all treated bitches followed over a period of 27 months [34,35].

Dopamine Agonists

Dopamine agonists, such as cabergoline or bromocriptine, can be used (off-label) in combination with PGF2-alpha therapy to treat pyometra. Dopamine agonists have antiprolactin activity and cause luteolysis indirectly through decreasing prolactin levels as early as 25 days after the luteinizing hormone (LH) peak. In the bitch, prolactin is one of the major supporters in the long-term maintenance of a functional corpus luteum. When used synergistically in conjunction with PGF2-alpha, dopamine agonists can potentiate luteolysis, leading to rapid progesterone decrease and cervical patency within 24–48 hours [36].

Progesterone Receptor Antagonists (Antiprogesterins)

Antiprogesterins, such as aglepristone, can be successfully used alone or in combination with PGF2-alpha for medical management of pyometra [37]. Since it has negligible uterotonic effects, aglepristone can be used relatively safely regardless of cervical patency [38]. When used to convert a closed-cervix pyometra into an open-cervix case, aglepristone (administration on day 1 and 2) safely perpetuates cervical opening with minimal uterine contractions by 25 hours (range 4–48 hours) after the first injection [38]. Cervical opening is associated clinically with voiding of copious amount of purulent discharge and significant improvement and increased appetite. Recurrence

of pyometra on subsequent heat cycles after treatment with aglepristone is generally thought to be lower, from no occurrence within a year to around 18% [32,37,39]. The use of aglepristone in combination with prostaglandin therapy results in better recovery rates for pyometra due to their synergistic actions, with reported success rates of 72–100% in bitches and 90% in queens [37,40,41].

Follow-Up Care, Monitoring Medical Management, and Recurrence Rates

After the initiation of medical therapy for pyometra, certain parameters should be closely monitored. A dramatic increase in vaginal discharge should be noted within 24–36 hours and generally lasts 7–10 days with medical therapy. Weekly CBCs are recommended to monitor decreasing neutrophilia. The left shift should resolve within the first week, and the neutrophilia should completely resolve within 10–15 days after starting medical management [16]. Any biochemistry abnormalities on presentation should be assessed until resolution as well. Serial uterine ultrasounds are recommended to assess response to treatment, and a visible reduction in luminal diameter should be noted in 5–7 days. The animal should be re-evaluated 10–20 days after recovery to assess the need for additional treatment and continuation of antibiotics [42].

With medical management, the rate of pyometra recurrence within 2 years is reported as 20–70% in bitches and slightly lower at 14% in queens [10,30,36], and 40–70% of bitches whelp normally [5,30]. Since pregnancy is considered protective, it is recommended the bitch or queen be bred on her next heat cycle. Treatment with prophylactic antibiotics may be considered during her subsequent proestrus and estrus period. Fertility is generally better in younger animals or those that develop pyometra as the result of exogenous hormone administration.

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Prostatic Disease

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Introduction

Prostatic disease is common in dogs but rare in cats. In the dog, prostatic disease is the most common disease of the male reproductive tract. Diseases of the prostate gland include benign hyperplasia (BPH), cystic benign hyperplasia (CBPH), squamous metaplasia (SM), paraprostatic cysts (PPCs), infectious prostatitis/prostatic abscessation (IP), and prostatic neoplasia (PN). BPH, CBPH, and IP are more common in intact dogs. PN is more common in neutered dogs compared to intact dogs, and is a disease of aged dogs. SM is associated with endogenous or exogenous estrogenic exposure. PPCs are more common in intact dogs and rare in cats [1,2].

Anatomy

The prostate gland is the only accessory sex gland in the dog; it surrounds the urethra just caudal to the urinary bladder and is normally easily palpated per rectum as a bilobed oval gland with a median septum. The prostate gland of the cat has four lobes and is located dorsal to the proximal urethra. The prostate gland in both species is primarily corpus (external to the urethra); the disseminate prostate (within the pelvic urethral wall) is vestigial. Additionally, the cat has bilobed bulbourethral glands found near the ischial arch on either side of the urethra.

Diagnostics

Multiple diagnostic techniques exist for evaluation of the prostate gland; most are more feasible in the dog than the cat. Obtain a thorough history including general

health, diet, supplements, and present and past medications; specific inquiry should also be made concerning urination, defecation, preputial discharge, and outcome of breedings (if any) or time of neutering.

Physical examination of the prostate includes transabdominal and rectal palpation which can require analgesia/sedation if painful. Evaluation of the size, symmetry, firmness, presence of pain or compression of the colon or urethra should be made. Careful examination of the testes, prepuce, preputial discharge, and penis should also be performed. Note signs of any orthopedic or abdominal pain. Most dogs under evaluation for prostatic disorders should minimally have a complete blood count, serum chemistry panel, urinalysis with culture (cystocentesis), and *Brucella canis* screen (slide or tube agglutination). Cytology of semen permits evaluation of the prostatic portion (first and third fractions) of the ejaculate, but can be too painful in an emergency presentation [3]. Additionally, culture of ejaculated semen requires special considerations for the presence of urethral and preputial normal flora; >100 000/mL organisms suggests a pathogen [4].

Ultrasound-guided fine needle aspiration (FNA) of the prostate under appropriate sedation/analgesia offers an alternative method of evaluation [5]. Prostatic massage, urethral catheterization, and urethroscopy are usually reserved for sampling urethral masses when concern about tumor seeding (transitional cell carcinoma (TCC)) exists. Surgical (open) biopsies are performed as indicated, usually when surgical intervention (marsupialization, excision) is planned. Radiography remains important for evaluation of anatomical sites not amenable to ultrasound (gas-filled) metastasis checks; computed tomography and magnetic resonance imaging provide more precise evaluations.

Prostatic Disorders

Benign Prostatic Hyperplasia and Cystic Benign Prostatic Hyperplasia

Pathophysiology

Dihydrotestosterone (DHT) causes symmetrical, progressive, eccentric prostatic parenchymal enlargement (BPH), which can become cystic (CBPH). Prostatic cell hyperplasia and hypertrophy are both contributory, but hyperplasia predominates. BPH occurs predictably in all intact dogs after the age of 5 years, and can be present as early as 2.5 years. An age-associated alteration in the intraprostatic estrogen:androgen ratio potentiates the hyperplastic response to DHT.

Clinical Findings

Benign prostatic hyperplasia and CBPH occur in the dog. Prostatic hyperplasia can occur without any clinical signs. Because prostatic enlargement in canine BPH is eccentric, urethral compression, as seen in men with concentric hyperplasia, is unlikely. Tenesmus secondary to colonic compression from marked prostatomegaly can be seen in advanced cases. The most common clinical signs of BPH and CBPH are blood (of prostatic origin) dripping from the urethra/prepuce, hemospermia, and hematuria, which can be alarming to clients, prompting an emergency presentation. Hemospermia is limited to the prostatic portion of the ejaculate. Semen quality is not affected; the sperm count, sperm cell morphology, and motility are not altered. Urinary outflow compromise, prostatic or lumbar pain, or semen quality deterioration should prompt closer evaluation for more serious prostatic disorders/disease.

Diagnostics

The physical examination is unremarkable; the prostate is not painful upon palpation but is usually prominent, sometimes with mild asymmetry. When physical examination findings and semen evaluation are normal (other than hemospermia), an aggressive diagnostic evaluation is not indicated. The CBC and chemistry panel should be normal. An abdominal ultrasound is prudent to evaluate the appearance of the prostate gland and guide the acquisition of a urine sample by cystocentesis to rule out urinary tract infection.

Benign prostatic hyperplasia and CBPH have a characteristic ultrasonographic appearance; a symmetrical parenchymal striation with increased echogenicity is apparent with variable hypoechoic to anechoic intraparenchymal cystic structures evident. The cystic structures vary in size. No associated lymphadenomegaly is evident. Urinalysis is normal other than hematuria and urine culture is negative.

Cytology from a prostatic parenchymal fine needle aspirate, intraprostatic cyst aspirate, or actual prostatic biopsy for histopathology can be used to confirm the diagnosis if ultrasound is not characteristic. BPH and CBPH can accompany infectious prostatitis or more serious prostatic disorders in older dogs, making ultrasonographic conclusions difficult. Fluid aspirated from prostatic cysts should always be submitted for cytology, culture, and sensitivity.

Therapy

Castration is curative and the most effective treatment. Atrophy of the prostate gland is noticeable in 2 weeks and maximizes in 4 months. Failure of such atrophy following castration suggests concurrent prostatic disease. In valuable stud dogs, medical antiandrogen therapy is an option, indicated if defecation is difficult or if the owners find the clinical signs of BPH/CBPH objectionable [6].

Squamous Metaplasia

Pathophysiology

Squamous metaplasia occurs as a consequence of hyperestrogenism, either of endogenous (functional Sertoli cell tumor, adrenal gland dysfunction) or exogenous (therapy for BPH, inadvertent exposure to transdermal hormone replacement therapy in human) origin. Prostatic epithelial squamous metaplasia is accompanied by secretory stasis; intraprostatic cysts can form.

Clinical Findings

The prostate gland enlarges and is firm on palpation. Compression of the urethra and colon can cause dysuria and tenesmus, prompting an emergency presentation. Other physical findings typical of hyperestrogenism can be present: attractiveness to males, gynecomastia, symmetrical alopecia, hyperpigmentation, testicular atrophy or dissymmetry (if a mass is present) and a pendulous prepuce. The presence of an abdominal (cryptorchid) testis should be ruled out when two scrotal testes are not present. Estrogen toxicity to bone marrow can cause pale mucous membranes (anemia), petechiation or hemorrhage (thrombocytopenia), and fever (secondary to neutropenia) (see Chapters 64, 65, and 67).

Diagnostics

A careful history should be taken concerning possible exposure to transdermal hormone replacement therapies in humans in contact with the dog, or past purposeful therapy with estrogen for prostatomegaly.

A complete blood count, serum chemistry panel, and urinalysis/culture should be performed to evaluate for myelotoxicity and metabolic status. Changes are variable and dependent upon exposure duration and

dose, and the time delay between insult and testing. Generally, in the initial 2–3 weeks both thrombocytopenia and thrombocytosis may be noted with progressive anemia and leukocytosis (WBC count may exceed 100 000/ μ L). After 3 weeks, pancytopenia and aplastic anemia may be noted. Hematuria may occur secondary to thrombocytopenia or due to blood of prostatic origin in the urine.

In an intact dog, semen collection will show deterioration of semen quality (primarily sperm count; oligospermia or azoospermia); squamous epithelial cells can be present in the prostatic fluid, and can often be sampled from the preputial mucosa. If a scrotal testicular mass is palpable (or discovered with ultrasound), a fine needle aspirate can reveal cytological evidence of a functional testicular neoplasia. Ultrasound will reveal enlarged prostate with hyperechoic parenchyma, often with cavitations; the typical striations of BPH are lacking. In a neutered dog with no scrotal testes, abdominal ultrasound should be performed to screen for a cryptorchid, malignantly transformed testis [7]. If negative, a serum luteinizing hormone (LH, Zoetis) screen can support the presence of a gonad; serum antimüllerian hormone assay (AMH, MOFA) would be positive. Cytology from a fine needle aspirate or biopsy of the prostate can be performed to support suspicions.

Therapy

Therapy is dictated by the clinical findings: discontinuation of exogenous estrogen exposure or therapy or castration if functional testicular neoplasia is present. Concurrent prostatic infection or abscessation can be present and should be treated appropriately.

Paraprostatic Cysts

Pathophysiology

Paraprostatic cysts are fluid-filled structures adjacent and attached to the prostate gland, which can be patent or not. They can be prostatic in origin or remnants of the uterus masculinus in both dogs and cats. They have been diagnosed in both intact and neutered dogs.

Clinical Findings

The chronicity and size of PPC dictate the clinical signs, which can be minimal to marked. Large cysts can encroach on the urethra or colon, causing dysuria, incontinence or tenesmus, abdominomegaly or perineal swelling, prompting an emergency presentation.

Diagnostics

Other than hematuria, the CBC, chemistry panel, and urinalysis are generally unremarkable. Ultrasound identifies a fluid-filled structure adjacent to the urinary

bladder. Ultrasound-guided centesis of the PPC provides fluid for cytology and culture.

Therapy

Ultrasound-guided cyst drainage can relieve emergent clinical signs until surgical removal is performed. Castration is recommended. Antibiotic therapy is dictated by culture and sensitivity and tailored for likely prostatic involvement (see Chapter 96).

Infectious Prostatitis

Pathophysiology

Infectious prostatitis occurs most commonly with bacterial organisms; mycotic prostatitis has been reported. Infection of the prostate gland can be acute and fulminant or chronic and progressive. Prostatic abscessation can occur. The most common route of infection is the ascension of urethral flora, but the hematogenous route of infection is also possible. The organisms most commonly isolated from the infected prostate are *E. coli* and *Staphylococcus*, *Streptococcus*, and *Mycoplasma* spp. Occasionally, *Proteus* spp, *Pseudomonas*, or anaerobic organisms are found. Mycotic prostatitis is uncommon and usually limited to endemic regions [8]. CBPH predisposes dogs to IP. This alteration of the normal architecture of the prostate gland predisposes to bacterial colonization by interfering with normal defense mechanisms and by providing an environment that supports bacterial growth; infectious agents gain access to intraparenchymal cysts, flourish, and can encapsulate to form abscesses.

Infectious prostatitis occurs most commonly in intact male dogs, but can occur in dogs neutered after infection is in place without appropriate antimicrobial therapy. Acute septic prostatitis can result in the later development of chronic septic prostatitis.

Clinical Findings

Clinical signs of IP can be mild to fulminant. Evaluation of the prostate is indicated in any male dog presenting with signs of lumbar or abdominal pain, lethargy, fever or tenesmus. The prostate is painful on palpation; sublumbar lymphadenomegaly can be present. Hemorrhagic and purulent urethral discharge, excessive preputial licking, dysuria, constipation and tenesmus can be present. Dogs are commonly febrile, anorexic, and lethargic, exhibiting pain on ambulation and kyphosis. Ejaculation can be painful, and affected dogs may be reluctant to breed or be collected. Peritonitis can cause nausea and abdominal discomfort.

Recurrent urinary tract infections imply chronic septic prostatitis. Chronic septic prostatitis may be asymptomatic, with deteriorating semen quality the only sign.

The prostate may be painful, firm, and irregular on palpation. Ultrasonographic findings are non-specific but typically will be of mixed echotexture with hyperechoic areas reflecting fibrosis. The ultrasonographic appearance can be similar to that of prostatic neoplasia. Additionally, multiple prostatic pathologies can be present in an individual patient.

Diagnostics

Septic prostatitis is best diagnosed on the basis of the findings from physical examination followed by ultrasonography and cytology and culture of urine and the prostate, with specific attention to any cystic structures within the parenchyma (Web Figure 124.1).

If IP is mild, semen collection can be attempted. Semen is typically abnormal, with suppurative inflammation, hemospermia, pyospermia, necrospermia, and decreased prostatic fluid volume evident. Because prostatic fluid normally refluxes into the urinary bladder, urinary tract infection is usually present whenever there is bacterial prostatitis (see Chapter 96). Culture of semen is not ideal as normal urethral flora will be acquired. Quantitating urethral versus prostatic ejaculate organisms can help differentiate normal flora from pathogens but is expensive and laborious. Prostatic massage/wash requires sedation and also will collect urethral flora. Pyuria and bacteruria should always prompt evaluation of the prostate in any intact male dog.

A complete blood count reflects systemic inflammation. Chemistries can be normal or reflect prerenal azotemia, hepatopathy, nephrogenic diabetes insipidus, sepsis or peritonitis. The urinalysis and urine culture reflect an infectious etiology.

Ultrasound provides the best opportunity for sampling IP with appropriate analgesia/sedation. IP is characterized by both hypoechoic and hyperechoic non-homogenous parenchyma and if abscessed, hypoechoic to isoechoic thick irregular-walled cystic structures in the parenchyma. Sublumbar lymphadenomegaly can be present.

The diagnosis of chronic septic prostatitis requires cytological and microbiological examination of urine and prostatic tissue, which may be obtained by ultrasound-guided fine needle aspiration.

Therapy

Acute PI is a serious disorder and can lead to sepsis and death. Treatment must be prompt and aggressive. Fluid therapy is necessary to correct dehydration and shock (see Chapters 153, 155, and 159). Large prostatic abscesses are treated most effectively by surgical drainage and omentization once stabilized. Abscesses may also be drained by FNA under ultrasound guidance if the dog is not stable.

Pending the results of culture and susceptibility, treatment with a fluoroquinolone and potentiated amoxicillin should be initiated. Antibiotic penetration in acute prostatitis is not as problematic as inflammation alters the blood–prostate barrier, allowing most antibiotics to penetrate. A negative culture of the urine or prostate should be obtained once therapy has been initiated to confirm effectiveness. Antibiotic treatment for acute prostatitis should be continued for a minimum of 4 weeks. Urine or prostatic fluid acquired via ultrasound guidance should be recultured a week after discontinuing antibiotic therapy and again 2–4 weeks later to be certain the infection has resolved.

Castration should be considered. Medical castration with finasteride is an acceptable alternative if the dog stabilizes rapidly and is valuable for breeding (finasteride does not affect spermatogenesis). Relapse is common, and can be diminished with the use of finasteride chronically.

Prostatic Neoplasia

Pathophysiology

Transitional cell carcinoma (TCC) and prostatic adenocarcinoma (ACA) are the most common primary prostatic malignancies. TCC is more common; regional lymphatic and distant pulmonary or bone metastasis occurs in <20% of cases. Scottish Terriers (18-fold), Shetland Sheepdogs, Beagles, Wirehaired Fox Terriers, and West Highland White Terriers are the breeds most commonly affected by TCC. It occurs in middle-aged to older dogs with a reported mean age of 11 years. ACA is locally invasive and metastasizes to regional lymphatics, lungs and the skeleton in 24–42% cases. There is an increased incidence in medium- to large-breed dogs >10 years of age, neutered early in life. Squamous cell carcinoma, fibrosarcoma, leiomyosarcoma, hemangiosarcoma, and lymphoma can occur in the prostate gland [9,10].

Clinical Findings

Malignant prostatomegaly commonly causes signs of tenesmus and constipation due to compression of the rectum accompanied by sublumbar lymphadenomegaly, overdistension of the urinary bladder due to urethral compression, lumbar pain from invasion into the lumbar vertebrae and nerve roots, and lower urinary tract signs of stranguria, dysuria, pollakiuria, and hematuria. Concurrent urinary tract infection is not uncommon. Pelvic limb ataxia and paresis or paralysis can occur. Physical examination findings commonly include prostatomegaly, sublumbar lymphadenomegaly, abdominal pain, and gait abnormalities. The prostate is unusually enlarged for a neutered dog. Anorexia and associated weight loss reduce body condition.

Diagnostics

Complete blood count and chemistry panel findings reflect chronic disease and inflammation. Postrenal azotemia can be present with obstructive masses. An elevation of alkaline phosphatase occurs in ~50% of cases. Hematuria, pyuria, bacteriuria, and atypical transitional cells can be found in the urinalysis. Malignant transitional cells appear similar to reactive transitional cells, making biopsy important.

Thoracic radiographs are indicated to screen for pulmonary metastasis. Lumbar spinal radiographs can show vertebral metastasis. Mineralization in the enlarged prostate and sublumbar lymphadenomegaly are suggestive of a malignant disease.

Abdominal ultrasound is the most useful diagnostic tool, permitting evaluation of the prostatic parenchyma, regional lymphatics, extension into the urinary bladder, urethral obstruction, and presence of hydroureter and hydronephrosis. Focal or multifocal hyperechoic prostatic parenchyma with asymmetry and irregular capsule outline and mineralization are common findings (Web Figure 124.2). Cavitory regions of necrosis and hemorrhage can be present. Sublumbar lymphadenomegaly can be marked.

Definitive diagnosis requires histopathological examination of affected tissues and can help differentiate between TCC and ACA or other malignancies. Tissue samples are usually obtained by surgical biopsy. If the mass extends into the urinary bladder, cystoscopic

biopsy is possible. Transabdominal ultrasound-guided biopsy is straightforward, but TCCs are very exfoliative and seed readily, making the procedure risky for iatrogenic spread [11].

Therapy

Poor quality of life is common with prostatic neoplasia; most dogs are euthanized within 2 months of the diagnosis. Castration has little benefit. Prostatectomy could be considered with local, intracapsular disease, but is associated with incontinence. Palliative radiation can relieve clinical signs for some time. Urethral stenting can relieve urethral obstruction but is associated with incontinence and dislodgment.

The use of NSAIDs is associated with prolonged survival with prostatic carcinomas. Concurrent use of gastric protectants is advised. Oral analgesics that can be combined with NSAIDs can be helpful in controlling pain. Stool softeners are indicated if tenesmus is present. Intravenous bisphosphonates such as pamidronate can help with pain relief from skeletal metastases. Chemotherapy can result in partial, short-term clinical responses. Agents used include mitoxantrone, vinblastine, carboplatin, gemcitabine, and cisplatin (TCC), and carboplatin, cisplatin, doxorubicin, and gemcitabine (ACA). Piroxicam in combination with mitoxantrone, carboplatin or gemcitabine improves success rates. Consultation with a veterinary oncologist is advised.

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Uterine and Vaginal Prolapse

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Uterine Prolapse

Etiopathogenesis

Uterine prolapse is a very rare reproductive disorder in the dog and rare in the cat [1–3]. The condition occurs most commonly during parturition or in the immediate postpartum period because the cervix must be dilated for the uterus to prolapse through it [1]. Rare cases of uterine prolapse in parturient dogs have been reported in which one horn prolapsed while fetuses were still present in the other horn [4]. In addition, there has been one report of uterine prolapse in a dog with functional ovarian cysts [5].

Predisposing factors for the development of uterine prolapse in the bitch and queen include severe tenesmus during or after parturition, dystocia, incomplete placental separation, large litters, an atonic, flaccid, usually diseased uterus, chronic coughing, advanced age or excessive relaxation of the pelvic and perineal region [4,6–8] but it can also occur following normal parturition [3].

Diagnosis

Uterine prolapse can either be complete (involving both uterine horns; Figure 125.1) or partial (with either one entire horn or part of one horn involved), with the latter being more common [1]. Diagnosis is based on physical examination, visual examination of the protruding mass, and careful digital examination of the vagina. Physical examination findings include acute abdominal distension, pain and splinting, tachycardia, tachypnea and vocalization, hemorrhagic vulvar discharge, excessive vulvar licking $\pm$ devitalized prolapsed tissue. Dogs with uterine prolapse generally present in an extremely hypotensive state secondary to

hemorrhage following the tear of a uterine or ovarian artery during the prolapse.

Treatment

The primary treatment goal is to replace the uterus and prevent uterine infection once supportive treatment for shock is implemented and the patient is stabilized [9].



Figure 125.1 Uterine prolapse in a 9-year-old mixed-breed dog. Notice the two uterine horns protruding from the vulva. Reproduced with permission of John Wiley & Sons.

Exposed tissues should be covered with warm, saline-soaked towels, and the tissues should be cleaned and lubricated. Hyperosmotic agents (e.g. 50% dextrose) may help slightly in reducing the size of the edematous tissue but in this author's experience, hyperosmotic agents have offered little, if any, benefit.

In simple, uncomplicated cases, the manual reposition under general anesthesia is the preferred method [3]. If the uterus is still viable, it should be cleaned gently and manual reduction should be attempted [9]. Replacement of the prolapsed uterus has been achieved using gloved fingers and copious obstetrical lubricant [1,10]. Performing an episiotomy may improve chances for a successful manual reduction [11]. Routine closure of an episiotomy is performed in four layers: mucosa, muscular and subcutaneous tissues, and skin. The mucosa is closed in a simple interrupted or continuous pattern of 3-0 monofilament absorbable sutures. The muscular and subcutaneous tissues can be closed together or separately, depending on the size of the animal, using a simple continuous pattern of 3-0 or 4-0 absorbable sutures. The skin edges can be closed with sutures (simple interrupted or cruciates) or surgical staples.

If a gloved finger is not long enough or has too wide a diameter, a variety of cylindrical objects have been used in the successful reduction of uterine prolapses in bitches and queens. Inserting a 6 mL syringe case [2], a 10 mL syringe followed by an insemination tube [12], a test tube [13], a sterile swab [14], or an endotracheal tube [6] into the uterine horn or infusing saline under pressure have all successfully been used in accomplishing inversion of a complete prolapse. Using the endotracheal tube technique, sterile physiological saline (5–10 mL) can be administered through the free end of the tube so that the uterine horns can be slowly distended and recede into the pelvic and abdominal cavities [6].

Once completely reduced without any uterine horn eversion remaining, the prolapse does not usually recur. However, placing a purse-string suture in the perineum around the vulva (bitch) [9] or a single mattress suture through the perineal skin to close the vulva (queen) [1,15] is typically performed for the first 48 hours following reduction. Once the uterus is *completely* replaced, 3–5 IU of oxytocin should be administered IM to facilitate rapid uterine involution and cervical closure [16].

If the prolapse cannot be completely reduced, a laparotomy will need to be performed. Using cranial traction from the abdomen by gently grasping the cervix with forceps may aid in external manual inversion of the prolapsed tissue and allow the uterus to be drawn back into the abdomen [13,17]. If the uterus is still viable after reduction and the female is still intended for breeding, a hysteropexy should be performed, in which the vagina and uterus are sutured to the ventrolateral abdominal

wall to prevent prolapse from recurring [7,13]. If the uterus is no longer viable or the female will be retired from breeding, ovariohysterectomy can be performed in conjunction with prolapse reduction.

An *en bloc* amputation of the prolapsed uterus is suggested if the patient is not stable enough to undergo a laparotomy with complete ovariohysterectomy at that time. To amputate the uterus, a smooth, cylindrical object should be placed into the uterine lumen and four stay sutures placed at equidistant points around the prolapsed uterus. All the layers of the uterus are incised to the inserted object, one quadrant at a time. Immediately after incising one quadrant, the inner and outer layers of the prolapsed uterus are anastomosed with simple interrupted absorbable sutures before incising the next quadrant. This process is repeated until the entire uterus is amputated [3,6,18]. Care must be taken to ligate the uterine arteries separately and the urethra must be catheterized and carefully protected [13,19]. Broad-spectrum systemic antibiotics for 7–14 days are warranted to reduce the risk of peritonitis following correction of a uterine prolapse (see Chapter 200).

Vaginal Prolapse

Vaginal prolapse has been reported in virtually all domestic mammals. True vaginal prolapses are rare in bitches and very rare in queens. However, vaginal fold prolapses of varying severity are the most common vaginal mass in the bitch [20].

True Vaginal Prolapse

Etiopathogenesis

Although the most severe form of vaginal fold prolapse can present as a true vaginal prolapse, the etiopathogenesis of a true vaginal prolapse is distinct from that of a vaginal fold prolapse. A true vaginal prolapse mainly occurs near parturition, as the concentration of serum progesterone declines and that of serum estrogen increases [21–24]. Excess prepartum pelvic relaxation and increased intra-abdominal pressure are believed to contribute to the development of a true vaginal prolapse [25]. Vaginal prolapse occurs less commonly in diestrus and normal pregnancy [21,22,26]. In the event of dystocia, extreme tenesmus may also predispose to this disorder. The reported incidence of periparturient true vaginal prolapse ranges from 8% [27] to 12% [28] of all vaginal prolapse cases.

Diagnosis

Although a true vaginal prolapse involves the entire vaginal wall, it may vary in appearance depending upon the duration of the prolapse (Figure 125.2 and Figure 125.3)



Figure 125.2 True vaginal prolapse in a 4-year-old Chihuahua 2 weeks prepartum. The prolapse was gently replaced and retained with a purse-string suture until parturition. Reproduced with permission of Matthew H. Goetz.



Figure 125.3 True vaginal prolapse in a 5-year-old mixed-breed dog following a dystocia. Notice the severe edema and tissue excoriation from the prolonged duration. Reproduced with permission of Elsevier.

as well as the involvement of other organs (e.g. urinary bladder, uterine body, and/or distal part of the colon) within the prolapse [29]. The cervix may or may not be exteriorized with a true vaginal prolapse [30].

Treatment

Jones and Joshua [31] reported that in most cases of vaginal prolapse that arise just prior to whelping, there is usually no need for any intervention and parturition can proceed normally. However, there is the possibility that the prolapse may prohibit normal parturition by narrowing the birth canal [32]. König and colleagues [23] reported on a case of a true vaginal prolapse that developed during the last weeks of gestation and caused no problem during delivery except for the last puppy. In cases in which the prolapse occurs a number of days before parturition, the outcome may depend upon the severity of swelling and tissue damage.

An alternative to the benign neglect approach is surgical correction by hysteropexy before delivery $\pm$ resection of the prolapsed tissue. Recurrence after surgical excision is uncommon but can occur. If surgery is not performed, following parturition the prolapsed tissue undergoes significant and rapid reduction in size until self-cure has been achieved. If the female is no longer intended as a breeding animal, ovariectomy or ovariohysterectomy should prevent further recurrence of the condition.

Vaginal Fold Prolapse (Canine Only)

Etiopathogenesis and Diagnosis

Vaginal fold prolapse is initiated by the protrusion of edematous vaginal tissue into the vestibule (type I) and then through the opening of the vulva (type II; Figure 125.4), which can progress to a true vaginal prolapse (type III) (Table 125.1). Reduction in venous and lymphatic circulation and inflammation secondary to exposure of the mucosa contribute to the progression from type II to type III [31].

Vaginal fold prolapses occur primarily during proestrus or early estrus [33]. During these stages of the canine estrous cycle, the vaginal mucosa becomes edematous and hyperplastic under the influence of estrogen [21]. In addition to its effects on the vaginal mucosa, estrogen may be responsible for relaxation of the vulvar and perivulvar musculature and associated tissues, predisposing to vaginal fold prolapse [29]. A vaginal fold prolapse was iatrogenically induced following estrogen administration for canine estrus induction [34]. Other suspected causes of vaginal fold prolapse include constipation, trauma from forced separation during coitus [35], size discrepancy between breeding animals [4,29,36], and vaginal tumors [37]. These factors, combined with a possible inherited weakness of the perivaginal tissue, may initiate or contribute to vaginal fold prolapse [29].

The reported incidence of vaginal fold prolapse ranges from 73% [28] to 86% [27] of all vaginal prolapse cases. Vaginal fold prolapse is more common in large-breed dogs, but may occur in small breeds [27,28,38]. The condition may be seen in families of pure-bred dogs,



Figure 125.4 Type II vaginal fold prolapse in a 1.5-year-old Greek hound dog that occurred during late gestation. Reproduced with permission of Elsevier.

suggesting a hereditary predisposition [4,27,28,30]. Breeds predisposed to vaginal fold prolapse include American Pit Bull Terrier, Boxer, Bulldog, Chesapeake Bay Retriever, Dalmatian, German Shepherd Dog,

Table 125.1 Three-stage classification scheme for vaginal prolapse in the dog, described by Schutte [38].

Type	Description
I	Slight-to-moderate eversion of vaginal mucosa originating from the vaginal floor cranial to the urethral opening but confined to the vestibulum. This appears as a bulge at the perineum
II	A well-developed swelling of the vaginal floor that may include the lateral vaginal walls with protrusion of the vaginal mucosa through the vulvar labia. This incomplete prolapse appears dome shaped
III	Complete protrusion of the entire circumference of the vaginal wall through the vulvar lips. This complete prolapse appears donut shaped

Labrador Retriever, Mastiff, Springer Spaniel, St Bernard, Walker Hound and Weimeraner.

Although somewhat similar in appearance, the etiopathogenesis as well as the urgency and method of treatment vary between a uterine prolapse and the types of vaginal prolapse. Uterine prolapse is a rare parturient condition typically associated with dystocia that requires immediate shock-supporting therapy in addition to replacement of the prolapsed tissue. While rare in queens, some types of vaginal prolapse are common in intact bitches and occur in association with elevated estrogen concentrations during proestrus. Most of these cases reduce spontaneously during diestrus but efforts should be made to keep prolapsed tissues moist, clean, and free from self-mutilation.

Treatment

In mild-to-moderate cases, the vaginal fold prolapse regresses spontaneously during diestrus [29]. It is important that the prolapsed tissue stay moist and clean and does not fall prey to self-mutilation. General anesthesia is required if attempting to replace the prolapsed mucosa. The prolapsed tissue should be cleaned with a mild antiseptic solution or saline. If the edema is severe, manual compression to the mucosal surface may decrease its size, therefore facilitating reduction. Similar to the descriptions for replacing a uterine prolapse, a lubricated plastic syringe can be used to reduce the vaginal fold prolapse. An episiotomy may be necessary to provide better exposure for reduction. Reduction can also be assisted by traction on the uterus via a ventral abdominal approach. Once the vagina is reduced, re prolapse can be minimized by suturing the uterine body or the broad ligament to the abdominal wall. A urinary catheter should be placed at the time of the episiotomy and maintained until the vaginal swelling resolves.

Dogs with long-standing prolapses may have secondary necrosis, infection, or hemorrhage of the prolapsed tissues. These dogs should be evaluated and treated as necessary for hypotension and/or sepsis (see Chapters 155 and 159). Surgical resection of the devitalized tissues is indicated in these patients to prevent further sepsis and self-mutilation. A stepwise full-thickness circumferential incision should be made through the vaginal wall. Then, a 1–2 cm section of the outer mucosal layer is incised, followed by resection of the inner non-inverted mucosal layer. Horizontal mattress sutures are used to close the incision edges. Hemorrhage can be significant and should be controlled with cautery and ligation. This is continued circumferentially in small sections until the entire prolapsed tissue is resected.

In a follow-up study of 13 bitches, vaginal fold prolapse recurred in all 13 during the second and third

subsequent estrous cycles [28]. Although more studies are needed to ascertain the hereditary aspect of the vaginal prolapse in dogs [33], it has been recommended that affected bitches should not be bred [28]. Furthermore, as

the recurrence rate in affected bitches is high, ovarioectomy or ovariectomy will fully eliminate the incidence of recurrence [30].

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126

Penile, Preputial, and Testicular DiseaseJames Lavelly, DVM, DACVIM¹ and Autumn P. Davidson, DVM, MS, DACVIM (SAIM)²¹VCA Animal Care Center, Rohnert Park, CA, USA²School of Veterinary Medicine, Davis, CA, USA**Priapism****Pathophysiology**

Priapism is a persistent penile erection lasting greater than 4 hours, without sexual stimulation. Priapism is infrequently reported in dogs and cats. Idiopathic, neurological, traumatic, neoplastic, and infectious causes have been reported [1]. Neurological causes have included spinal injury, canine distemper virus, post hemilaminectomy and lumbosacral stenosis; priapism has occurred in a dog with a syringohydromyelia in the lumbar spine and a concurrent meningocele in the cauda equina [1,2].

A dysregulatory hypothesis has been considered. Dyssynergic stimulation of inflow and outflow penile blood vessels causes prolonged vascular and smooth muscle spasms. Dysregulation may occur within the penis or at other neurological regulatory centers of penile erection [3]. The pelvic nerve (S1–S2) is composed of parasympathetic fibers and mediates the canine erection. Pelvic nerve stimulation dilates penile arteries, partially inhibits venous drainage, and increases penile blood pressure, thus resulting in an erection. The pudendal nerve (S1–S3) stimulates contraction of the extrinsic penile muscles. Sympathetic chain fibers inhibit erection by decreasing venous resistance, decreasing corpus cavernosal pressure, and increasing arterial resistance. Sympathetic inhibition of erection is mediated by the alpha-1 adrenergic system [1].

Anesthesia or perioperative medications, including alpha-adrenergic antagonists, such as phenothiazine drugs can cause priapism in people and horses. In horses, this risk is due to the retractor penis muscle being solely controlled by alpha-adrenergic fibers. In dogs, intracorporeal chlorpromazine injection caused consistent erection but intravenous chlorpromazine injections were not shown to result in erection [1].

Priapism in people is differentiated between ischemic (veno-occlusive or low flow) and non-ischemic (arterial or high flow) types. Recurrent episodes of ischemic priapism can occur and is termed stuttering priapism. Identifying the type of priapism is essential. Ischemic priapism is most common in people and treatment is considered an emergency, recommended within 4 hours. Delayed treatment can result in diminished therapeutic success and irreversible corporal fibrosis. Histological changes occur within 12 hours of ischemic priapism. Ischemic priapism lasting greater than 48 hours is highly likely to result in fibrosis and permanent erectile dysfunction [4].

Clinical Presentation

Ischemic priapism has been reported in cats and a dog (Web Figures 126.1 and 126.2). A traumatic cause is common, with priapism often developing during mating attempts or after castration. Ischemic priapism occurred in a cat with feline infectious peritonitis and an idiopathic cause has been suspected in other cats. Siamese cats have been overrepresented thus far [1,5].

Diagnostics

Clinical examination can help differentiate ischemic from non-ischemic priapism. The examination findings of ischemic priapism include a rigid and painful corpora cavernosa, while the glans and corpus spongiosum are soft. In non-ischemic priapism, the corpora cavernosa are tumescent but not rigid or painful and the glans and corpus spongiosum are soft or partially tumescent [4].

Aspiration of blood from the corpus cavernosum may differentiate non-ischemic and ischemic priapism. Cavernous blood gas evaluation in ischemic priapism typically results in a pH < 7.25, a PO₂ < 30 mmHg and a PCO₂ > 60 mmHg, while non-ischemic priapism typically

Table 126.1 Features of ischemic versus non-ischemic priapism.

	Ischemic	Non-ischemic
Pain?	Usually	Uncommon
Corpora cavernosa fully rigid	Usually	Uncommon
Cavernous blood gas	Abnormal	Normal
pH	<7.25	7.4
PO ₂	<30	>90
PCO ₂	>60	<40

results in pH 7.4, PO₂ >90 mmHg and PCO₂ <40 mm Hg [3,4] (Table 126.1).

Ultrasound of the penis confirms tumescence (Web Figure 126.3). Ultrasonography may also detect anatomical abnormalities such as emboli, neoplasia, and other obstructive causes. Ultrasonography of the perineum and then the entire penile shaft should be done. Perineal portions of the corpora cavernosa may be abnormal in trauma. Color flow Doppler ultrasonography can detect high systolic flow into the cavernosal artery or can help evaluate for an arterial to cavernosum fistula. Retrograde urethrography can also be used to evaluate for urethral obstruction that may be related to the priapism [1].

Therapy

In the cat, penile amputation and perineal urethrostomy has been the most common treatment, due to penile damage and infection [1,5]. Successful surgical treatment has been reported in a cat via small bilateral incisions in the tunica albuginea of the corpora cavernosa penis and portions of the corpora cavernosa. The corpora cavernosa were then irrigated with heparinized saline. Skin sutures were placed, but the tunica albuginea was not sutured. Similarly, a dog was treated successfully via bilateral incisions to the longa glandis and the tunica albuginea. Blood was pressed out and heparinized saline irrigation was carried out until red blood flow returned. The tunica albuginea was then sutured [6].

Guidelines for the treatment of priapism in people have been established [7,8]. First-line management in the treatment of ischemic priapism is decompression of the corpora cavernosa via penile aspiration with a 19 gauge butterfly needle or a 16–18 gauge angiocatheter. The catheter is placed in the corpora cavernosa on either lateral aspect of the proximal penile shaft. Blood is evacuated until fresh red blood is obtained. Saline irrigation may be done in conjunction with aspiration. The use of two catheters or two butterfly needles can be helpful, with one used for saline irrigation and the other for aspiration.

If priapism returns after aspiration then intracavernosal injection of a sympathomimetic agent such as

phenylephrine is done. The phenylephrine is diluted with normal saline to 100–500 µg/mL and given in 1 mL doses every 5 minutes. A maximum dose of 1 mg for no more than an hour is used in people. Lower dosages are used in patients with cardiovascular risks. Careful monitoring is recommended when giving phenylephrine. The penis may be semi-rigid following intracavernosal injections due to residual edema. This can make it challenging to determine if the priapism has been successfully treated.

Aspiration + /– saline irrigation is about 30% successful in people. Success increases up to 80% with concomitant use of intracavernosal injection of a sympathomimetic agent. A longer duration of ischemic priapism (>12 hours) prior to first-line treatment is thought to decrease the chance of success. When drug-induced priapism is of short duration, a single injection of a sympathomimetic agent on each side of the penis may be attempted. “Milk-ing” or massaging the penis after the injection can help distribute the sympathomimetic agent [4].

When first-line management is not successful then surgical therapy may be pursued. This consists of shunting blood via a surgically created vent that allows blood to exit the corpora cavernosa. The vent is anticipated to close spontaneously following resolution of priapism. Surgical intervention can cause erectile dysfunction [4].

Treatment of stuttering priapism in people is directed toward prevention of episodes. Various systemic medications have been used. Hormonal therapies are most commonly used, such as gonadotropin-releasing hormone agonists, estrogen and androgen receptor antagonists. Baclofen, pseudoephedrine, terbutaline, gabapentin, hydroxyurea, and phosphodiesterase type 5 inhibitors have also been used [7,9].

Non-ischemic priapism is less urgent in people and thus conservative management is recommended. Applying ice to the perineum and compression may be used [8]. Monitoring is typically recommended in people with non-ischemic priapism as 62% have spontaneous resolution [3,7]. Embolization procedures and surgical ligation of cavernous fistulae may be considered, but carry the risk of erectile dysfunction. Blood aspiration is diagnostic, but not carried out for treatment of non-ischemic priapism. Alpha-adrenergic antagonists are not recommended due to the potential for severe adverse effects [7,8].

Non-ischemic priapism in dogs has been treated with pseudoephedrine (from 0.86 mg/kg q8–12 h to 1.74 mg/kg PO q12 h) with possible success [1]. Terbutaline sulfate is available as tablets in strengths of 2.5 mg and 5 mg; terbutaline is also available as an injectable medication and may be administered subcutaneously or intramuscularly. In both dogs and cats, the typical dose of terbutaline as an injectable is 0.01 mg/kg every 4 to 6 hours prn. In tablet form for dogs, the typical dose is 1.25 to 5 mg per dog every 8 hours. In tablet form for cats, the dose is 0.1

to 0.2 mg/kg every 12 hours [10]. Very few controlled data exist to evaluate systemic therapies in people. The limited number of reported cases in dogs and cats and the possibility of spontaneous resolution make evaluation of systemic therapies difficult.

The pathophysiology and histopathology findings of priapism in people and dogs are similar so following similar algorithms is likely reasonable. Distinguishing ischemic from non-ischemic priapism, identifying and treating the underlying cause are important. Veterinary patients likely have a longer duration of signs at presentation so success may be diminished. Protecting the integrity of penile tissue with lubrication and an Elizabethan collar is important. Surgical incisions in the tunica albuginea, longa glandis or corpora cavernosa to evacuate accumulated blood, followed by saline irrigation, may be considered if initial therapy is not successful. Penile amputation and perineal urethrostomy may be indicated if penile tissue damage is significant.

If non-ischemic priapism is present then cold compresses, monitoring, and possible systemic therapy are reasonable provided that the medication is not contraindicated and adverse effects are monitored for. Protecting penile integrity via lubrication + /– an Elizabethan collar is essential. Self-trauma may necessitate antibiotic therapy or surgical intervention.

Paraphimosis

Pathophysiology

Paraphimosis could be confused with priapism. With paraphimosis, the typically non-erect penis cannot be ensheathed within the prepuce and can become edematous from exposure. Paraphimosis can be caused by trauma, inadequate length of the prepuce, weakened preputial muscles or too small a preputial orifice compared to the size of the penis during detumescence. Paraphimosis can occur after manual semen collection as the erect penis is exposed to air rather than being encased within the vulva of a bitch until detumescence. Dry mucous membranes, long preputial hair, and enfolding of the preputial orifice then prevent normal detumescence. Entrapment of the distal tip of the penis can then induce severe edema (in moments) which exacerbates the problem. Chronic infolding can result in desiccation of the tip of the penis.

Clinical Presentation

Penile enlargement with paraphimosis is a result of failure of detumescence exacerbated by edema, rather than a chronic erection. Typically, dogs with paraphimosis are uncomfortable, attempting to groom the penis and not



Figure 126.1 Paraphimosis in an 11-month-old Cane Corso mastiff after breeding. The penis is severely edematous and cannot be returned into the prepuce.

enthusiastic about ambulating. Dogs can be presented after breeding or manual semen collection.

Diagnostics

The diagnosis is made on the basis of physical examination. Priapism is the main differential. Acute paraphimosis usually presents with the penis completely extruded from the prepuce (Figure 126.1). Chronic paraphimosis presents with only partial extrusion and excoriation and scarring of the distal penis. Usually a history of sexual stimulation exists (even in neutered dogs) such as an estrual bitch, actual breeding or masturbation.

Therapy

Treatment of paraphimosis consists of saline irrigation and generous lubrication as the penis is manipulated back into the prepuce (Web Figure 126.4). Diuretics do not significantly reduce penile swelling. The use of topical osmotic agents has been helpful in some cases. Temporary purse-string sutures can be beneficial in some cases but interference with urination must be avoided. Surgical correction of underlying preputial anatomical abnormalities may be required if the penis cannot be ensheathed in the prepuce, if the problem recurs repeatedly or becomes chronic (Web Figure 126.5). The most common surgery required is a revision of the preputial opening. Antibiotic and anti-inflammatory therapy, prevention of mutilation, and pain management should be used as clinically indicated. Castration can be helpful if the dog is not valuable for breeding, but neutered male dogs can still achieve erection and ejaculation if stimulated and habitually masturbating.

Phimosis

Pathophysiology

Phimosis is a condition in which the penis is trapped within the preputial cavity. It usually occurs as a congenital defect in which the preputial opening is abnormally small and the penis, even when not erect, cannot protrude or be extruded manually. Phimosis can occur from the presence of a persistent penile frenulum. It can also occur as a consequence of erection without prior extrusion of the penis during manual semen collection.

Clinical Presentation

Phimosis is uncommon in dogs and rare in cats. It may be recognized in young dogs as a cause of partial urinary tract outflow obstruction resulting in dribbling of urine that has accumulated in the preputial cavity. Phimosis may be recognized in a postpubertal affected dog when he is unable to copulate (or have manual semen collection) due to a small preputial opening. The preputial hair of long-coated cats may entangle the preputial orifice, causing clinical signs similar to phimosis.

Diagnostics

Phimosis is diagnosed by physical examination of the prepuce and penis. Preputial endoscopy and ultrasound of the prepuce can be performed to rule out other causes of penile entrapment such as a hematoma, ruptured tunica albuginea or penile mass lesion.

Therapy

Phimosis is treated by conservatively surgically enlarging the preputial orifice. Exposure of penile mucosa can result if the opening is too large.

Persistent Penile Frenulum

Pathophysiology

Under the influence of androgens, the surfaces of the glans penis and the preputial mucosa normally separate before or within weeks of birth. If this separation does not occur, connective tissue persists between the penis and the prepuce. In dogs, the persistent penile frenulum is usually located on the ventral midline of the penis.

Clinical Presentation

A persistent penile frenulum may cause no clinical signs, or it may be associated with preputial discharge or

excessive licking of the prepuce. Persistent frenulum may cause the penis to deviate ventrally or laterally so that the dog is unable or unwilling to mate, or it may interfere with normal tumescence.

Diagnostics

The diagnosis is made by visual examination.

Therapy

Treatment is surgical excision, which can often be done using just sedation with local anesthesia as the frenulum tends to be a sheer, avascular membrane.

Balanoposthitis

Pathophysiology

Balanoposthitis is inflammation or infection of the preputial cavity and penis. The causative organisms are usually members of the normal preputial flora, although overgrowth of one organism or a predominance of *Pseudomonas* spp can occur [11]. Lymphoid follicular hyperplasia is commonly also present and thought to develop as a result of chronic irritation.

Clinical Presentation

Balanoposthitis is common in dogs and rare in cats. It usually causes no clinical signs other than a purulent preputial discharge that is quite variable, from a scant white smegma to a copious green pus, and excessive licking. The discharge associated with balanoposthitis is not sanguineous unless the cause is neoplasia or accumulated foreign material.

Diagnostics

The diagnosis of balanoposthitis is made by physical examination of the penis and preputial cavity all the way to the fornix, in a search for foreign material, neoplasia, ulceration, or inflammatory nodules. Cultures and cytological studies are rarely helpful unless a mycotic infection or neoplastic process is suspected.

In persistent or refractory cases, cytology, culture, and endoscopic examination of the prepuce and urethra should be considered. Preputial discharge from benign prostatic hyperplasia, prostatitis, urethritis or cystitis should be ruled out if the penis and prepuce appear normal. Penile mass lesions can cause excessive preputial discharge. Transmissible venereal tumor (TVT) is the most commonly reported penile tumor in dogs.

Cytological evaluation of TVT is supportive; biopsy is diagnostic. The macroscopic appearance of TVT and penile papilloma virus may be similar.

Therapy

The treatment of balanoposthitis is usually conservative. The hair should be clipped from the preputial orifice and the surrounding area if discharge has been accumulating there. Flushing the preputial cavity with very dilute, gentle antiseptic solutions (e.g. chlorhexidine, povidone-iodine) can be helpful. Topical antibacterial or combination corticosteroid antibacterial medications may be instilled into the preputial cavity. Penile warts often resolve spontaneously after biopsy of the lesion.

Urethral Prolapse (see Chapter 104)

Pathophysiology

Eversion of the urethral mucosa at the distal tip of the penis results in focal refractory hemorrhage. The condition is associated with the increased intra-abdominal pressure associated with the brachycephalic syndrome [12].

Clinical Presentation

Urethral prolapse occurs most commonly in bulldogs and Boston terriers, and is likely familial.

Diagnostics

Urethral prolapse is evident upon physical examination. Urethral obstruction due to urolithiasis and a urethral mass are rule-outs.

Therapy

Surgical revision is indicated as the condition will not resolve spontaneously. Preventing erection with sedation during recovery is important; breeding these dogs can cause relapse, and castration should be suggested.

Penile Trauma

Pathophysiology

Laceration of the penis and prepuce can occur secondary to trauma (most commonly in hunting dogs on rough terrain or through barbed wire fencing), dog fights or in animal abuse cases (Web Figures 126.6 and 126.7).

Rupture of the tunica albuginea and fracture of the os penis can occur from blunt trauma in the dog (Web Figure 126.8). Self-trauma can be significant from urolithiasis, priapism or paraphimosis.

Clinical Presentation

Because of the vascularity of the penis, trauma usually results in impressive hemorrhage.

Diagnostics

Physical examination with sedation and analgesia is indicated. Radiography can identify a fractured os penis. Ultrasound of the penis can identify internal hematomas, thrombi, uroliths, and loss of linear integrity of the os in the case of a fracture [13,14]. Evaluation of the integrity of the urethra with contrast radiography should be made as indicated (see Chapter 100).

Therapy

Surgical repair of lacerations has a good prognosis if significant tissue devitalization is not present (Web Figure 126.9). Temporary catheterization (3–7 days) can enable healing of urethral tears if not extensive. Amputation of the penis and permanent urethrostomy are indicated in severe cases.

Infectious Orchitis and Epididymitis

Pathophysiology

Bacterial orchitis and epididymitis not associated with brucellosis (canine) can occur separately or in concert. Bacterial contamination of the testis or epididymis can originate hematogenously, by extension from other genitourinary organs or by injection (bite wounds) [11].

Clinical Presentation

Male dogs and cats are typically presented because their owners noticed an enlarged scrotum. Scrotal enlargement can be due to scrotal neoplasia, scrotal dermatitis, scrotal edema, intrascrotal effusion or hemorrhage, testicular enlargement or epididymal enlargement. Testicular or epididymal enlargement can be due to an acute infectious process or infiltrative disease, which can be granulomatous or neoplastic. Foreign bodies such as grass awns can be a cause of infection of the testes or epididymis. Animals with infectious orchitis/epididymitis are typically painful and febrile.

Diagnostics

Brucellosis should always be ruled out in the dog. A careful palpation of the scrotum and contents with appropriate analgesia and sedation can differentiate the source of enlargement; ultrasound evaluation is very helpful in identifying pathology and localizing the cause of enlargement. Ultrasound-guided sampling will permit cytology and culture/sensitivity to be performed.

Therapy

Dogs or cats should be treated with appropriate antibiotic therapy based on culture and sensitivity profiles, and keeping in mind penetration into the prostate gland (dog) if suspected to be involved (see Chapters 96 and 200). Appropriate antimicrobial therapy should continue for a minimum of 2–8 weeks, longer in the case of chronic bacterial prostatitis. The prognosis for fertility is guarded (but not hopeless), even with therapy; thermal damage from heat associated with inflammation affects spermatogenesis, and the potential for sperm autoantibody formation exists following such an inflammatory process. Males not valuable for breeding can be castrated to hasten recovery [12].

Testicular Torsion

Pathophysiology

Other than malignant transformation, the most common complication of uncorrected cryptorchidism in the dog is testicular torsion, which occurs with an increased incidence in neoplastic intra-abdominal testes [15]. Intrascrotal testicular torsion is rare.

Clinical Presentation

Cryptorchid testicular torsion presents as an acute abdomen. The dog can appear to be neutered when actually cryptorchid. Intrascrotal testicular torsion presents as acute, severe scrotal pain.

Diagnostics

Ultrasound is commonly performed in dogs with acute abdominal distress. Cryptorchid testes can be positioned anywhere between the ipsilateral kidney and the inguinal canal, but tend to gravitate to the midventral abdomen when enlarged by neoplasia. Testicular torsion can appear similar to orchitis with a diffuse hypoechoic appearance to the testis; malignant transformation and

gangrenous change can make their appearance less recognizable. Doppler examination reveals aberrant blood flow [13,14].

Therapy

Stabilization and immediate surgical intervention for removal are indicated.

Scrotal Dermatitis

Pathophysiology

Scrotal dermatitis most commonly results from superficial irritants, contact or insect bite hypersensitivity, ophitoxemia (snake envenomation; Web Figure 126.10), thermal insult (heat or cold), excessive grooming/clipping, or trauma. Self-excoriation often complicates the initial insult. Cutaneous neoplasia, most commonly mast cell tumors, can also produce scrotal dermatitis. Uncommonly, a varicocele can produce scrotal dermatitis. Heat from inflammation of the scrotum can damage spermatogenesis; this may not be apparent for days to weeks.

Clinical Presentation

Scrotal dermatitis is most common in intact dogs. The scrotum can be markedly edematous, erythemic, and ulcerated. Affected dogs are painful with an abnormal gait.

Diagnostics

The diagnosis is based on physical examination and palpation of the scrotum under adequate sedation/analgesia. Differentiation of scrotal enlargement secondary to a testicular mass, orchitis/epididymitis, intrascrotal testicular torsion or entrapment of tissue through an inguinal hernia should be made. Ultrasound can be helpful in identifying the origin of scrotal enlargement [13].

Therapy

Prevention of further excoriation by the use of an Elizabethan collar is important. Treatment depends on the etiology identified. Non-specific dermatitis should be treated with systemic antibiotics, analgesics, and anti-inflammatories as indicated. Gentle cleansing of the scrotum with saline is advised, avoiding antiseptics with irritant potential.

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I. Common Toxins

Decontamination and Toxicological Analyses of the Poisoned Patient

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Introduction

The goal of decontamination in the poisoned veterinary patient is to “inhibit or minimize further toxicant absorption and to promote excretion or elimination of the toxicant from the body” [1,2]. When treating the poisoned patient, the clinician should have an understanding of the toxic dose (if available), the pharmacokinetics (including absorption, distribution, metabolism, and excretion), the underlying mechanism of action, and the potential clinical signs that can be observed with the toxicant [2]. This will help determine appropriate decontamination and therapy for the patient. If this information is not readily available, the reader is advised to contact the ASPCA Animal Poison Control Center (APCC) (888-426-4435) for life-saving, 24/7 advice.

There are several methods of decontamination for use in the poisoned patient. While the gastrointestinal (GI) route is the most common type of decontamination used in veterinary medicine, other types include ocular, dermal, inhalation, injection, forced diuresis, blood purification (see Chapter 129), or surgical removal of the toxicant (Table 127.1) [1,2]. Additionally, lipid therapy is now recognized as a potentially useful treatment for lipophilic drug intoxications (see Chapter 128).

Gastrointestinal Decontamination

Gastrointestinal decontamination can be safely performed at home by the pet owner (for dogs) or by the veterinary professional. Keep in mind that the medical recommendation to decontaminate a pet at home must be thoroughly evaluated by the veterinarian, veterinary staff, or the ASPCA APCC first. Prior to inducing emesis, one should be aware that there is a narrow time frame to perform decontamination. Also, note that the effectiveness of emesis induction is dependent on several factors (Box 127.1) [1–6]. Lastly,

decontamination is contraindicated in certain circumstances (Table 127.2).

Prior to emesis induction, a complete history should be obtained from the pet owner. Particular information that should be obtained includes the time frame since ingestion, confirmation of the active ingredient, the amount of toxicant ingested (in order to calculate the toxic dose), the presence of clinical signs, previous medical history, and the toxin's potential to cause severe illness.

Emesis induction should only be performed with recent ingestion of a toxicant or unknown time of ingestion in an *asymptomatic* patient. The sooner that emesis induction can be performed, the greater the amount of gastric contents that will be recovered [2]; the gastric recovery volumes decrease as time passes. Studies have shown that gastric recovery within 1 hour after toxin ingestion was approximately 17–62% [1,3–6]. When emesis was induced within an even shorter time span (within 11–30 minutes), mean recovery of gastric contents was approximately 49% (range 9–75%) [1,3]. If several hours have elapsed since ingestion, the contents have likely moved out of the stomach and emesis may no longer be of benefit [1,2]. That said, induction of emesis can be performed in *asymptomatic* patients up to 1–2 hours post ingestion, particularly with certain toxicants [1,2].

Emetic Agents

Veterinary professionals should recommend or use safe, effective emetic agents, as several agents have fallen out of favor. Many home or internet remedies are used without success and have the potential of causing further harm.

Emetic agents work by causing local gastric irritation, stimulating the central nervous system (CNS) chemoreceptor trigger zone (CRTZ), or a combination of the two [1,2]. Emetic agents are not effective if an antiemetic

Table 127.1 Other routes of decontamination [1,2].

Type of decontamination	Treatment	Treatment	Avoid
Ocular	With ocular exposure to a corrosive or caustic toxicant, the pet owner should attempt to copiously flush the eyes at home with tepid water or physiological saline (e.g. contact lens solution <i>without</i> any soaps or cleaners), ideally for 15–20 minutes, prior to seeking veterinary attention	Elizabethan collar Immediate veterinary evaluation	Prevent rubbing/scratching Avoid contact lens chemicals (e.g. cleaners, soaps, etc.)
Dermal	Prevent pet from grooming (which can result in secondary re-exposure)	Prevent exposure to pet owner (e.g. protective gear) Wash with tepid or lukewarm water and mild, gentle, degreasing liquid dish soap (e.g. Dawn, Palmolive, etc.)	Avoid scrubbing or pressurized sprays which can result in further dermal injury Avoid “neutralizing” agents on the skin (e.g. an alkaline for an acid exposure); this may cause a chemical or thermal reaction, resulting in additional injury
Inhalation	Prompt removal from environment	Humidified oxygen source Immediate veterinary evaluation Monitoring of oxygenation and ventilation	
Injection	The stinger or venom sac should be gently and carefully removed from the patient’s skin	Immediate veterinary evaluation	Pet owners and veterinary professionals should avoid the following with a snake bite: making an incision and “sucking” the affected area; applying cold or hot compresses; applying a tourniquet
Forced diuresis	The concurrent use of aggressive intravenous fluids and concurrent diuretic therapy Used ideally for certain toxicants that have a high level of excretion through the kidney including salicylates, phenobarbital, bromide, amphetamines, lithium, etc.	Monitor for electrolyte abnormalities, acid–base disturbances, and fluid overload	Avoid fluid overload Consider urinary catheterization to remove urine and quantify output
Surgical removal	For certain toxicants that result in a FBO, bezoar, or life-threatening, acute abdomen (e.g. unbaked yeast bread dough, di-isocyanate glues, bone meal, etc.), surgery may be required	Gastric lavage should be attempted first to help break up the potential toxicant (e.g. bezoar). If the toxicant cannot be removed by gastric lavage, or if it is sharp, surgical removal may be necessary	Immediate surgical intervention (following radiographs) is warranted with di-isocyanate glues (Gorilla Glue), due to rapid formation of a FBO

FBO, foreign body obstruction.

(e.g. ondansetron, maropitant, etc.) has been previously administered. Currently, the only home recommendation for dog owners is 3% hydrogen peroxide [1,2,7]. There is no safe at-home emetic agent that is recommended for cats; anecdotally, 25% of cats can develop a severe hemorrhagic gastritis secondary to hydrogen peroxide administration and deaths have rarely been reported (personal communication, ASPCA APCC, Urbana, USA) [8].

Methods that are no longer recommended for emesis induction include digital induction of emesis (e.g. stimulation of the gag reflex), syrup of ipecac, liquid dishwashing detergent, liquid soaps, dry mustard powders, and table salt (sodium chloride) [1,2,9]. Digital induction of emesis often results in physical injury to the pet owner (dog bite), or injury to the pet’s throat and soft palate. Syrup of ipecac has historically been recommended to

Box 127.1 Factors affecting the effectiveness of emesis induction [11,12].

When recommending or performing emesis induction, keep in mind that the following factors affect gastric recovery of the toxicant [1,2].

- What type of emetic agent was used
- Time since last meal fed (e.g. presence of gastric acid or amount of gastric contents)
- How much time has passed since time of ingestion of the toxicant
- The texture or physical characteristics of the toxicant ingested (e.g. gel caps are rapidly absorbed, etc.)
- Whether the toxicant affects gastric emptying (e.g. opioids, salicylates, tricyclic antidepressants, etc.)
- The amount ingested (e.g. massive ingestions which can result in concretions or bezoars, causing delayed gastric emptying)

induce emesis, but is no longer the standard of care. Its cardiotoxic potential and tendency to result in prolonged vomiting, lethargy, hematemesis, depression, and diarrhea have caused it to fall out of favor in both human and veterinary medicine [1,2]. Soaps, mustard powders,

and table salt are not reliable as emetic agents and may be detrimental (e.g. resulting in further complications such as hypernatremia) [9].

Common veterinary emetic agents include apomorphine (e.g. tablets, capsules, or injectable) for dogs and alpha-2 adrenergic agonist agents (e.g. dexmedetomidine, xylazine) for cats [10–12]. Hydrogen peroxide is commonly used by veterinarians as an emetic agent in dogs and is equally effective as apomorphine [7]; however, it has been recently associated with gastrointestinal inflammation and ulceration even in dogs [13]. See Table 127.3 for more information.

Gastric Lavage

Gastric lavage, while less commonly performed than emesis induction, is still indicated in certain situations or with certain ingested toxicants in the veterinary patient. Gastric lavage should be performed when emesis induction is unproductive or contraindicated, yet the toxicant is still thought to be present in the stomach; the goal is to assist in removal of gastric contents and ease of administration of activated charcoal.

Table 127.2 Emesis induction: indications and contraindications [1,2].

Indications to induce emesis	Contraindications to inducing emesis
Following a recent toxicant ingestion (<1–2h) in an asymptomatic patient	Following ingestion of caustic or corrosive toxicants (e.g. batteries, ultra-bleach, lye, oven cleaning chemicals) or when emesis induction may result in further injury to the oropharynx, esophagus, and gastrointestinal tract when these agents are expelled
With unknown time of toxicant ingestion in an asymptomatic patient	Following ingestion of petroleum distillates or hydrocarbons (e.g. kerosene, gasoline, motor oil, transmission fluid, etc.); these toxicants can be easily aspirated into the respiratory system and result in severe aspiration pneumonitis
Following ingestion of a product known to stay in the stomach for a long time period in an asymptomatic patient (e.g. bezoar, massive ingestions, grapes/raisins, chocolate, wads of xylitol gum, foreign body, etc.)	In symptomatic patients that have a decreased gag reflex (e.g. sedation, coma, hypoglycemia, etc.) or a lowered seizure threshold (e.g. tremoring, seizuring, etc.) that may be unable to protect their airway, resulting in aspiration pneumonitis
	In patients with underlying medical conditions that may predispose them towards aspiration pneumonitis or complications associated with emesis induction (e.g. megaesophagus, history of aspiration pneumonia, upper airway disease, laryngeal paralysis)
	Brachycephalic breeds (e.g. English bulldog, pug, shih-tzu) with an elongated soft palate, everted sacculles, a hypoplastic trachea, or stenotic nares may be better candidates for sedation, intubation, and gastric lavage rather than emesis induction due to the risks of aspiration
	Species that anatomically cannot vomit or cannot safely have emesis chemically induced such as birds, rabbits, ruminants (e.g. sheep, cattle, llamas, and goats), horses, and rodents (e.g. chinchillas, rats, gerbils)

Table 127.3 Drug doses for common emetic agents and their reversal agents [1,2,7,10–12].

Drug	Mechanism of action	Dose
Apomorphine (available as tablets, capsules or injectable)	Acts on the CRTZ	Dose: dogs, 0.02–0.04 mg/kg IV or IM; can also apply the tablet or capsule contents directly into subconjunctival sac [1,2,10] Generally not used in cats as not effective If administered via the subconjunctival route, flush well after emesis, or eye irritation and protracted vomiting can occur If emesis does not occur, a second dose of apomorphine can be used. The author does not recommend additional dosing thereafter; rather, an oral dose of hydrogen peroxide may be beneficial, if needed (dogs only)
3% Hydrogen peroxide	Acts as a direct gastric irritation on the stomach In dogs, effective for at-home or veterinary use. [7] Due to the risk of GIT irritation and ulceration, antacid therapy should be used (e.g., famotidine, sucralfate X 5-7 days) [13] Not recommended for use in cats due to risks of hemorrhagic gastritis and rarely, death [8]	1–2 mL/kg, PO once; repeat if needed [1,2] Maximum dose: 50–150 mL/large dog [1,2]
Atipamezole (Antisedan)	Alpha-2 adrenergic antagonists Reverses the effects of dexmedetomidine and xylazine	0.1 mg/kg IM, IV [10]
Dexmedetomidine	Used as an emetic for cats due to alpha-2 adrenergic agonist properties	7-10 mcg/kg IM, SC [11,12] Adverse effects from dexmedetomidine include respiratory depression, hypotension, and excessive sedation
Liquid dish detergent (e.g. Dawn, Palmolive, Joy)	Acts as a direct gastric irritant Generally not recommended, due to the increased effectiveness and wider margin of safety of hydrogen peroxide (for dogs) Eco-friendly products (without phosphate) are anecdotally not as effective as an emetic agent	Dose: 10 mL/kg of a mixture of 3 tablespoons of detergent to 8 ounces of water [1,2] Can take longer to result in emesis; as hydrogen peroxide has a faster onset of action as an emetic agent, dish detergent is rarely used or recommended any more NOTE: When counseling pet owners on how to decontaminate a pet at home (e.g. whether for emesis induction or for dermal decontamination), appropriate detailed communication must occur; one should not use corrosive products used for automatic dishwashers (e.g. Cascade)
Table salt	Acts as an emetic by direct gastric irritation While readily available within the household, the use of salt is <i>no longer</i> recommended as an emetic due to potential side-effects Rare reports of electrolyte disturbances (e.g. hypernatremia, hyperchloremia); hematemesis, and persistent emesis can be seen [9]	Dose: 1–3 teaspoons orally [1,2] Emesis induction typically occurs within 10–15 min [2] In children treated with salt as an emetic, hypernatremia, secondary cerebral edema, and neurological complications have been seen [1,2]. Rarely, death has been reported [9]
7% Syrup of ipecac	Syrup of ipecac contains the alkaloid compounds cephaeline and emetine, which act as a direct gastric irritant and stimulate the CRTZ [1,2] Due to the availability of safer emetic agents, the use of syrup of ipecac or ipecac fluid extract (which is more potent) is <i>no longer</i> recommended in either human and veterinary medicine [1,2]	Dose: dogs, 1–2 mL/kg PO; cats, 3.3 mL/kg; cumulative dose in either species is not to exceed 15 mL [1,2] Emesis induction typically occurs within 10–30 min [1,2] Several adverse effects can be seen with syrup of ipecac including cardiotoxicity, lethargy, diarrhea, weakness, diarrhea, protracted vomiting, hematemesis, hypersalivation, distaste (cats), ineffectiveness, and delayed onset of action (which can take up to 1 hour) [1,2]

Drug	Mechanism of action	Dose
Xylazine hydrochloride	Used as an emetic for cats due to alpha-2 adrenergic agonist properties Due to the availability of more effective, safer emetic agents in dogs (e.g. hydrogen peroxide, apomorphine), xylazine is not recommended in this species.	Dose: cats, 0.44 mg/kg, IM or SC [10,11,12] In the author's experience, only 50% of cats given xylazine have effective emesis Delayed emesis may be seen following administration Adverse effects from xylazine include respiratory depression, hypotension, and excessive sedation
Yohimbine	Alpha-2 adrenergic antagonists Reverses the effects of xylazine	0.1 mg/kg IM, SC, or IV slowly [10]

CRTZ, chemoreceptor trigger zone; IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

Human studies have shown minimal gastric lavage recoveries (range 29–38%) when gastric lavage was performed within 15–20 minutes after toxicant ingestion [1–5,14]. Gastric lavage recoveries drop even further to 8.6–13% when lavage is performed at 60 minutes post ingestion [1–5,14]. In the veterinary scenario, most poisoned patients are presented to the veterinary clinic more than 60 minutes post ingestion, making the clinical usefulness of gastric lavage debatable [1,2]. Knowing that gastric lavage can be labor intensive and may yield low gastric recovery, veterinarians are often hesitant to perform this potentially life-saving procedure [1,2]. That said, the use of gastric lavage is warranted in the following situations [2].

- When the patient is already significantly affected by the toxicant, thereby predisposing the patient to aspiration if emesis induction is performed (e.g. unconscious, excessively sedate, tremoring, seizing, etc.).
- With toxicants that have a narrow margin of safety that may still require decontamination with a controlled airway (e.g. baclofen, macrocyclic lactones, metaldehyde, marijuana, organophosphates, carbamates, calcium channel blockers, beta-blockers, etc.).
- With toxicants that can result in a bezoar formation or concretion (e.g. massive ingestions, unbaked yeast bread dough, prenatal iron tablets, bone meal, etc.).
- With ingestions approaching the LD₅₀.

Rare complications may occur when performing gastric lavage, including aspiration pneumonitis, complications from sedation, hypoxemia secondary to aspiration pneumonia, hypercapnia from sedation or anesthesia, laryngospasm, fluid and electrolyte abnormalities, or mechanical injury to the mouth, oropharynx, esophagus, or stomach [1,2,14].

Contraindications for gastric lavage include ingestion of sharp objects (e.g. sewing needles, etc.), corrosive agents (where perforation to the oropharynx, esophagus, and stomach can occur during orogastric tube placement), petroleum distillates or hydrocarbons (e.g.

low-viscosity liquids that can result in severe aspiration pneumonia), or in patients with underlying pathology that could increase the risk of esophageal or gastric perforation or hemorrhage [1,2].

Many veterinarians may not feel comfortable performing gastric lavage, but it can be easily accomplished when organized with the appropriate supplies and a team-oriented approach. Box 127.2 gives a step-by-step guide on how to perform this important procedure [1,2].

Lastly, whole-bowel irrigation (WBI) is listed in the literature as a means of decontaminating the gastrointestinal tract (GIT) by removing toxins and normal intraluminal GI contents. This is typically done by the enteral administration of large amounts of polyethylene glycol electrolyte solution (PEG-ES or PEG, e.g. Golytely) until effluent (e.g. stool) is clear. Anecdotally, this is rarely indicated for the management of the poisoned veterinary patient. The reader is referred to another toxicology source for more information on this technique [1,2].

Activated Charcoal

Activated charcoal (AC) has been used for over 100 years for the treatment of toxic ingestions [15]. Activated charcoal is created by controlled pyrolysis of petroleum, coconut shells, lignite (coal), peat, and wood, which then produces charcoal [1,15]. Once charcoal is created, it is activated by heating at high temperatures (600–900°C) with steam, air, or carbon dioxide [1,2,15]. This results in a small particle size, a large surface area (950–2000 m²/g), and a highly developed internal pore structure which contributes to adsorptive properties and extent of adsorption at equilibrium [15].

Activated charcoal works by adsorbing poison in the GIT and decreasing the extent of systemic absorption of the poison [1,10,15]. In order for AC to work, it must physically contact the toxicant. To maximize AC absorption of the toxicant, the administration of

Box 127.2 Performing gastric lavage [1,2].

- While gastric lavage can be labor-intensive and require several assistants, it can be potentially life saving for the poisoned patient.
- Prepare the following materials in advance:
 - IV catheter supplies
 - Sedatives and an anti-emetic (predrawn and labeled appropriately)
 - Endotracheal tube (ETT)
 - Syringe to inflate the ETT cuff
 - Gauze (to secure the ETT in place)
 - Anesthetic machine and appropriate monitoring
 - Orogastric tube
 - 2" roll of white tape
 - Mouth gag
 - Lubrication (for orogastric tube)
 - Empty bucket
 - Warm lavage water in a bucket
 - Bilge or stomach pump; alternatively a funnel can be used with gravity assistance
 - Step stool
 - Activated charcoal predrawn in the appropriate dose in 60 mL syringes ready for administration
 - Sedation reversal agents
 - Oxygen supplementation
 - Monitoring equipment
- After placing an IV catheter, preoxygenate patient, then sedate and intubate. Ensure the airway is protected. Connect to an oxygen $\pm$ inhalant anesthesia source. Place in either sternal (clinician preference) or right lateral recumbency.
- Administer a potent antiemetic to prevent secondary aspiration pneumonia (e.g. maropitant, ondansetron).
- Prepare an appropriately sized orogastric tube and premeasure to the outside of the patient's body (to the last rib); mark this location with white tape so you know how far to insert the tube.
- Lubricate the orogastric tube, and gently pass it through the oropharynx, down the esophagus, and into the stomach. Simultaneous inflation (e.g. blowing into the orogastric tube) and using gentle, twisting motions of the tube will help with passage of the tube into the stomach.
- Confirm appropriate placement of the orogastric tube. This can be done by palpating the tracheal region for two "tubes," by blowing into the tube while simultaneously auscultating over the stomach region (to listen for gurgling or bubbling), and by the presence of gastric gas coming from the end of the tube. Once in the stomach, infuse tepid or warm water through the orogastric tube via the bilge/stomach pump. The volume of the stomach is estimated to be approximately 60 mL/kg; therefore, copious amounts of fluid can be used to gavage. Some sources recommend using 10 mL/kg per gavage, and performing 15–20 gavage cycles [1].
- The stomach should be frequently palpated during gavage to prevent overdistension.
- Aggressive agitation and palpation of the stomach can be performed by an assistant to help break up the gastric contents to enhance gastric lavage recovery.
- Once all the gavage liquid is removed, activated charcoal can be administered via the orogastric tube and flushed into the stomach (to clear the tube).
- Gastric lavage fluid can be saved for toxicological testing at a veterinary diagnostic laboratory as needed. The clinician should physically evaluate the gastric lavage contents to look for the presence of the toxicant(s).
- The orogastric tube must be kinked off prior to removal to prevent lavage fluid from being accidentally aspirated from the oropharynx.
- Recover the patient in a sternal position with the head elevated to prevent aspiration. The patient should be kept intubated until a strong gag reflex is present, allowing for extubation.
- A video example of gastric lavage can be found here: <http://vetgirlontherun.com/veterinary-continuing-education-how-perform-gastric-lavage-dog-vetgirl-video/>

AC should be implemented as soon as possible, as delayed administration reduces its effectiveness [15]. Non-polar compounds bind to AC well [2] while heavy metals and alcohols (e.g. ethylene glycol, sugar alcohols, etc.) [16] are not adsorbed by AC [2,15]. In general, *in vitro* adsorption to AC reaches equilibrium in less than 30 minutes [1,15]. While desorption of toxicants to AC can occur, as binding to AC is a reversible process, this clinical effect is not known or well described [1,2,15]. For this reason, a cathartic should be given with the first dose of AC to enhance fecal expulsion of the bound AC and toxicant [1,2].

Over the past few decades, the use of AC has fallen out of favor in human medicine. The American Academy of Clinical Toxicology (AACT) and European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) created a position paper in 1997 (revised again in 2004) which clearly stated that “single-dose AC should not be administered routinely in the management of poisoned patients ... [as] ... there is no evidence that administration of AC improves clinical outcome” [15]. Since then, the use of AC in human medicine has continued to decline, according to the American Association of Poison Control Centers Toxic Exposure Surveillance System (from 7.7% to 5.9% in 2003) [15].

That said, the administration of AC is still considered part of the mainstay of treatment for GI decontamination in the veterinary poisoned patient [1,2]. Current recommended dosing for single-dose AC is 1–5 g AC/kg with a cathartic (e.g. sorbitol) [1,2]. Likewise, AC can be administered with food, but ideally small amounts should be used to prevent interference with absorptive properties [17].

Multidose Activated Charcoal

Certain situations or toxicities warrant the administration of multiple doses of AC including ingestion of sustained- (SR), extended- (XR), or long-acting (LA) release products; drugs undergoing enterohepatic recirculation; drugs with a long half-life (e.g. naproxen; 72 hours), or drugs that diffuse from the systemic circulation back into the GIT down the concentration gradient [2]. When administering multiple doses of AC, the use of a one-time dose of a cathartic is recommended to help promote GIT motility [1,2]; however, continued use of cathartics can result in profound dehydration, fluid losses, and hypernatremia due to water moving into the GIT. While veterinary studies are lacking, there is likely an added benefit from multidosing AC, provided the patient is well hydrated and monitored appropriately. Current recommended dosing for multiple doses of AC is 1–2 g AC *without a cathartic* per kg of body weight, PO, every 6 hours for 24 hours.

Complications

In both human and veterinary medicine, there are relatively rare reports of AC-related adverse events, especially when considering the widespread use of AC [1,2,15]. Complications include vomiting [1], fluid, electrolyte, and acid–base abnormalities (including hypernatremia, hypokalemia, hypermagnesemia, and metabolic acidosis) [1,2,15], respiratory complications (e.g. aspiration pneumonia) [15], difficult endoscopy (due to the presence of AC in the GIT), constipation, and, rarely, corneal abrasions (if accidental contact with the eye occurs). In humans given multidose AC, complications of ileus and small intestinal obstruction (from charcoal bezoars) requiring surgical intervention have been reported [15]. When AC is used appropriately in a hydrated patient, the majority of adverse events are not directly related to AC; rather, they may be due to the cathartic effects or pulmonary complications (e.g. aspiration into the lungs) [15].

Administration of Charcoal

Prior to administration of AC with or without a cathartic, the patient's hydration status should be assessed carefully. Appropriate fluid supplementation (SC, IV) should be administered to prevent dehydration and hypernatremia. In addition, the concurrent use of parenteral antiemetics (e.g. maropitant, dolasetron, etc.) should be considered due to the high incidence of vomiting from cathartic administration (or from the emetic agent which was previously used to decontaminate the patient); this will also allow for rapid return to oral water and help minimize the risks of hypernatremia and aspiration pneumonia. Cathartics should not be used in the dehydrated poisoned patient due to the risks of free water loss into the GIT and subsequent hypernatremia [2]. For patients receiving multiple doses of AC with or without cathartics, serum sodium levels should be monitored daily, along with hydration status (personal communication, ASPCA APCC, Urbana, USA). Patients with underlying diseases that may affect hydration status and water balance (e.g. renal disease, diabetes mellitus, psychogenic polydipsia, diabetes insipidus, etc.) may have an increased risk for the development of significant, clinical hypernatremia secondary to AC and/or cathartic administration.

Toxicological Analyses

In certain situations, routine and advanced diagnostic testing for toxicological analyses may be indicated in the poisoned veterinary patient. Routine testing may include a complete blood count, biochemistry panel, venous or arterial blood gas, coagulation testing (e.g.

prothrombin (PT), activated partial thromboplastin time (aPTT)), and urinalysis. For example, hepatotoxicants (e.g. acetaminophen, sago palm, xylitol, etc.) may result in increased liver enzymes, bile acids, bilirubin, and prolonged coagulation times. With nephrotoxicants (e.g. NSAIDs, grapes, ethylene glycol (EG), *Lilium* or *Heimerocallis* spp, etc.), elevated SDMA, BUN and creatinine, metabolic acidosis, electrolyte abnormalities, along with presence of isosthenuria, crystalluria, or urinary casts may be seen. With anticoagulant rodenticides (e.g. bromadiolone, brodifacoum, etc.), prolongation of PT/aPTT may be seen at 36 hours post exposure. Electrolyte changes may also be seen with calcium-related toxicants (e.g. vitamin D, calcipotriene, etc.), cardiac glycoside-containing plants, calcium channel blocker medications, albuterol, etc.

Keep in mind that certain in-house diagnostic tests commonly used in veterinary medicine have limitations.

The results of rapid in-house tests for certain toxicants (e.g. EG, anticoagulant rodenticide, urine illicit drug testing) must be interpreted carefully and appropriately based on limitations of the test (e.g. false-positive or negative results) and the pharmacokinetics of the toxicant (e.g. mechanism of action, metabolism of the toxicant, half-life). For example, over-the-counter (OTC) urine illicit drug screening tests (designed for humans) are often utilized by emergency veterinarians. These commonly test for heroin, cocaine, tetrahydrocannabinol (THC), methamphetamines, and phencyclidine (PCP). The clinician must be aware that these OTC qualitative tests have limitations. False positives can occur with exposure to opioids, lidocaine, amphetamines, tramadol, trazodone, diphenhydramine, NSAIDs, etc. Dogs often test false negative for THC, due to an altered metabolite (e.g. 8-OH- Δ^9 -THC versus 11-OH- Δ^9 -THC). For this reason, the author does not routinely advocate

Table 127.4 Drug doses for common medications used to treat the poisoned patient [1,2,10].

Drug	Use	Dose
Activated charcoal	To minimize toxicant absorption from the GIT	1–5 g/kg PO once. If multiple doses are used, dose at 1–2 g/kg orally q6h $\times$ 24 h, without a cathartic
Atropine	Competes with both acetylcholine and muscarine at cholinergic muscarinic receptor sites; used for muscarine mushroom toxicosis	0.02–0.2 mg/kg, divided IV and IM
Diazepam	Anticonvulsant	0.25–0.5 mg/kg IV PRN
Dolasetron	Antiemetic	0.6 mg/kg, SC, IM, IV q24h
Maropitant	Antiemetic	1 mg/kg SC or IV q24h
Metoclopramide	Prokinetic Antiemetic	0.2–0.5 mg/kg, SC, IM q6–12 h; or CRI at 1–2 mg/kg/day IV Generally less effective than maropitant or ondansetron, but provides gastric emptying and a prokinetic effect
N-acetylcysteine	Hepatoprotectant; used for hepatotoxicants (e.g. <i>Amanita</i> mushrooms, acetaminophen, xylitol, blue-green algae, sago palm, etc.)	140–280 mg/kg IV* or PO once, followed by 70 mg/kg IV or PO q6h $\times$ 48–72 h as needed
Ondansetron	Antiemetic	0.1–1.0 mg/kg, SC, IM, IV q6–12h
Phenobarbital	Anticonvulsant	4–20 mg/kg IV as needed
Plasma (as fresh frozen plasma or frozen plasma)	Used to treat coagulopathy secondary to hepatotoxicants	10–20 mL/kg IV PRN if coagulopathic
S-adenosylmethionine	Hepatoprotectant	18–20 mg/kg PO q24h
Silibinin	Hepatoprotectant	50 mg/kg IV, 5 h and 24 h after <i>A. phalloides</i> exposure. Alternatively 2–5 mg/kg PO q24h
Vitamin K1	Used to treat coagulopathy secondary to vitamin K-dependent factors inactivated during hepatic injury or anticoagulant rodenticide toxicosis	2.5–5 mg/kg PO, SC q12h

*Intravenous route preferred to prevent interaction with activated charcoal.

CRI, constant-rate infusion; GIT, gastrointestinal tract; IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); PRN, as needed (*pro re nata*); SC, subcutaneous.

the use of this testing method without careful interpretation. When in doubt, the use of a human or veterinary diagnostic laboratory should be considered for more accurate testing.

Advanced diagnostic testing can be performed with a reputable human or veterinary diagnostic laboratory. Toxicological analysis may include broad-spectrum screening tests utilizing gas chromatography, mass spectrometry, immunological technology, ELISA testing, quantitative analysis, necropsy, etc. [18]. While this is less commonly performed, toxicological analysis is particularly important with the unknown, suspected, or malicious poisoning situation. For example, the most accurate way of detecting EG toxicosis in dogs and cats is by submitting a quantitative serum EG level. Likewise, acetaminophen levels can be easily measured at a human hospital. Unfortunately, the cost of testing and delay in results (which can take several days to weeks) often preclude clinical utility in the veterinary poisoned patient.

If a necropsy is performed, the following necropsy specimen tissue samples are recommended for collection.

- Brain (with half frozen and half submitted in formalin)
- Ocular fluid
- Injection site (if applicable)
- Gastrointestinal contents (e.g. stomach, intestinal and colonic contents)
- Kidney

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- Liver
- Urine (with half frozen and half chilled)

For more information on toxicological analyses, readers are referred to a veterinary toxicology book or consultation directly with a human or veterinary diagnostic laboratory.

Conclusion

In veterinary medicine, the primary treatment for toxicant exposure should be decontamination and detoxification of the patient to inhibit or minimize further toxicant absorption and promote excretion or elimination of the toxicant from the body [1,2]. Aggressive decontamination and detoxification of the poisoned patient are imperative and still considered the mainstay therapy in veterinary medicine. As the majority of toxicants do not have an antidote, treatment of the poisoned patient should be aimed at decontamination and symptomatic supportive care, including fluid therapy, GI support (e.g. antiemetics, gastric protectants, etc.), cardiovascular support, neurological support (e.g. muscle relaxants, anticonvulsants, etc.), miscellaneous therapy (e.g. hepatoprotectants, reversal agents, vitamin K1, intravenous lipid emulsion, etc.), and antidotal therapy, when available (Table 127.4). The clinician should feel well versed in how to appropriately decontaminate the poisoned veterinary patient.

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Lipid “Rescue” Therapy

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Introduction

Intravenous lipid emulsion (ILE) has been routinely used in human and veterinary medicine for decades as a component of partial or total parenteral nutrition (PN) as well as a vehicle for certain drugs (e.g. propofol). The first documented successful use for the treatment of local anesthetic systemic toxicity was in 2006 when it was used to treat seizures and subsequent cardiopulmonary arrest (CPA) in a patient following a local anesthetic protocol of bupivacaine and mepivacaine after standard resuscitation efforts failed to result in return of spontaneous circulation (ROSC) [1]. Since then, ILE has been more frequently used in human medicine as a treatment for local anesthetic systemic toxicities and more recently as a treatment for various lipophilic drug toxicities.

This application is clinically useful in veterinary medicine where lipophilic medications make up a large portion of reported exposures to the ASPCA Animal Poison Control Center (APCC) [2]. While further evaluation is needed to fully understand the mechanism of action, efficacy, and potential safety concerns associated with ILE therapy when used as an antidote, current case studies and anecdotal reports suggest clinical efficacy of ILE in the treatment of various lipophilic drug toxicities, especially where morbidity and mortality may be high and no known antidote or alternative is available.

Available Formulations

Intravenous lipid emulsion is commonly composed of medium- to long-chain triglycerides found in various oils (soybean oil, safflower oil, etc.), a phospholipid emulsifier, and glycerin [2]. The various formulations are classified by droplet size and the available compositions used in PN or for antidotal therapy are similar in size to endogenous chylomicrons and are thought to be eliminated by the body tissues in a similar fashion. These molecules are

typically cleared by skeletal muscle, splanchnic viscera, myocardial cells, and subcutaneous tissues where they are broken down into glycerol, free fatty acids, and choline to be used as energy by the tissues [3].

The most commonly used commercial product is Intralipid 20% which is a 20% fat emulsion and is the formulation used in dosing strategies. This is the preferred formulation due to the lower proportion of free phospholipids as higher free phospholipids may be associated with adverse effects due to interference with lipoprotein lipase activity and decreased clearance [2]. Stored correctly at room temperature, the shelf-life of ILE is typically up to 2 years. Once opened, strict aseptic technique is required when handling to reduce the risk of bacterial contamination [4]. Unused product must be refrigerated between uses and should be discarded after 24 hours. An emulsion of 20% or less is isotonic and can be administered through a peripheral catheter. Emulsions of 30% are intended to be combined with other components for PN and are not to be administered alone.

Historical Use in Human Medicine

As mentioned previously, ILE therapy was first used in the treatment of CPA secondary to local anesthetic systemic toxicity that was not responsive to traditional resuscitative efforts after 20 minutes [1]. As resuscitation continued, the patient was given a bolus of ILE followed by a constant rate infusion. Shortly after, return of spontaneous circulation (ROSC) with a normal sinus rhythm on EKG was achieved.

Another instance was in a patient treated for bupropion and lamotrigine intoxication where conventional life support measures were unsuccessful for 52 minutes. Treatment with ILE resulted in ROSC [5]. In this case, plasma concentrations of both drugs were measured serially. Peak plasma concentrations of bupropion occurred after ILE administration, which supports the

“lipid sink” theory mechanism of action to be described later. Similar results were not seen with lamotrigine, a less lipophilic medication, suggesting that the beneficial clinical effects of ILE therapy may be dependent on the lipid solubility of the toxic agent.

Various other case studies are available in the human medical literature highlighting the successful use of ILE in treatment of local anesthetic systemic toxicities. Due to the nature of the cases in which ILE therapy is warranted in human medicine, randomized controlled clinical trials are not possible. However, there is an effort by investigators to collaborate by contributing case reports and anecdotal accounts. These are available at www.lipidrescue.org – a web resource established by Dr Guy Weinberg [6].

Use in Veterinary Medicine

Although considered safe in people, ILE is reserved for patients with severe toxicity and life-threatening clinical signs and only after conventional methods of treatment and resuscitation have failed. Conversely, extra-label use of ILE therapy in veterinary patients for lipophilic drug toxicities has been initiated early in the course of treatment to mitigate severe clinical signs and shorten the anticipated clinical course. This strategy may be particularly beneficial for patients in which conventional supportive care, including intensive nursing care, prolonged hospitalization, and mechanical ventilation, may be a barrier to further treatment.

When ILE therapy is considered as an antidote for lipophilic drug toxicities, it should always be in addition to reasonable and appropriate medical management and supportive care and should not be initiated prior to addressing appropriate emergency treatment (i.e. fluid therapy, oxygen, etc.). This is particularly important because ILE, in the face of hypoxia, can potentially result in a negative myocardial inotropy and subsequent decreased contractility and cardiac output [2].

The majority of research on the use of ILE in animal patients is from experimental animal studies, beginning in 1974 when ILE was evaluated for the treatment of chlorpromazine toxicity in a rabbit model. ILE-pretreated rabbits survived and all control animals died [7]. Dr Guy Weinberg has contributed a large portion of the research done with ILE therapy. A seminal study was published in 1998 in which ILE reduced the LD₅₀ by 48% in rats with bupivacaine-induced asystole [8]. He also evaluated ILE resuscitation in a bupivacaine-induced CPA model in 12 dogs. All dogs treated with ILE in addition to cardiopulmonary resuscitation survived compared to 100% mortality in the control group [9].

There are multiple reports of ILE therapy for lipophilic toxicities, including moxidectin toxicity in a Jack Russell terrier puppy [10], ivermectin toxicity in a border collie not affected by the MDR-1 gene mutation [11], and lidocaine toxicity in a cat undergoing wound closure [12]. ILE use in these instances has remained controversial due to the inability to establish a causal relationship between ILE therapy and the outcome. Additionally, there have been two experimental studies in a porcine model which showed that ILE failed to result in reversal of cardiotoxicity of bupivacaine; however, there is concern that the cardiac effects of the anesthetic drugs administered prior to the bupivacaine overdose contributed to these results [13,14]. Currently, there is a single prospective, randomized, controlled study evaluating the use of ILE as a treatment for permethrin toxicosis in cats [15]. The study established a reliable algorithm for staging toxicosis ranging from stage A (no clinical signs) to stage F (grand mal seizures). Cats receiving ILE achieved lower clinical stages (B or A) earlier, but there was no significant difference in duration of hospitalization between the groups. Further controlled trials are necessary to fully evaluate the efficacy and safety of ILE as a first-line therapy for various lipophilic drug toxicities.

Currently, ILE therapy has promise in the treatment of the following toxicities in veterinary medicine: local anesthetics, calcium channel blockers, macrolytic lactones, muscle relaxants, cyclic antidepressants, and psychotropic drugs. The ASPCA APCC also reported its successful use in the following intoxications: amlodipine, baclofen, benzocaine, bromethalin, bupropion, CCNU, chlorpyrifox, diltiazem, doramectin, endosulfan, ivermectin, moxidectin, minoxidil, marijuana, permethrin, and phenobarbital [4].

Mechanism of Action

The exact mechanism of action by which ILE therapy decreases recovery time and ameliorates clinical signs is unknown, but multiple theories have been proposed based on the available studies and the pathophysiology of lipid metabolism. The two most widely accepted theories are improved myocardial performance and the “lipid sink” theory [2–4] and there may be multiple mechanisms at play in the way ILE exerts its beneficial effects.

Intravenous lipid emulsion therapy is thought to improve myocardial performance by delivering free fatty acids (FFA) to the myocardium as this is the preferred substrate. Bupivacaine inhibits the mitochondrial use of FFA by blocking carnitine acylcarnitine translocase and preventing movement of FFA into the mitochondria. It is thought that rapid infusion of ILE overcomes this inhibition of the mitochondria either by competitive inhibition

or some other unknown mechanism of action. The influx of FFA also stimulates the voltage-gated calcium channels and results in an increase in intracellular calcium and increased myocardial function. This may be particularly helpful when cardiac dysfunction is secondary to calcium channel blocker toxicity.

The "lipid sink" mechanism of action involves the creation of an expanded lipid phase within the plasma that acts to sequester various lipophilic compounds and reduce the effective concentration at the target tissues. The pull into this compartment may be strong enough to pull lipophilic toxins out of brain and heart tissue into the intravascular space, thereby decreasing the clinical signs and accelerating clearance of the toxin. This is supported by the previously mentioned study where peak plasma levels of bupropion were identified after treatment with ILE [5]. If this is the predominant mechanism of action, the variable response of different toxins to therapy with ILE may be due to differences in lipid solubility and therefore the pull that the "lipid sink" exerts on these compounds. The lipophilicity is related to the log P value where P is a partition coefficient and is the measure of the solubility of a compound between two solvents – one hydrophilic (water) and one lipophilic (typically octanol). A compound is considered to be lipophilic if log P is >1.0 , but the higher the log P value, the more lipophilic the compound is. For a list of lipophilic drugs which may be amenable to treatment with ILE therapy and their corresponding log P values, see the review by Fernandez et al. [3].

Recommended Dosing

There is no single recommended dosing strategy in veterinary medicine and all values are extrapolated from human data. Use in veterinary medicine of ILE as an antidote is considered extra-label. The current human resources include *Guidelines for the Management of Severe Local Anesthetic Toxicity* as provided by the Association of Anaesthetists of Great Britain and Ireland [16] and recommendations by Dr Guy Weinberg available on his website www.lipidrescue.org [6].

Dosing is based on the use of lipid emulsion in PN with a maximum not to exceed 10 mL/kg/day of a 20% emulsion. A commonly published dosing strategy using the 20% emulsion is a rapid 1.5 mL/kg IV bolus over 1–3 minutes followed by a constant-rate infusion (CRI) at 0.25–0.50 mL/kg/min for 30–60 minutes [4]. Serial serum evaluation for lipemia should be performed if multiple doses are considered. If the serum is not lipemic, the bolus and CRI dosing may be repeated as needed if clinical signs have not improved for up to 24 hours; however, ILE therapy should be discontinued

if no improvement is seen following three total doses. In some human protocols, continued intermittent bolus dosing of 1.5 mL/kg every 4–6 hours until clinical signs improve is advocated, but again not to exceed 24 hours. There are no safety studies available for the use of ILE in this manner, so caution should be exercised with careful monitoring and risk assessment for all patients undergoing antidotal treatment with ILE.

Potential Complications

As with any therapy, particularly in the somewhat novel use of ILE as an antidote for lipophilic drug toxicity, there are potential adverse effects and complications that must be considered prior to administering this therapy to any patient. A safety study performed in rats identified an LD₅₀ of 67.7 mL/kg in rats for a 20% soybean oil emulsion. Few adverse effects have been reported and the majority are associated with more chronic lipid emulsion infusion such as that associated with long-term PN, including immunological, pulmonary, and hepatic dysfunction. Clinical signs may include nausea, vomiting, fever, or respiratory distress. The significant difference between the two uses of ILE therapy is the administration rate. PN is a slower infusion over a prolonged period of time versus a high volume given over a short period of time as an antidote, so further safety studies are necessary to evaluate its use in this manner.

Aseptic technique and cautious handling are crucial to avoid bacterial contamination which could result in local or systemic infection, venous irritation, and subsequent thrombophlebitis. This is more likely with PN due to the length of treatment. Patients may also have a hypersensitivity reaction to the components of the emulsion (often egg phospholipid or soybean oil), developing clinical signs such as fever, nausea, dyspnea, cyanosis, arrhythmias, hypotension, and cardiovascular collapse. Lipemia can interfere with certain laboratory tests, including showing a false hyperglycemia on certain analyzers. If lipemia is persistent, pancreatitis is a theoretical sequela, particularly in patients with a history of pancreatitis, though no cases have been reported in veterinary medicine when using ILE as an antidote.

In patients with acute respiratory distress syndrome (ARDS) or other severe inflammatory diseases, ILE therapy has been shown to decrease the arterial partial pressure of oxygen to fraction of inspired oxygen ratio (PaO₂:FiO₂). Pulmonary lipid emboli have been reported in children, but similar lesions have not been reproduced when using ILE as an antidote. The final reported complication associated with ILE for PN in people is "fat overload syndrome" which is typically due

to high volume or excessive administration rates that overwhelm the lipid clearance mechanisms and lead to hyperlipidemia, hepatomegaly, icterus, splenomegaly, thrombocytopenia, abnormal clotting times, and hemolysis [2–4]. This syndrome has not yet been reported in animals.

Further investigation is needed to evaluate the safety and determine the efficacy of ILE therapy when used as an antidote, but given the case reports and case series, it can be considered in certain lipophilic drug toxicities where morbidity and mortality may be high and no known antidote or alternative is available.

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Blood Purification Techniques for Intoxications

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Introduction

Extracorporeal therapies involve the removal of blood from a patient's circulation with subsequent processing of the blood before it is returned to the patient. Processing of blood or "blood purification" can include removal of endogenous substances (e.g. BUN, creatinine or malignant antibodies) and exogenous substances (e.g. drugs and intoxicants). Extracorporeal therapies utilized in veterinary medicine include hemodialysis (HD) (both intermittent and continuous modalities), hemoperfusion (HP), and apheresis [1]. Peritoneal dialysis, which is not an extracorporeal therapy because blood is not removed from patient circulation, utilizes the peritoneum as a semi-permeable membrane for solute removal and is the least effective for treatment of intoxications of the therapies above.

This chapter will focus on the use of extracorporeal therapies for the removal of intoxicants and poisons in the emergency setting, with a focus on the decision-making process for pursuing use of these technologies and concurrent medical therapy. As specific information regarding the role of blood purification for many individual toxins is lacking, the clinician must use their understanding of the nature of the toxic substance to determine which, if any, blood purification technique is appropriate.

Intermittent Hemodialysis

Hemodialysis is an extracorporeal therapy, where blood is removed from the patient and is passed through a hemodialyzer or "artificial kidney." The hemodialyzer is composed of thousands of small semi-permeable tubes with microscopic pores that are too small for the passage of blood cells and proteins, but do allow the passage of many small molecular weight molecules. As blood passes through the lumens of these tubes, the tubes are

bathed in a specifically prescribed dialysate. Specific solutes, such as ethylene glycol (EG) in an intoxicated patient, move down their respective concentration gradient across the semi-permeable dialyzer membrane from the blood and into the dialysate. This *diffusion* is the primary method that allows for toxin removal via intermittent HD, where a toxin moves from the blood down its concentration gradient into the dialysate and subsequently down the drain. Likewise, for an intoxicant such as EG, where ethanol is a specific antidote to prevent breakdown of EG into its toxic components, the ethanol is placed into the dialysate, where it moves down a concentration gradient and then into patient circulation [2,3].

There are several characteristics of drugs and toxins that allow for the most efficient removal via diffusion. Small molecular weight substances (less than 500 Da) can readily move across the dialysis membrane, allowing for efficient removal; newer, more efficient dialyzers allow passage of larger molecules and can therefore provide efficient removal of larger molecular weight poisons (Table 129.1). Albumin is too large to fit through dialyzer pores, so significant protein binding of the toxin prevents efficient removal with HD.

Since HD removes substances directly from the vascular space, drugs and toxins with large volumes of distribution (i.e. into the interstitial and intracellular compartments) are less efficiently removed. This can be overcome by performing longer HD sessions and/or repeat treatments. This extra time allows for redistribution of toxins into the vascular space (as they move down their concentration gradient), where removal can occur via extracorporeal therapies (see Chapter 167, Figure 167.1). High water solubility increases ease of toxin removal, as toxins distributed into lipids do not readily pass into the intravascular space. HD has been utilized in the removal of poisons, such as ethylene glycol and barbiturates, as well as many others.

Table 129.1 General characteristics of toxins suited to extracorporeal therapy (ECT) with examples of toxins treated at the authors institution with ECT.

Therapy	Remarks
Hemodialysis	Drugs less than 500 Da, moderate to large volume of distribution, minimal protein binding Examples: <ul style="list-style-type: none"> Ethylene glycol Antibiotics <ul style="list-style-type: none"> Enrofloxacin* Barbiturates*
Hemoperfusion	Intoxicant size and protein binding do not affect efficiency (provided charcoal has the highest affinity for the compound), moderate to large volume of distribution
Combined hemodialysis/hemoperfusion	Intoxicants Examples: <ul style="list-style-type: none"> Non-steroidal anti-inflammatory drugs <ul style="list-style-type: none"> Acetaminophen Ibuprofen* Carprofen* Deracoxib Barbiturates <ul style="list-style-type: none"> Phenobarbital* Caffeine* Theobromine* Chemotherapeutics <ul style="list-style-type: none"> Vincristine
Apheresis (total plasma exchange)	Small volume of distribution, efficiency unaffected by protein binding and size Examples: <ul style="list-style-type: none"> Chemotherapeutics <ul style="list-style-type: none"> Vincristine <i>Amanita</i> intoxication

Note: Scientific evidence regarding definitive benefits of ECT for various intoxicants is currently lacking. The decision to pursue ECT for treatment of intoxications should be based on individual patient and intoxicant data and should be instituted immediately following ingestion. Note that there are many additional intoxications that may benefit from ECT.

*Anecdotal evidence (based on clinical outcome and serial drug levels) that a benefit was incurred by ECT. Note that for intoxicants treated with combined HD/HP, serial drug levels were not always collected, so it is difficult to discern the individual contribution for each therapy.

Prolonged Intermittent HD and Continuous Therapies

For drugs with a high volume of distribution or significant enterohepatic recirculation, therapies can be extended to provide continued prolonged treatment (hours to days), whereby constant removal from the intravascular space occurs as the toxin or poisoning redistributes there. This prolonged treatment can be done by prolonging therapy with an intermittent platform (up to 8 hours) or by using a continuous renal replacement platform, which can allow

treatment to be extended for days. By definition, continuous therapies are meant to allow for slow, continual solute removal, which may not be ideal for treatment of intoxications; however, treatment prescriptions can be altered to allow for more rapid removal [4]. The application for such a prolonged therapy does require a trained treatment team to be available for the entire treatment period. At the author's institution, when prolonged therapy is indicated, repeated prolonged intermittent treatments are performed, rather than continuous therapy.

Another treatment modality for toxin removal is removal of large volumes of plasma water by convection (alone or in combination with diffusive therapy). This technology is available on many of the machines designed for continuous renal replacement therapy. With this method, specifically designed filters allow for significant volumes of plasma water to be removed by hydrostatic pressures and this can aid in toxin removal. This may allow for removal of larger compounds (up to 50 kDa) than can be achieved with diffusive dialysis, but does not remove protein-bound drugs.

Hemoperfusion

Hemoperfusion is an extracorporeal therapy where large volumes of blood are exposed to an adsorbent (typically activated charcoal/carbon) that binds toxic substances. The removal of toxins by HP is dictated by the affinity of the activated charcoal for the toxin (see Table 129.1). As opposed to HD, molecular weight and protein binding of the toxin do not decrease removal efficiency with HP, provided that the affinity of the charcoal for the toxin is high enough. In contrast to HD, where there is a constant supply of fresh dialysate allowing for continuous toxin removal by diffusion, charcoal-binding sites can become saturated over time, preventing further toxin removal unless a new cartridge is used. Since online blood testing for most toxins is not available, previous experience and educated estimations are used to determine when therapy should be finished or a new cartridge be replaced.

Combination Hemodialysis/Hemoperfusion

An optimal treatment in many cases is to combine HD and HP (see Table 129.1). When performing these two modalities in combination, blood is pumped through the HP cartridge and then into the dialyzer. The advantages of this combination include more efficient toxin removal, as both diffusion and charcoal binding are utilized, as well as normalization of blood through the dialyzer before it is returned to the patient. For example, glucose, which can be bound by the charcoal, is returned to the extracorporeal blood through the dialysate before return to the patient.

One disadvantage of this combined therapy is the increased volume of blood in the circuit and outside the patient, when both a dialyzer and charcoal cartridge are used. This can limit the size of patient that can be safely treated with HP, although an experienced team can often make alterations to the prescription that allow for treatment of smaller patients. Figures 129.1 and 129.2 show dogs receiving combined HD and HP. In the author's institution, HP is always combined with HD.

Apheresis

Apheresis is an extracorporeal therapy in which blood is removed from the circulation, separated into components and one or more of the components is removed or processed. For treatment of intoxications, apheresis in the form of therapeutic plasma exchange (TPE) is most commonly utilized. During this therapy,

as the blood is separated, the plasma component (containing toxic substances) is removed, discarded and replaced with plasma, colloids, and other fluids. TPE can allow for efficient removal of toxins that have a small volume of distribution and are limited primarily to the intravascular space, because only the intravascular volume is treated (see Table 129.1) [5]. In addition, because all plasma components are removed, intoxicants with significant protein binding will also be removed.

Of the extracorporeal therapies available, apheresis is the newest technology being evaluated in veterinary patients, and the indications and outcomes of this therapy are still unknown for many intoxications. At the author's institution, apheresis has been used for treatment of advanced stages of *Amanita* mushroom intoxications with minimal success. As in human medicine, earlier intervention of patients with *Amanita* poisoning may allow for better outcomes [6–8].



Figure 129.1 A dog with life-threatening caffeine and theobromine intoxication that is receiving mechanical ventilation for drug-induced respiratory arrest, while combined hemodialysis and hemoperfusion is performed. The hemoperfusion activated charcoal canister can be seen in line with the hemodialysis circuit. This dog was discharged with mild neurological deficits 4 days after initial presentation.



Figure 129.2 A dog receiving combined hemodialysis and hemoperfusion for ibuprofen ingestion (2000 mg/kg). She was presented immediately after ingestion, was stable at the time of presentation and remained stable during hospitalization. She received medical management in conjunction with hemodialysis and hemoperfusion and never developed any adverse clinical manifestations of intoxication. She remains normal 2 years post treatment.

Indications for the Use of Extracorporeal Therapies in Treatment of Poisoning

Before extracorporeal therapies are employed, several factors should be considered. Considerations for treatment of intoxications with extracorporeal therapies include the associated morbidity and mortality of the intoxication, treatment outcome with traditional medical therapies, patient characteristics (co-morbidities, patient size, dose of intoxication, time of exposure), endogenous clearance of the intoxicant, and characteristics of the intoxicant (molecular weight, volume of distribution, protein binding, solubility, and half-life). It is important to ensure (as far as possible) that benefits from the treatment outweigh the potential risks. In the author's opinion, any intoxication with severe adverse consequences for the patient should be considered for treatment with an extracorporeal therapy, provided that the characteristics of the patient and the intoxicant support its potential use, especially if the treatment is carried out by an experienced team.

It is critical to obtain a thorough history of ingestion from the owner. Owners may be able to provide information concerning the type and amount of toxin ingested, as well as the time of ingestion. Knowing this information can improve the ability of the treating clinician to provide an accurate prognosis and determine if an extracorporeal therapy is indicated. If toxin ingestion was days before presentation, an extracorporeal therapy is likely not indicated, as the toxin will have been metabolized and/or excreted. It is also important to determine

specific characteristics of the toxin, such as molecular weight and pharmacokinetics, so that informed decisions can be made. If the patient has not already vomited, ingestion was recent (within 1–2 hours) and there are no contraindications, such as a comatose patient or ingestion of a caustic substance, vomiting should be induced (see Chapter 127). If a large amount of the ingested material is eliminated during vomiting, extracorporeal therapy may not be necessary; however, this can be very difficult to judge. If the consequences of intoxication are life threatening, then it still may be reasonable to consider pursuing an extracorporeal therapy.

For many intoxicants, information regarding drug metabolism in veterinary patients is limited, and in these cases, extrapolation from human and other animal studies is often performed. In addition, in cases of massive overdose, volume of distribution may increase beyond what has been reported with therapeutic dosing. For example, with a massive overdose of a highly protein-bound compound, protein-binding sites may become saturated, and unbound drug may therefore distribute into interstitial and possibly intercellular spaces (beyond what occurs with therapeutic dosing).

Rapid initiation of an extracorporeal therapy is critical for successful treatment of intoxications. The location of facilities that are capable of performing HD and HP or apheresis must therefore be considered, and referral and transfer should occur quickly. In addition, initiation of medical management (see below) must be instituted immediately, and not delayed while making final decisions regarding benefits of an extracorporeal therapy. If

other treatments (other than extracorporeal therapies) are available, these should be considered as a sole therapy or in conjunction with an extracorporeal therapy. Figure 129.1 shows a dog with caffeine intoxication that required mechanical ventilation as part of its supportive care while HD/HP were performed.

Finally, when making decisions regarding extracorporeal therapy for intoxications, patient size should be a consideration. The volume of the extracorporeal circuit can be variable, depending on the machines and cartridges used, but can range from 70ml to several hundred milliliters. While variations can be made to the extracorporeal circuit, treatment of very small patients can be more complicated. Nonetheless, use of blood priming (filling the extracorporeal circuit with cross-matched compatible blood) can allow for treatment of almost any patient size.

Hemodialysis and HP procedures are not inexpensive. In many cases, however, rapid removal of the toxin via HD/HP can lead to much shorter hospital stays, compared with traditional medical management. Clients need to be properly informed of potential risks. In addition, it is important to note that controlled veterinary studies evaluating the efficacy of HD/HP treatment for treatment of many poisonings are lacking.

Medical Management for Intoxications

Decontamination may be indicated prior to initiation of HD/HP (see Chapter 127). As discussed above, induced emesis may be performed in alert patients that have ingested non-caustic substances or patients that have recently ingested toxins. Gastric lavage may be performed in selected cases. Cathartics such as sorbitol may be indicated. Depending on the timing of toxin ingestion, activated charcoal may be indicated, and can be given either orally or rectally in obtunded patients. Repeat dosing may be necessary for drugs with significant enterohepatic circulation, whereby a drug concentrated in bile is re-excreted into the intestines where further absorption can occur [9]. Forced diuresis via administration of intravenous fluids may increase renal tubular flow and decrease reabsorption of toxin in the distal tubule.

In certain cases where the toxin was recently ingested and the owner knows the ingested toxin, antidotes may be considered. For example, the administration of ethanol or fomepizole (4-methylpyrazole) is indicated in cases

of EG ingestion to prevent formation of toxic metabolites. For cases of suspected EG ingestion, early administration of alcohol can be life saving and should be started immediately.

It is critical for the treating clinician to have a solid knowledge base regarding optimal medical management for each intoxication encountered. While medical management is mandatory, it is ideal to minimize trauma to jugular veins when possible, so that appropriate catheters can be placed rapidly for initiation of extracorporeal therapy.

Manipulation of urinary pH, typically via alkalinization, can be used to force certain toxins into an ionized form. Ionized substances do not readily cross cell membranes, so ionization may prevent reabsorption across the tubular membrane with subsequent excretion in urine. This process is known as “ion trapping.”

Since many toxins have volumes of distributions beyond the vascular space, these compartments are not as readily cleared of toxin and can redistribute following a HD/HP treatment, leading to recurrence of clinical signs or ongoing adverse effects. This phenomenon may necessitate repeat treatments of HD and HP. Additionally, medical management may need to be prolonged and combined with these extracorporeal therapies to optimize outcomes.

Conclusion

In conclusion, extracorporeal therapies can be life-saving treatments for poisonings. Use of these therapies can improve patient outcome and may decrease hospitalization time. It is essential to inform owners of the available treatment options and prognosis associated with certain toxins. Cost and risks of extracorporeal therapies must also be discussed. Clinicians should consider both medical management strategies and extracorporeal therapies, and it is critical to recognize that these two therapies may need to be combined. At our institution, HD and/or combined HD/HP have been used to treat poisonings of EG, non-steroidal anti-inflammatory drugs, chemotherapeutics, caffeine, barbiturates, and antibiotics. At this time, many of the extracorporeal therapies used for the treatment of poisonings are based on human studies and small veterinary case series, but current research into the utility of these therapies for various intoxications is ongoing.

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Rodenticide Toxicity

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Introduction

Rodenticide ingestion is a common concern in dogs, and clinical signs vary widely depending on the type and amount ingested. Cats rarely present with known or suspected rodenticide ingestion, but many of the same principles for case identification and management apply in this species [1]. As with all toxicities, a known dose and time frame of toxin ingestion can be extremely helpful in determining which signs to monitor for, and over what time period monitoring is necessary. Data available from the ASPCA Animal Poison Control Center identify a downward trend in anticoagulant rodenticides and an upward trend in neurotoxic rodenticide exposures from 2008 to 2014 (Figure 130.1). This trend correlates with EPA legislature changes that restricted use of second-generation anticoagulant rodenticides availability to consumers, increasing exposure to other types of compounds.

As practitioners, it is important to be aware of all types of rodenticides as many different compounds are packaged nearly identically. Any pet that produces teal or blue-green pigmented feces or vomitus should be examined and monitored for various potential rodenticide toxicities; paint ball toxicity would be another important consideration.

Decontamination

If a known toxic dose or unknown dose of any rodenticide is ingested within 4 hours of presentation and the animal is mentally appropriate, decontamination is the most appropriate first action (see Chapter 127). Inducing emesis with intravenous apomorphine is preferred to other methods (0.03–0.04 mg/kg IV, which may be repeated once). Apomorphine can also be applied conjunctivally and rinsed out following successful emesis.

Xylazine (0.4–1.1 mg/kg IM or SC) and dexmedetomidine (7 mcg/kg IM, 3.5 mcg/kg IV) are first-line emetics in cats although the likelihood of rodenticide ingestion is low. If veterinary treatment is delayed by transport time, or owners are unable to bring the dog to the clinic, hydrogen peroxide 3% solution may be used (1 mL/lb or 2.2 mL/kg), but this induces emesis by means of physical gastric irritation. Hydrogen peroxide is unlikely to induce emesis in cats. If mental status is significantly affected, gastric lavage is recommended over induction of emesis.

Caution should be exercised if zinc phosphide ingestion is known as the vomitus produced is likely to contain noxious gases that can affect staff and owners. Emesis for these patients should be performed in a well-ventilated room or an outdoor location in accordance with AVMA guidelines [2]. If an unknown rodenticide is ingested, activated charcoal is recommended at 1 g/kg PO every 6–8 hours for the first 24 hours as some rodenticides are enterohepatically recirculated.

Anticoagulant Rodenticides

Anticoagulant rodenticides all inhibit physiological recycling of vitamin K by inhibiting vitamin K epoxide reductase in the liver [3]. First-generation (chlorphacinone, diphacinone, dicoumarol, warfarin) and second-generation anticoagulants (brodifacoum, bromadiolone, difenacoum, difethialone) both inhibit vitamin K synthesis, but the second-generation products are more acutely toxic and have longer half-lives [4]. Many concentrations and preparations (pellets, blocks, powders, etc.) are available for consumers to purchase, so it can be very helpful to have access to the rodenticide package during patient evaluation.

Clinical signs may range from no visible or clinically appreciable abnormalities (within the first 72 hours) to animals presenting with hemorrhagic shock from

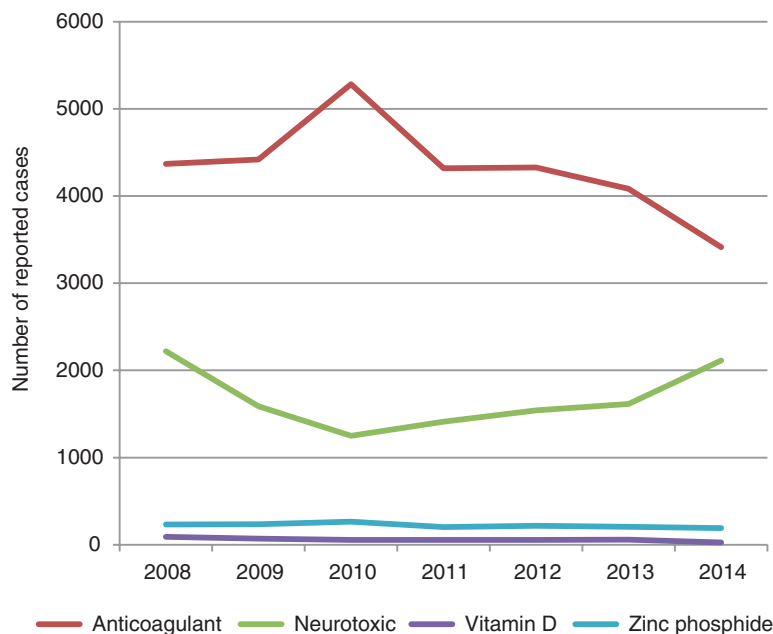


Figure 130.1 ASPCA reported rodenticide exposures by year. Rodenticide exposures are displayed by category of rodenticide and year. Note the recent downward trend in anticoagulant rodenticides and the upward trend in neurotoxic rodenticides.

internal or external blood loss. Dyspnea, lethargy, coughing, and hemoptysis are the most common presenting signs, but signs may vary depending on the location of bleeding for each pet [3]. Anticoagulant rodenticide ingestion classically results in conspicuous large-volume bleeding events (e.g. hemothorax, hemarthrosis) rather than surface mucosal bleeds that are more consistent with a primary hemostatic disorder (e.g. severe thrombocytopenia).

If no clinical signs are apparent and ingestion is uncertain, gastrointestinal decontamination should be considered, including the administration of a single dose of activated charcoal (as these compounds do not undergo enterohepatic recirculation). Prothrombin time should be measured in 48 hours to confirm diagnosis prior to administration of vitamin K1. The likelihood of coagulopathy development, as assessed by prolongation of prothrombin time, is low after timely gastrointestinal decontamination in dogs that have recently ingested anticoagulant rodenticide [5]. Administration of vitamin K1 will mask clinical signs of rodenticide toxicity until all administered vitamin K is inactivated.

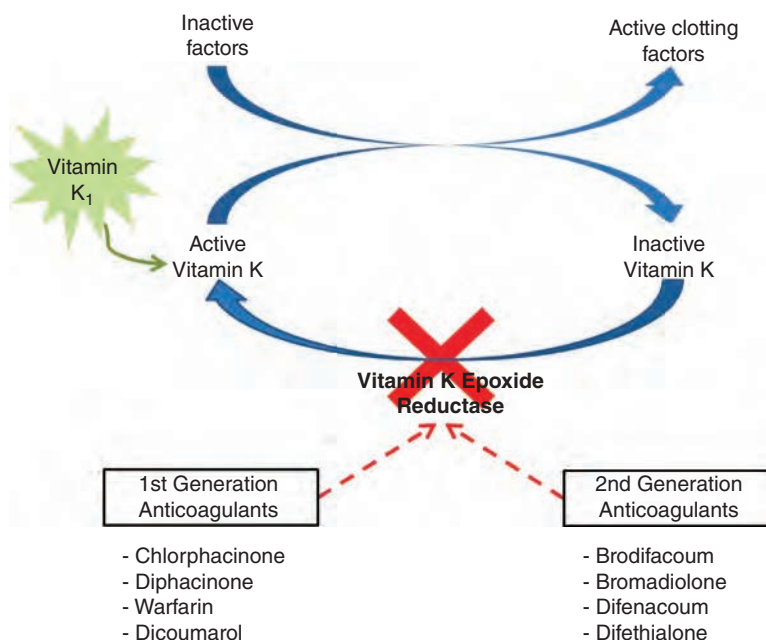
Coagulopathies are not routinely apparent for 48–72 hours after ingestion. Vitamin K is required for the post-translational carboxylation of clotting factors II, VII, IX, and X required for functional activation. Vitamin K is also necessary for function of the antithrombotic factors C, S, and Z (Figure 130.2). Clinical signs of hemorrhage will not become apparent until bodily stores of these factors are depleted. In order, protein C levels, one-stage prothrombin time (OSPT, factor VII), prothrombin time

(PT, factor VII), activated partial thromboplastin time (aPTT, factor IX), and activated clotting time (ACT, factor IX) are all affected after a toxic dose of anticoagulant rodenticide and each test can be used for diagnosis in combination with other baseline testing [6]. Protein C estimation has the potential to be the earliest clinical indicator of clinically relevant anticoagulant rodenticide ingestion [7] but is uncommonly available to the emergency practitioner. In clinical cases, these coagulation tests are typically markedly prolonged (e.g. out of range high), which may differ from other causes of coagulopathy (e.g. disseminated intravascular coagulation).

Anticoagulant rodenticide screening panels are available to help characterize whether hemorrhagic tendency is due to rodenticide ingestion or an alternative diagnosis. Patients with severe coagulopathies that tested negative on anticoagulant rodenticide screening had a worse outcome compared to dogs that were coagulopathic associated with anticoagulant rodenticide ingestion [8]. The major limitation of these panels is the test turnaround time, since few centers offer this test routinely, usually necessitating sending out samples to remote laboratories. Point-of-care anticoagulant rodenticide tests for dogs have been of limited clinical utility to date [9].

Management of anticoagulant rodenticide ingestion will vary depending on the presence or absence of severe coagulopathy. In the dog with known or suspected ingestion but no evidence of coagulopathy, management is focused on decontamination initially. Vitamin K1 can be started prophylactically at this point, being continued for 30 days, or alternatively held off until laboratory evidence

Figure 130.2 Vitamin K rodenticide mechanism of action. Inactive clotting factors include antithrombotic factors C, S, and Z and clotting factors II, VII, IX, and X. Administration of vitamin K1 restores normal function by providing fresh influx of active vitamin K.



of coagulopathy is rechecked at 48 hours. If the dog has a normal hemostatic profile at this point, no further treatment is necessary, while dogs with evidence of coagulopathy can then be started on a 30-day course of vitamin K1. Coagulation tests should be repeated 48 hours following cessation of vitamin K1 therapy to ensure no residual coagulopathy remains.

In the case of the clinically affected animal with severe coagulopathy and bleeding, treatment is focused on vitamin K1 administration and clotting factor replacement via either fresh frozen plasma or frozen plasma transfusion (see Chapter 176). If the dog has evidence of impaired oxygen delivery due to anemia, red cell supplementation may be necessary, as packed red blood cell transfusion. Fresh whole blood could be administered alternatively as an efficient means of administering both red cells and clotting factors. Coagulopathies resolve rapidly after the administration of vitamin K1 and plasma in these cases, with the expectation that the coagulopathy should not recur. If an animal develops recurrent coagulopathy or fails to correct its coagulopathy, alternative differential diagnoses for coagulopathy should be considered. Despite rapid laboratory improvement in coagulopathy, some clinical consequences of bleeding that have already occurred may still take days to resolve (e.g. resorption of hemorrhagic pleural effusion).

If the animal can tolerate oral administration of vitamin K1, this route is preferred, and as a fat-soluble vitamin, it is best absorbed with food. If oral administration is not tolerated, subcutaneous administration is recommended. Intramuscular administration is likely to cause increased bleeding and pain relative to subcutaneous

administration. Intravenous administration should be avoided as it may cause serious anaphylactic reactions.

Prognosis for anticoagulant rodenticide ingestion ranges from excellent (up to 98.7% in one study [8]) to guarded, depending on the severity of clinical signs at presentation and the promptness of instituting appropriate therapy.

Neurotoxic Rodenticides

With the decline in production of second-generation rodenticides, neurotoxic rodenticides are becoming increasingly common (see Figure 130.1). Bromethalin, the active ingredient in these rodenticides, is a neurotoxin that uncouples oxidative phosphorylation, decreasing adenosine triphosphate (ATP) production [10]. Most bromethalin is sold as one ounce 0.01% blocks, with each block containing 2.84mg bromethalin. Clinical signs depend heavily on ingested dose and may be seen at 10% of the LD₅₀ (which constitutes a lethal dose in 50% of exposed animals) [11]. The LD₅₀ for bromethalin is reported as low as 0.3mg/kg in cats and 2.4mg/kg in dogs [11].

The onset of clinical signs is associated with severity of toxicosis: low doses may not show signs for up to 5 days, but larger doses may present as quickly as 2 hours after ingestion. Clinical signs initially manifest as hind-limb ataxia and weakness, and may progress to include lethargy, depressed mentation, seizures, coma, respiratory paralysis, and death. There are no distinguishing findings on routine laboratory tests, and there is no specific screening test available.

Unfortunately, there is also no antidote available for treatment of bromethalin intoxication, so very early decontamination is crucial in these cases. Emesis and gastric lavage are unlikely to be useful after 1.5 hours of ingestion as the toxin is very rapidly absorbed [11]. Repeated doses of activated charcoal are recommended at 1 g/kg every 4–6 hours for 48–72 hours as bromethalin does undergo enterohepatic recirculation [11]. Intravenous lipid emulsion therapy is also a possible consideration, as it reduced blood levels significantly in one case report [13]. In affected animals, supportive care is recommended, including intravenous fluids, nutritional support, hypertonic saline or mannitol administration, antiepileptic medications, and mechanical ventilation if necessary. Prognosis is guarded to poor if clinical signs develop.

Cholecalciferol Rodenticides

Ingestion of cholecalciferol (vitamin D3) rodenticides induces potentially fatal hypercalcemia and hyperphosphatemia. Cholecalciferol is rapidly absorbed and converted to calcifediol in the liver. Calcifediol is then converted to calcitriol (active vitamin D, 1-25-dihydroxycholecalciferol) in the proximal convoluted tubule of the kidney. Excess levels of active vitamin D cause increased absorption of calcium and phosphorus from the GI tract, bone, and kidneys. Metastatic mineralization of tissues can occur at calcium-phosphorus products over 60 (mg/dL), and can affect many tissues throughout the body irreversibly. Most cholecalciferol rodenticides are sold as 0.075% (0.75 mg/kg of product) baits. Clinical signs may be seen with doses as low as 0.5 mg/kg, and fatalities have been reported with doses of 2 mg/kg in dogs [12].

Clinical signs are related to the effects of hypercalcemia and hyperphosphatemia and can affect the GI, renal, and CNS systems most noticeably. Patients often present for inappetence, vomiting, diarrhea, polyuria, polydipsia, lethargy, depression, muscle tremors, and seizures, depending on which systems are most affected. Acute renal failure and irreversible GI tract mineralization are primary contributors to the morbidity and mortality of cholecalciferol rodenticides.

Initial laboratory testing should include a biochemical profile, complete blood count, and urinalysis. Hyperphosphatemia generally precedes hypercalcemia, and ionized calcium is the most clinically relevant form of calcium. Confirmatory testing for cholecalciferol exposure consists of increased serum calcium, increased serum phosphorus, and decreased serum parathyroid hormone levels. Important differentials include other sources of cholecalciferol (jasmine, vitamin D supplements or creams) and other causes of hypercalcemia (see Chapter 110). As calcifediol has a functional half-life of

29 days [12], both short- and long-term treatment plans must be formulated for affected patients.

Decontamination by emesis or gastric lavage is only warranted if rodenticide has been ingested in the prior 2 hours, as cholecalciferol is rapidly absorbed (see Chapter 127). Activated charcoal is recommended every 4–6 hours for 24 hours as cholecalciferol undergoes significant enterohepatic recirculation. Cholestyramine resin administration (0.3–1 g/kg PO q8h for 4 days, between charcoal administrations) is also recommended to help decrease GI absorption. Chemistry profiles should be monitored daily until calcium and phosphorus levels decrease and stabilize.

Additional supportive care for hypercalcemia includes IV fluid support with 0.9% saline diuresis (4–6 mL/kg/h, or twice maintenance), furosemide (0.66 mg/kg loading dose, then 0.66 mg/kg/h CRI), and steroid administration (2–3 mg/kg/day prednisone or 1 mg/kg/day dexamethasone SP) until calcium levels decrease appropriately. Close monitoring for seizures or tremors is warranted. In very severe cases, treatment with bisphosphonates may be warranted (pamidronate 1.05–2 mg/kg IV diluted in saline and given over 2 hours) [14], although this will result in less immediate reduction in hypercalcemia compared to the aforementioned options. Control of hyperphosphatemia involves use of phosphate binders once the patient is eating or able to be medicated enterally.

Short-term goals are aimed at controlling calcium levels, and this may take days to weeks in the hospital setting. Once calcium levels are controlled, patients may be released for at-home monitoring over the coming weeks with twice-weekly biochemical profiles recommended. Return of clinical signs warrants immediate re-evaluation.

Prognosis is good to guarded depending on severity and duration of clinical signs, degree of renal insufficiency and tissue mineralization, and client commitment to long-term care.

Phosphide Rodenticides

Zinc and aluminum phosphide are relatively uncommon rodenticides that elicit toxicity by several potential mechanisms [15]. These salts produce phosphine, the active agent, that may inhibit cytochrome C oxidase, disrupt the mitochondrial membrane, and generate free radicals that peroxidize lipids. Phosphine has rapid, directly toxic effects on the heart, adrenal glands, and kidneys, and is a corrosive agent. Death may result from a combination of cardiogenic and non-cardiogenic pulmonary edema, neurological consequences, acid–base disturbances, and renal failure.

Zinc phosphide rodenticides are available in various strengths and preparations (pellets, paste, tablets,

powders, etc.). The lowest reported lethal dose in dogs and cats is 40 mg/kg, but the LD₅₀ for most other animals is listed at 20 mg/kg [16]. The phosphide component reacts with water and acid to release phosphine gas, which is then absorbed across the gastric mucosa. Phosphine gas may be odorless or may have a garlic or rotten fish odor. Exposure to phosphine gas may result in fatigue, headaches, vomiting, dizziness, and shortness of breath in people if exposure doses are high enough. Emesis should therefore be induced in a well-ventilated area or outdoors, and owners should be cautioned about vomitus produced or induced at home. Consult AVMA guidelines regarding zinc phosphide for additional information [2].

According to the AVMA zinc phosphide guidelines, common presenting clinical signs include vomiting, hematemesis, depression, abdominal pain, diarrhea, convulsions, paralysis, coma, and death within minutes to hours of exposure. Liver and kidney injury may develop within 48–72 hours, if the patient survives initial exposure. As there is no antidote, supportive care is recommended based on initial presenting signs. Activated charcoal is not indicated as the active compound is a gas, mental status is likely to deteriorate rapidly, and addition of liquid components to the GI tract increases rate of production of the toxic gas.

Prognosis is guarded to grave if clinical signs are present from phosphide salt ingestion.

Aldicarb Rodenticide

“Tres Pasitos” is an uncommon rodenticide whose name quite accurately implies that death happens so quickly that only “three little steps” can happen after ingestion. This rodenticide may be imported illegally, and its active ingredient, aldicarb, is a carbamate that acts as a reversible inhibitor of acetylcholinesterase, preventing breakdown of acetylcholine in the synapse [17,18]. It is often sold in poorly labeled plastic baggies and looks like a brown grain, occasionally mistaken for a food product. This rodenticide is unfortunately still used in South America and South Africa in intentional pet poisonings.

Common clinical signs include those of an acute cholinergic crisis: dyspnea, vomiting, diarrhea, seizure, and/or acute death. If presented in time, treatment with atropine may slightly improve clinical signs by blocking muscarinic receptors, but ventilation and intense supportive care are also necessary to prevent respiratory arrest as there is no antidote to prevent stimulation of the nicotinic receptors. Prognosis is grave in symptomatic patients.

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131

Ethylene Glycol Intoxication

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Introduction

Ethylene glycol (EG) is a sweet-tasting, odorless substance extremely toxic to humans and animals. Antifreeze is the most common source of exposure for small animals and contains the highest concentration of EG at greater than 95% in some products. EG can also be found in a variety of other household items, including paint, adhesives, wood stain, and windshield deicers. As little as 6.6 mL/kg of EG is fatal for dogs and only 1.5 mL/kg in cats [1].

Ethylene glycol is absorbed from the GI tract as rapidly as 30 minutes after ingestion and metabolized primarily in the liver, with the remainder being eliminated unchanged in the urine. Within the liver, EG is oxidized by alcohol dehydrogenase (ADH) to glycoaldehyde, then to glycolic acid and then to glyoxylic acid (Figure 131.1). EG itself is a CNS depressant and can also cause direct

gastrointestinal irritation. However, EG's metabolites are primarily responsible for the acute kidney injury (AKI) and metabolic acidosis that are hallmarks of this toxicosis. Glycoaldehyde is thought to be the principal metabolite responsible for the CNS signs. Glycolic acid accumulation results in severe metabolic acidosis and elevations in the anion gap. Circulating calcium binds to oxalic acid, resulting in calcium oxalate crystalluria, as well as calcium oxalate crystal deposits in multiple organs; hypocalcemia may develop due to utilization during crystal formation. AKI, the most severe consequence of EG intoxication, is caused by the direct toxic effects of glycolic acid on the renal tubular epithelium as well as calcium oxalate crystal deposition within the tubular lumen [2]. Mortality rates are reported as high as 96–100% in cats, and 59–70% in dogs [3,4].

Clinical Signs

The clinical signs of EG toxicosis can vary depending on the amount of toxin ingested and the time after toxin exposure. EG toxicosis is classically described as occurring in three phases.

The first phase occurs within several hours of ingestion; clinical signs may include vomiting, lethargy, paresis, ataxia, and muscle fasciculations, and may progress to seizures and coma. These signs are attributed to the direct effects of EG on the GI and CNS systems. Polyuria and polydipsia may also develop, driven by increases in serum osmolality and osmotic diuresis. In dogs, neurological signs can resolve after 12 hours, falsely suggesting recovery. Cats do not typically show recovery from the CNS phase of the toxicosis. The second phase occurs approximately 12–24 hours after ingestion. During this time, CNS signs abate and cardiopulmonary signs can develop, including tachyarrhythmias and tachypnea due to severe metabolic acidosis, and hypocalcemia if

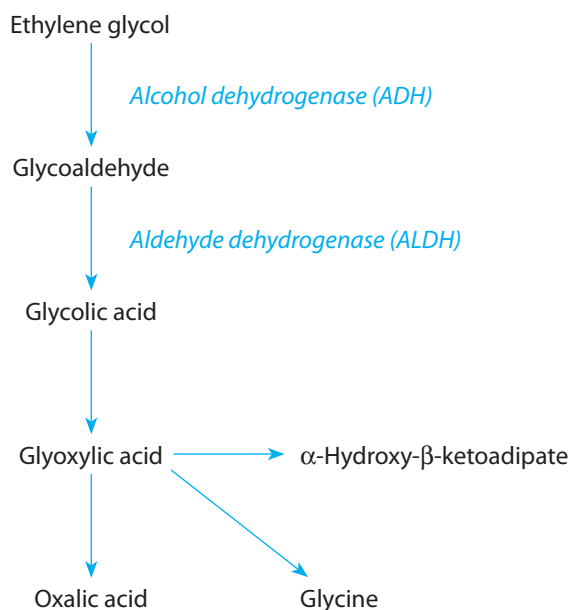


Figure 131.1 Metabolism of ethylene glycol.

present. Oliguric or anuric AKI then develops during the third phase of toxicosis, approximately 24–72 hours following ingestion in dogs and 12–24 hours in cats. Clinical signs of AKI at this stage may include lethargy, anorexia, vomiting, oral ulceration, ptyalism, coma, and seizures.

Diagnostic Testing

Since clinical signs of EG can vary depending on the amount of metabolite accumulation, bloodwork abnormalities and other diagnostic test results can also vary depending on the stage of intoxication. One of the earliest biochemical changes identified is a rise in the osmolal gap, which is the difference between the patient's measured and calculated osmolality. Increases in the osmolal gap indicate the presence of unmeasured osmotically active particles, such as mannitol, acetone, propylene glycol, and ethylene glycol [5]. A rise in serum osmolality can occur as early as 1 hour after EG ingestion, facilitating early recognition and treatment if recognized. The osmolal gap peaks at 6 hours after ingestion, but remains elevated for up to 18 hours after ingestion. Measurement of osmolality can be performed using freezing point osmometry or vapor pressure osmometry. These tests are rarely available in general practice and may delay diagnosis and treatment when sent out to laboratories. Calculated osmolality can be obtained using the equation $2(\text{Na} + \text{K}) + [\text{glucose}/18]$ $[\text{BUN}/2.8]$, and the normal osmolal gap using this formula in dogs is $< 10 \text{ mOsm/L}$ [6,7].

Blood gas analysis should be performed in all patients with suspected EG toxicity. Glycolic acid accumulation results in a profound normochloremic metabolic acidosis characterized by a decreased plasma bicarbonate concentration, and an increased anion gap due to the presence of unmeasured anions. The anion gap rises within 3 hours after ingestion and peaks at 6 hours, but remains elevated for approximately 48 hours [1]. Electrolyte abnormalities include hyperphosphatemia due to decreased glomerular filtration, hyperkalemia due to oliguria and anuria, and hypocalcemia. Serum biochemistry may reveal hypocalcemia in approximately 50% of patients due to binding of calcium to oxalic acid, and hyperglycemia is seen in 50% of cases due to inhibition of glucose metabolism by aldehyde metabolites of ethylene glycol [1]. An erroneous hyperlactatemia may be reported by enzymatic point-of-care (POC) machines and can be attributed to the measurement of glycolate, a chemically similar metabolite of EG [8]. As lactic acidosis also results in a high anion gap metabolic acidosis, this could result in a missed diagnosis of EG intoxication.

Urinalysis can also aid in the diagnosis of EG intoxication during its early stages. Isosthenuria is observed

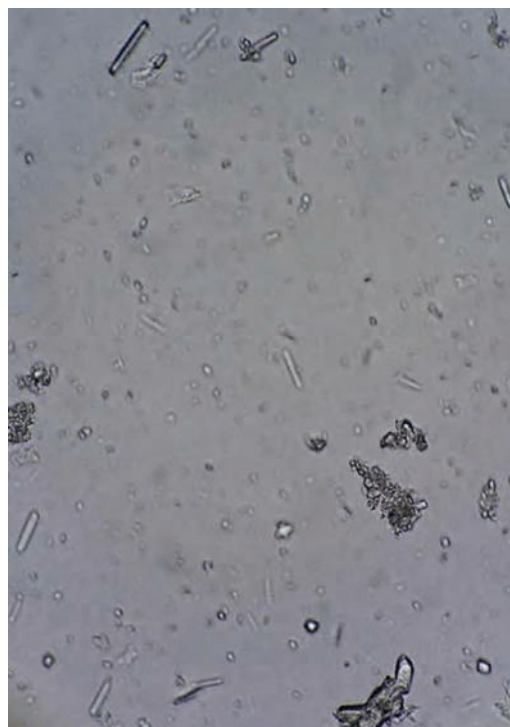


Figure 131.2 Calcium monohydrate crystals in a dog with antifreeze toxicity.

as soon as 3 hours post ingestion secondary to osmotic diuresis and polydipsia. Patients remain hyposthenuric as renal dysfunction develops. Calcium oxalate crystalluria is commonly seen, developing within 3–6 hours after ingestion. Calcium oxalate monohydrate crystals are the most common type observed and have a distinct appearance, looking like long, clear, six-sided or “picket fence” shaped structures, versus the square envelope shape of the dihydrate crystals (Figure 131.2). Other urinalysis findings may include decreased pH, hematuria, proteinuria, glucosuria, casts, white blood cells, and red blood cells.

Examination of the urine, mouth or paws with a Wood's lamp to look for fluorescence can be performed as many antifreeze solutions are made with sodium fluorescein dye in order to detect radiator leaks. Since this is not found in all solutions, and is only excreted in the urine for 6 hours following ingestion of antifreeze [9], a negative test does not exclude the diagnosis of EG intoxication.

Abdominal radiographs may reveal signs of renomegaly and renal mineralization late in the toxicity. Abdominal ultrasound can show increased renal cortical echogenicity, which combined with areas of lesser echo intensity in the medulla is referred to as a “halo sign” [10].

Complete blood count findings are non-specific in EG intoxication, and typically relate to dehydration (i.e.

elevated hematocrit and elevated plasma protein); a stress leukogram can be identified.

Specific tests for detection of EG are commercially available and vary in respect to their specificity and sensitivity, as well as their ability to make a diagnosis in dogs versus cats. EG levels peak within 1–6 hours following ingestion, and are typically not detectable in serum or urine 48–72 hours after ingestion, so testing for EG is only successful early on in the toxicosis. The gold standard for testing for EG is gas chromatography. This is performed in human medicine but is not a POC test so is not as readily available.

There are several commercially available POC test kits for EG detection that have been evaluated in veterinary medicine. A semi-quantitative POC test (Kacey EG Test Strips, Kacey Inc, Asheville, NC) is available for use on canine or feline plasma, with a lower limit of detection at 20 mg/dL, which is the lethal dose for cats. The Kacey EG Test Strips were compared to a second qualitative POC test in dogs, the VetSpec Qualitative Reagent Test Kit (Catachem Inc, Oxford, CT) [11]. In this study, the semi-quantitative Kacey EG Test Strips had 100% sensitivity and 100% specificity and good agreement between those reading the test. The VetSpec Qualitative Reagent Test Kit was both less sensitive (65–95%) and less specific (40–70%), with less agreement between those reading the test, suggesting for dogs that the Kacey EG Test Strips were more accurate as well as being easy to use. Additionally, it was found that the Kacey EG Test Strips showed good agreement with measurements via gas chromatography, the gold standard for EG measurement.

However, when evaluated in cats, the Kacey EG Test Strips had a large number of false negatives and false positives at varying EG concentrations, indicating that the results of this test should be interpreted cautiously and it should not be used as a stand-alone test in cats [12]. Additionally, this test can cross-react with ethanol, glycerol, and propylene glycol. Propylene glycol can be found as a carrier in several medications, including diazepam, and as an ingredient in activated charcoal. A quantitative test, designed as an add-on test on the Hitachi-P chemistry analyzer (Roche Diagnostics, Indianapolis, IN), has been evaluated in both dogs and cats, and was found to be both highly accurate and precise, correlating well with measurements via gas chromatography (Quantitative Ethylene Glycol Assay, Catachem Inc, Oxford, CT) [13]. Additionally, unlike the POC tests, it does not cross-react with propylene glycol.

Treatment

Decontamination procedures, including induction of emesis and/or gastric lavage, as well as administration

of activated charcoal are typically of little benefit in patients with EG intoxication due to its rapid absorption (see Chapter 127). For that reason, the mainstay of treatment of EG intoxication is preventing its metabolism in the liver and increasing its excretion. Preventing metabolism of EG is accomplished by competitively inhibiting the function of alcohol dehydrogenase (ADH) with ethanol or fomepizole (4-methyl-1H-pyrazole, or 4-MP). These two antidotes have a higher affinity for the enzyme than EG, which allows excretion of the toxin unchanged into the urine. If EG has already been metabolized, administration of ethanol or fomepizole may be of minimal to no benefit. In fact, these antidotes increase the half-life of EG and thus if renal damage has already occurred then EG may not be effectively eliminated. Therefore, antidotal therapy should be administered as quickly as possible after ingestion. In human toxicology, fomepizole is the preferred antidote as it effectively inactivates ADH without the adverse effects of ethanol, but evidence supporting benefits in mortality or morbidity rates between the two antidotes is lacking [14].

The recommended 4-MP dose in dogs is 20 mg/kg 5% IV initially, followed by 15 mg/kg IV at 12 and 24 hours and 5 mg/kg IV at 36 hours. In cats, a higher dose is required at 125 mg/kg IV initially, then 31.25 mg/kg IV at 12, 24, and 36 hours. This dose was safe and effective in cats with EG intoxication, being more effective than treatment with ethanol, and preventing AKI when initiated within 3 hours of ingestion [15,16]. Ethanol is more readily available and less costly than fomepizole, but it compounds the CNS depressant effects of EG, increases serum osmolality, and induces diuresis.

Because of ethanol's short half-life, ideally it should be administered as a CRI with a 1.3 mL/kg IV bolus of 30% ethanol followed by a CRI of 0.42 mL/kg/h for 48 hours [17]. Intermittent bolus dosage recommendations in dogs include 5.5 mL/kg of 20% ethanol IV every 4 hours for five treatments and then every 6 hours for four additional treatments, and 5 mL/kg of 20% ethanol IV every 6 hours for five treatments and then every 8 hours for four additional treatments in cats [17]. Ethanol can also be given orally when IV therapy cannot be provided, although this is less ideal due to its emetogenic properties and neurological status of the animal; one suggested dose is 2–3 mL/lb of an 80 proof (40% ethanol) alcoholic beverage [1].

Concurrent fluid therapy is recommended to enhance renal excretion of EG and its metabolites, correct dehydration, and increase tissue perfusion. Additional therapy includes treatment of seizure activity and arrhythmias, and correction of electrolyte imbalances.

Hemodialysis

The use of hemodialysis for treatment of EG toxicity is two-fold: *early* during the toxicity (first 12–24 hours), in order to remove EG and its metabolites from the system and prevent AKI, and/or *late* (after 24–48 hours) once AKI has occurred (see Chapter 129). Because of its low molecular weight and lack of protein-binding capacity, approximately 90–100% of EG and its metabolites can be removed from circulation with a single treatment of intermittent hemodialysis [18,19].

Ethylene glycol and methanol poisoning in people are amongst the most common toxin indication for extracorporeal treatments (ECTR) [20]. Despite this, a low percentage of reported EG and methanol intoxications in people are treated with ECTR. The current recommendations for ECTR use versus ADH antagonism in less severely intoxicated people are limited by regional differences in price and availability of fomepizole and possible complications associated with either technique [21].

In veterinary medicine, no guidelines are available for the use of ECTR in animal intoxications. Similar limitations such as availability of fomepizole, complications associated with ADH antagonism and the small number of veterinary dialysis centers are likely to affect the

choice of treatment for small animals. In the authors' experience, if EG toxicity is recognized early (within 24 hours), referral to a dialysis center may provide partial to complete removal of the toxin from circulation, correct any acid–base and electrolyte disturbances, prevent AKI, and decrease hospitalization time. Administration of fomepizole or ethanol, whichever is available, is recommended before transportation and while preparing the patient for hemodialysis in order to inhibit metabolism of EG.

Once metabolism of EG has occurred and AKI has developed, treatment with supportive care and ADH antagonism is likely to be ineffective. Therefore, hemodialysis is indicated for the removal of any remaining EG and metabolites, as well as management of AKI. The prognosis for these cases varies depending on the timing of diagnosis and initiation of dialysis. In one study, 3/9 cats with AKI secondary to EG toxicosis and managed with intermittent hemodialysis alone survived to discharge; an average number of 12 treatments were required [22]. Another study showed a more negative outcome with only 8% survival, but fewer dialysis treatments were provided in these animals [23]. In dogs managed with hemodialysis for AKI, EG toxicosis was associated with a worse outcome when compared to other identified etiologies [24].

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Acetaminophen Intoxication

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Introduction

Acetaminophen is an analgesic and antipyretic that has been used in human medicine since 1893 [1]. It is an over-the-counter drug and can be found in many medications. Dogs and cats are exposed to acetaminophen through accidental ingestion or following administration by well-intentioned owners.

Pharmacokinetics and Toxicokinetics

Acetaminophen (APAP) appears to exert its analgesic effects via central cyclo-oxygenase (COX) inhibition. APAP crosses the blood–brain barrier and inhibits the central COX enzyme pathway, with only weak peripheral COX inhibition [2,3]. Other theories of APAP's mechanism of action include blockade of substance P's nociceptive actions via N-methyl-D-aspartate inhibition and activation of serotonergic nociception pathways centrally [2]. COX enzymes are important for prostaglandin production [4]. Prostaglandins are important in the regulation of many bodily functions, including gastric mucosal integrity and kidney function [4]. Non-steroidal anti-inflammatory drugs (NSAIDs) are known to inhibit peripheral COX enzymes and are associated with adverse effects such as gastric irritation, including ulceration, and renal insufficiency, among others [4]. Since APAP primarily inhibits central COX enzymes, it lacks the adverse local gastric and renal effects of NSAIDs.

Acetaminophen is metabolized by the liver [2,3] (Figure 132.1). Glucuronidation is the main metabolic pathway in dogs, followed by sulfuric acid conjugation [2,3]. In contrast, cats primarily use the sulfation pathway [5,6]. If the glucuronidation and sulfation pathways are saturated, residual APAP is metabolized by CYP2E1 and CYP1A2 (cytochrome p450) oxidation to the toxic compound N-acetyl-p-benzoquinone

imine (NAPQI), which is converted into non-toxic metabolites by glutathione [2,3]. These metabolites are further converted into cysteine and mercapturic acid conjugates that are excreted in urine along with APAP-glucuronide and APAP-sulfate in dogs and cats respectively [2,5]. Peak plasma APAP levels occur within 4 hours of ingestion [5,7] and correlate with the dose ingested [5]. In mice, some APAP is metabolized by CYP2E1 in the proximal tubules of the kidney, causing NAPQI formation [8].

If glutathione stores are depleted to less than 70% of normal, NAPQI remains in its toxic form and binds to hepatic cell membranes, causing necrosis and hepatotoxicity [2,3,5,7,9]. Glutathione depletion also leads to oxidative damage to the heme in red blood cells, causing methemoglobinemia in dogs and cats and Heinz body anemia in cats [7,10]. It is theorized that subcutaneous edema can occur due to anoxia and increased capillary wall permeability secondary to methemoglobinemia [11]. Methemoglobin levels peak within 4 hours of APAP ingestion [12]. When renal glutathione stores in mice are depleted, NAPQI damages renal proteins and cell death ensues [8]. This is likely the underlying pathophysiology of APAP-induced nephrotoxicity in dogs and cats.

Cats are more sensitive to APAP as they lack a specific form of glucuronyl transferase, hepatic acetaminophen-directed uridine 5'-diphosphate [13], which is needed to conjugate APAP to glucuronic acid [9,10,12]. Cat erythrocytes are also more susceptible to oxidative damage by NAPQI due to the increased number of sulfhydryl groups on feline heme compared to other species [9,10,14].

It has been suggested that a metabolite other than NAPQI, para-aminophenol (PAP), may cause methemoglobinemia in dogs and cats [15]. PAP is metabolized by N-acetyltransferase. *In vitro*, dog and cat erythrocytes are more susceptible to oxidative injury (causing methemoglobin) by PAP than NAPQI [15]. Dogs and cats accumulate higher levels of PAP in erythrocytes compared

[†]Deceased

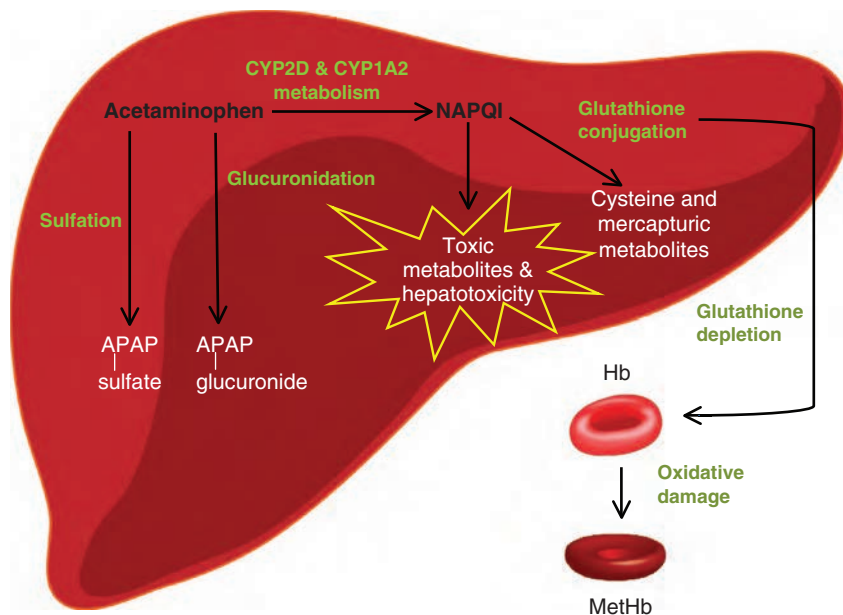


Figure 132.1 Acetaminophen metabolism in the liver and mechanism of toxic effects.

to other species, as canine erythrocytes do not contain N-acetyltransferase and feline erythrocytes only contain one N-acetyltransferase enzyme [15].

Toxic Doses

Therapeutic doses of APAP exist in dogs and range from 10 to 15 mg/kg every 8–12 hours [7,16]. Dogs usually do not show clinical signs of acetaminophen toxicity until over 100 mg/kg of acetaminophen has been ingested [5].

There is no therapeutic APAP dose in cats. Toxic doses in cats tend to occur with ingestion of 50–100 mg/kg, which represents one regular strength OTC human tablet (325 mg) [9]. However, there are reports of cats developing clinical signs after ingestion of as little as 10 mg/kg [10].

Clinical Signs

Common clinical signs in dogs and cats presenting with acetaminophen toxicity include depression, vomiting, lethargy, anorexia, icterus, cyanosis, muddy or brown mucous membranes, hypothermia, hyperthermia, tachycardia, tachypnea, respiratory distress, pigmenturia, and facial, paw, or forelimb edema [1,5–7,10,12,14,17]. The severity of clinical signs is correlated with the dose ingested [5].

Gross and Histological Lesions

Dogs develop centrilobular hepatic necrosis [5,18,19] that may or may not be accompanied by gross lesions

of hepatic congestion and hemorrhage. Liver necrosis is less common in cats; instead, cats may have histological evidence of peripheral hepatocyte degeneration [5]. Gross hepatic lesions may include a nutmeg appearance, or a pale and mottled or edematous liver [5].

Renal cortex and medullary congestion, proteinaceous tubular casts, nephrosis, jejunal hemorrhages, and hemoglobin imbibition throughout other organs can also be seen [5]. Studies in humans show that upper gastrointestinal complications, such as ulceration, can occur at increasing doses of APAP [20,21]. Although weak, APAP does inhibit COX enzymes and, in theory, high doses could affect gastrointestinal mucosal integrity.

Diagnosis

The diagnosis of APAP toxicity is usually based on a patient's history of exposure to APAP, clinical signs, and laboratory abnormalities [7]. Plasma levels of acetaminophen can be measured at some human hospitals [7]. Laboratory evidence of hepatotoxicity is not seen until 24–36 hours after acetaminophen ingestion [7].

Bloodwork abnormalities in dogs include elevated values for alanine aminotransferase (ALT) [5,18], serum alkaline phosphatase (ALP) [5], total bilirubin and ammonia, and decreased serum concentrations of albumin and cholesterol [18]. Ingestion of higher doses of acetaminophen in dogs can cause nephrotoxicity [5,7], with an increase in BUN and creatinine, and decreased glomerular filtration rate (GFR) [7]. Abnormalities in cats include increased ALT, aspartate transaminase (AST), lactate dehydrogenase (LDH), and total bilirubin,

as well as Heinz body anemia [10,14,22], low cholesterol, and low albumin [10].

Treatment

The goals of treatment are to decrease acetaminophen absorption, increase its elimination, limit NAPQI formation, supplement glutathione stores, and provide supportive care [13] (Figure 132.2).

Patients presented for acetaminophen ingestion should have emesis induced if the ingestion was recent (within <1–3 hours) [23], unless contraindicated (see Chapter 127) [7]. Contraindications include CNS depression, underlying conditions placing the patient at risk of aspiration pneumonia, and concurrent ingestion of a corrosive, caustic, or volatile substance [23]. If emesis is contraindicated, gastric lavage may be a safer alternative for detoxification [7]. Activated charcoal at a dose of 1–3 g/kg should be administered to bind any remaining APAP in the gastrointestinal tract [7]. Contraindications for activated charcoal administration are the same as for emesis induction [23]. Since APAP undergoes enterohepatic recirculation, activated charcoal administration should be repeated [7]. Repeated doses should be administered every 4–8 hours for 2–3 days at half of the original dose [23]. Repeat doses should not contain cathartics.

In addition to specific treatments listed below, supportive care includes correcting dehydration, electrolyte, and acid–base abnormalities. Depending on clinical signs and hematocrit, some patients may need

transfusion with packed red blood cells (pRBC). Patients clinical for methemoglobinemia may require oxygen supplementation.

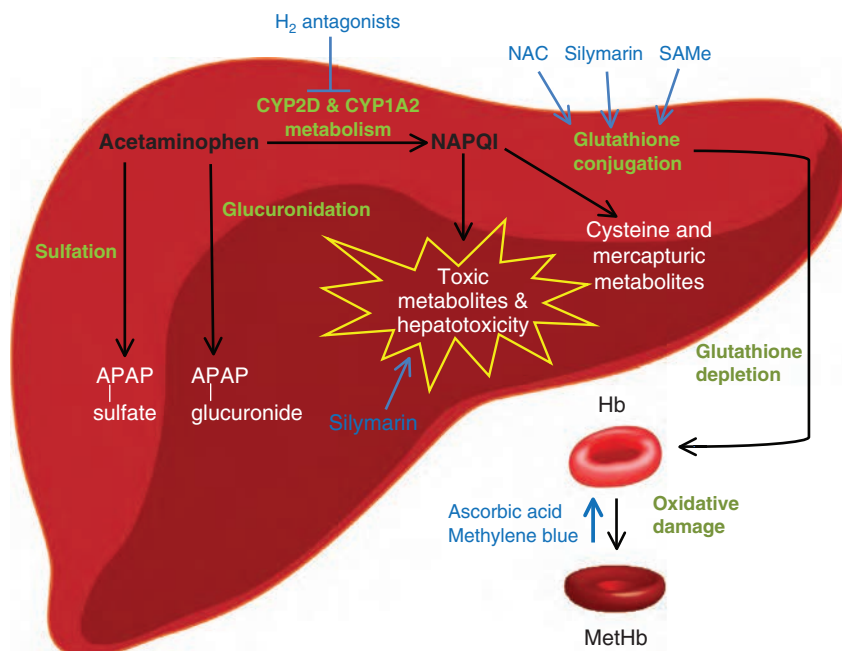
N-Acetylcysteine

Administration of N-acetylcysteine (NAC) is currently the best treatment for APAP toxicity in dogs and cats. NAC is a glutathione precursor [7,10,14,17,24] and it binds with APAP metabolites, making them inactive [10,14], and it can increase sulfate conjugation by being a sulfur donor [12,14]. In dogs, NAC administration has been proven to increase acetaminophen elimination [24]. In cats, NAC administration decreased methemoglobinemia and Heinz body formation [6]. A loading dose of 140 mg/kg should be administered IV or PO followed by 70 mg/kg IV or PO every 4 hours for 3–7 treatments [7,10,17,24]. Intravenous use of NAC is off-label [7] and when administered by this route it should be diluted with 5% dextrose [25] to a 5% solution and administered slowly over 15–20 minutes [7]. If oral NAC is administered, it should be given 2–3 hours apart from activated charcoal [7].

Ascorbic Acid

Ascorbic acid reduces methemoglobin to hemoglobin, but its effectiveness in patients with acetaminophen toxicity is questionable [7,10]. Recommended doses include 10 mg/kg PO or IV every 6–12 hours [7] or 30 mg/kg IV every 6 hours [10].

Figure 132.2 Acetaminophen intoxication treatment locations based on acetaminophen metabolism pathways. Hb, hemoglobin; metHb, methemoglobin; NAC, N-acetylcysteine; SAME, s-adenosyl methionine.



Silymarin

Silymarin is a milk thistle extract composed of an antioxidant flavonoid complex. It is used non-specifically to treat liver disease by scavenging free radicals, stabilizing membrane permeability via lipid peroxidation, and preventing liver glutathione depletion [22]. A study showed that 30 mg/kg PO in cats administered at the time of APAP ingestion or 4 hours after ingestion had a similar hepatoprotective effect as NAC [22].

Histamine Receptor Antagonists

Cimetidine is an H₂ antagonist that decreases APAP metabolism by inhibiting the cytochrome p450 oxidation system, but its ability to prevent hepatotoxicity is controversial [7,10,14]. Recommended doses are 5–10 mg/kg PO, IM, or IV every 6–8 hours in dogs and cats [7].

Ranitidine is an H₂ antagonist that at high concentrations binds to cytochrome p450 and prevents oxidation of acetaminophen [18]. One study showed that a high dose (120 mg/kg) of ranitidine was protective against hepatotoxicity.

S-Adenosyl Methionine

S-adenosyl methionine (SAME) initiates transmethylation and transsulfuration pathways in hepatocytes and in theory should help prevent hepatotoxicity from APAP ingestion [13]. A study comparing cats treated with SAME for APAP toxicity versus no treatment did not show a significant difference in the amount of Heinz body formation between the groups, but did show that the SAME group cleared Heinz bodies faster than the control group [26]. SAME may be considered a benign

therapeutic option in dogs. There is one case report of administration of SAME (40 mg/kg given PO then 20 mg/kg PO SID for 1 week) to a dog with severe APAP toxicity (ingestion of over 500 mg/kg) that survived [13].

Methylene Blue

Methylene blue reduces methemoglobin to hemoglobin but it should be used cautiously in cats as a treatment for APAP toxicosis [27]. At high doses, it has the potential to induce methemoglobinemia by oxidizing heme [27]. Methylene blue is generally not recommended as a treatment for methemoglobinemia in cats [10], although one study showed that one or two doses did not induce hemolytic anemia in cats [28]. Another study compared methylene blue alone, NAC alone, and NAC plus methylene blue as treatments for APAP toxicosis in cats; results showed that methylene blue decreased the plasma APAP half-life better than NAC alone in female cats but prolonged the plasma APAP half-life in the male cats [12]. The cause for this gender difference is unknown [12].

Prognosis

The prognosis varies from guarded to good for dogs and cats with APAP toxicosis, depending on the time between ingestion and treatment. The earlier treatment is implemented, the better the prognosis. One study of APAP toxicosis in cats showed that four of five non-survivors did not receive treatment for 17 hours after ingestion, but the 10 survivors received treatment within 14 hours of ingestion. One cat in the non-survivor group ingested as little as 10 mg/kg, and one cat in the survivor group ingested 400 mg/kg [10].

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133

Non-Steroidal Anti-Inflammatory Drug Intoxications

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Mechanism of Action

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of drugs whose actions are typified by the inhibition of cyclo-oxygenase (COX). This drug class includes aspirin. Acetaminophen is not considered a traditional NSAID as it has only minimal anti-inflammatory activity so it is excluded from further discussion in this chapter unless stated otherwise (see Chapter 132).

Non-steroidal anti-inflammatory drugs exert their analgesic, antipyretic, and anti-inflammatory actions by direct inhibition of COX by competing with arachidonic acid (AA) for the active site of the enzyme [1]. All NSAIDs other than aspirin cause reversible inhibition of COX. The COX pathway uses AA, which is released from membrane phospholipids during trauma, infection, inflammation or platelet aggregation, to produce prostaglandins and thromboxane (PGD₂, PGE₂, PGF_{2α}, PGI₂, TXA₂) [1–3]. Prostaglandins are local, bioactive hormones with a short half-life of seconds to minutes. They are important for many physiological functions in the body as well as promotion and resolution of inflammation [3].

There are two isoforms of COX enzymes that are responsible for synthesis of prostaglandins and thromboxane [2]. COX-1 is a constitutive enzyme, responsible for prostaglandin production for many normal physiological functions such as renal and gastric blood flow [4]. COX-1 is mainly found in the stomach, kidney, endothelium, and platelets. COX-2 is a mostly inducible enzyme, synthesized in response to inflammation by macrophages, monocytes, fibroblasts, and chondrocytes after stimulation by cytokines and other mediators of inflammation [4]. Many currently marketed NSAIDs have higher COX-2 selectivity with the goal of providing analgesia and suppressing inflammation while sparing

physiologically important COX-1-mediated prostaglandins [2–5]. However, COX-2 appears to be constitutive in canine pyloric and duodenal mucosa, where COX-2 enzyme products are important for healing of gastroduodenal ulcers [6]. It appears that both COX-1 and COX-2 play a role in prostaglandin synthesis and maintenance of gastric mucosal integrity. COX-2 appears to play a “back-up” role by alleviating prostaglandin deficiency induced by COX-1 inhibition [7]. Hence, newer NSAIDs can still produce gastrointestinal adverse effects.

Aspirin (acetylsalicylic acid) is a non-selective, irreversible dual COX inhibitor that has more COX-1 selectivity at low doses [4]. By acetylating COX, aspirin irreversibly inhibits TXA₂ and PGI₂. Platelets are unable to synthesize new COX enzymes as they lack a nucleus. As a result, COX inhibition following aspirin exposure will persist for the lifespan of the platelet [8].

Acetaminophen is an analgesic and antipyretic but does not produce anti-inflammatory effects at clinically relevant doses [9,10]. The mechanisms of action of acetaminophen are still not well understood but recent research has shown that acetaminophen is a COX inhibitor in cells with low concentrations of arachidonic acid. Acetaminophen appears to be inhibiting the peroxidase portion of prostaglandin H₂ synthase (traditional NSAIDs inhibit the cyclo-oxygenase portion). There is also evidence that acetaminophen is a selective COX-2 inhibitor in selected tissues. Additionally, it appears to have an effect on a central COX-1 variant (previously called COX-3), inhibiting centrally mediated pain and pyrexia, especially in dogs [4,10–12]. Other proposed mechanisms of analgesia of acetaminophen include direct activation of serotonin receptors with serotonin-mediated stimulation of inhibitory pain pathways [4]. Readers are referred to Chapter 132 for further discussion on this topic.

Pharmacokinetics

Non-steroidal anti-inflammatory drugs have excellent bioavailability after parenteral and enteral administration but considerable species-specific differences exist in drug elimination [1]. Most NSAIDs are weak acids that are ionized at a physiologic pH while all NSAIDs are highly protein bound to albumin (98–99%), hence the volume of distribution (V_d) is very small. Only the unbound drug is pharmacologically active. Most NSAIDs are metabolized in the liver to inactive compounds via glucuronidation followed by renal and biliary excretion [1,4,13]. The high degree of protein binding limits renal excretion of the parent drug and restricts these drugs to the plasma compartment [1,4,13]. Once all albumin-binding sites are saturated, free drug concentrations increase quickly, leading to rapid efficacy of many NSAIDs while the kidney rapidly excretes free, unbound drug, preventing accumulation [13]. Elimination half-lives and enterohepatic recirculation vary considerably between drugs and species.

Aspirin is a weak acid that undergoes hepatic metabolism into salicylic acid; 70–90% of the drug is protein bound, mostly to albumin. Aspirin is minimally ionized and rapidly absorbed in the acidic environment of the stomach. Salicylic acid is eliminated via hepatic conjugation with glycine and glucuronidation followed by renal excretion [8].

Adverse Effects

From 2005 to 2010, the ASPCA Animal Poison Control Center reported 22 206 cases of dogs and cats exposed to different NSAIDs. Of these, 71% were dogs and 6% were cats [13]. A systematic review that evaluated prospective original studies on the safety of NSAID administration in dogs from 1990 to 2012 reported adverse effects in 55% of the studies [5]. Most common side-effects reported included vomiting, diarrhea, anorexia, lethargy, and melena. Less common clinical signs were fecal blood, bleeding, colitis, abdominal pain, aggressiveness or behavioral changes, hypersalivation, polydipsia, polyuria, adipsia, constipation, icterus, skin reactions, and weight loss. Two studies reported gastrointestinal perforations [5]. In general, the clinical effects of NSAID intoxication depend on the dose ingested. Lower toxic doses are likely to cause gastrointestinal signs while moderate doses can lead to gastrointestinal and renal injury and high doses can cause acute neurological signs (Table 133.1).

Gastrointestinal Toxicity

It is believed that NSAIDs cause gastrointestinal damage by direct and systemic effects. Direct effects are due to

local irritation caused by NSAID-ion trapping. Systemic effects are mostly due to inhibition of COX-1-mediated endogenous PGE₂ but also PGI₂ production [1,13,14]. Gastrointestinal prostaglandins play an integral part in gastrointestinal cytoprotection by production of a protective, mucous gel layer, regulation of mucosal blood flow, cell turnover, and repair. Prostaglandin inhibition will diminish these protective effects. Aspirin may cause direct gastric irritation by disrupting surface phospholipids of the gastric mucosa [15]. Cats have limited ability to glucuronidate aspirin, which leads to prolonged excretion and half-life of aspirin and a higher incidence of gastrointestinal toxicity.

Renal Injury

Prostaglandin E₂ and PGI₂ play an important role in renal blood flow, and salt and water regulation. NSAIDs usually have little effect in healthy animals, but during episodes of decreased renal perfusion, they cause afferent arteriolar vasodilation and help to maintain renal blood flow. The kidneys become dependent on the vasodilatory effects of prostaglandins to maintain renal blood flow and glomerular filtration rate during episodes of dehydration, hemorrhage, anesthesia, heart failure and other conditions that would lead to decreased renal perfusion. Hence the use of NSAIDs during hemodynamic compromise is contraindicated. NSAID-induced renal injury includes papillary necrosis and interstitial nephritis [16].

Hepatic Injury

Hepatotoxicity induced by NSAIDs has been infrequently reported and is often idiosyncratic in origin. Clinical signs are often seen within the first 3 weeks of NSAID administration but can also occur after months to years of NSAID use. Idiosyncratic reactions are usually unpredictable and not dose related. Hepatocellular injury appears to be multifactorial in origin, including genetic variation in drug activation and detoxification and direct cellular effect leading to membrane dysfunction or cytotoxic T-cell response. It is unclear if pre-existing hepatic disease predisposes animals to hepatic injury due to NSAID administration [4,17,18]. Cats have limited ability to conjugate and glucuronidate aspirin as well as a relative deficiency in glutathione, all of which account for prolonged elimination, drug accumulation, and toxicity [15].

Coagulation and Hematological Issues

As COX inhibition can lead to inhibition of TXA₂ production by platelets, many NSAIDs can cause thrombocytopathy. Aspirin reduces platelet aggregation because it

Table 133.1 Pharmacokinetics and toxic doses of commonly administered NSAIDs in dogs and cats.

NSAID	Toxic dose	COX-1/COX-2 ratio*	Half-life (hr) [†]	V/D [§] (L/kg)	Log P-value	Enterohepatic recirculation
Aspirin [4,32–36]	Dog: 25–50 mg/kg, BID-TID, gastric ulcerations, ≥ 450 mg/kg once, coma, hyperthermia, alkalosis, death Cat: 25–100 mg/kg SID, gastric ulcerations, ≥ 100 mg/kg, lethal	0.3–0.39	7.5–12 (25 mg/kg)	0.17	1.19	No
Carprofen [4,29,35,37]	Dog: 5.3 mg/kg, vomiting, ≥ 50 mg/kg, renal damage Cat: 3.9 mg/kg, vomiting, ≥ 8 mg/kg, renal damage	1.75–129	22 (20 mg/kg)	0.12–0.22	4.13	Yes
Deracoxib [4,33,37]	Dog: ≥ 15 mg/kg, SID, vomiting, melena, ≥ 30 mg/kg renal injury Cat: ≥ 4 mg/kg, gastrointestinal signs, ≥ 8 mg/kg, renal injury	1275	3 8	1.5	–	Yes
Diclofenac [13,38,39]	Dog: 59–500 mg/kg LD ₅₀	1–3.9	1.2–2	1.4 (human)	4.51	Yes
Etodolac [4,13,37,40]	Dog: 40 mg/kg/day, gastrointestinal ulcers, weight loss, emesis, 80 mg/kg/day, death, gastrointestinal and renal disease	0.52–7.92	8–12	>1	3.39	Yes
Firocoxib [33,37,40–42]	Dog: ≥ 25–50 mg/kg, gastrointestinal lesions in adult dogs, hepatic lesions, pancreatic edema. Duodenal ulcerations, death in 10–13-week-old dogs Cat: not established	348 58	6–8 10	3–4.6 2–3	1.94	Yes
Flunixin [35,37,43,44]	Dog: ≥ 1.1 mg/kg, gastrointestinal lesions Cat: not established	0.3 (horse)	3.7 1–6 (1–2 mg/kg)	0.15 (horse)	–	Yes
Ketoprofen [35,37,38,45]	Dog: 0.44 mg/kg, gastrointestinal ulceration, 2000 mg/kg LD ₅₀ Cat: 0.7–15 mg/kg renal toxicity	0.6	1.6 0.5–1.5	0.22	3.12	Yes
Ibuprofen [3,4,13,46–48]	Dog: 8–16 mg/kg, SID for 30 days, gastric ulcerations, 100–125 mg/kg once, gastrointestinal problems, 175–300 mg/kg once, renal failure, > 400 mg/kg, CNS effects, > 600 mg/kg once, lethal Cat: ~ twice as sensitive	0.6–15	3.9–5.3	0.05	3.97	Yes
Meloxicam [4,13,37]	Dog: not established Cat: acute renal failure and death have been reported after repeat dosing	2.7–10	12–36 15	0.3 0.27	3.43	Yes
Naproxen [37,49,50]	Dog: > 5 mg/kg, gastrointestinal signs, 10–25 mg/kg, renal damage, > 50 mg/kg, CNS signs Cat: not established	0.7	74	0.13	3.18	Yes
Phenylbutazone [4,35,37,38]	Dog: 332 mg/kg, LD ₅₀ Cat: 44 mg/kg bone marrow suppression, gastrointestinal, renal and liver injury, death	0.6–9.7	2.5–6	0.14	3.16	Yes
Piroxicam [4,13,33,37]	Dog: 0.8 mg/kg, EOD for 10 days, gastric ulceration, hemorrhage, 1 mg/kg/day for 12–18 months, renal papillary necrosis, > 700 mg/kg LD ₅₀ Cat: not established	1.27–2	35–74 12	0.3	3.06	Yes
Robenacoxib [37,51,52]	Dog: not established Cat: 24 mg/kg/day for 21 days neurological signs, periportal hepatic necrosis, renal damage	32.2	1.2–1.7 1.7	0.19	–	Yes

BID, twice a day (*bis in die*); CNS, central nervous system, COX, cyclo-oxygenase; EOD, every other day; NSAID, non-steroidal anti-inflammatory drug; SID, once a day (*semel in die*); TID, three times a day (*ter in die*); V/D, volume of distribution.

*In dog and human cell lines, based on 50% inhibitory concentration (IC₅₀), the higher the value above 1.0, the more specific the drug is for COX-2.

[†]Half-life for therapeutic dose unless indicated otherwise.

[§]Volume of distribution in dogs unless indicated otherwise.

irreversibly inhibits TXA₂ production. Consequently, as TXA₂ synthesis is inhibited for the lifespan of the platelet, new formation of TXA₂ requires the synthesis of new platelets [8]. The impact of other NSAIDs on platelet function is variable. Experimental research found decreased platelet aggregation in dogs that received aspirin and carprofen, increased clot strength in dogs that received deracoxib, and a minimal effect on clot strength with meloxicam administration [19]. In cats, experimental research showed that administration of aspirin and meloxicam had no effects on platelet aggregation, even though aspirin decreased TXA₂ significantly [20]. Unlike the effects of aspirin, the reversible inhibition of TXA₂ by other NSAIDs will allow platelet function to return to normal following metabolism of the drug.

Neurological Complications

Aseptic meningitis induced by NSAIDs has been reported in humans but not in veterinary medicine [21]. Salicylate-induced seizures in a dog have been reported [22]. Central nervous system (CNS) effects including seizures, ataxia, depression, and coma have been reported after ingestion of high doses of ibuprofen, naproxen, and robenacoxib (see Table 133.1).

Treatment of NSAID Intoxication

Animals that have ingested an accidental overdose of a NSAID should be treated promptly.

Decontamination should be performed immediately if the animal does not show clinical signs that prevent emesis (e.g. comatose, seizing, trembling, absent gag reflex) and if the ingestion was within the last 2 hours (see Chapter 127). Emesis can be induced with apomorphine (0.03–0.04 mg/kg IV once or a crushed tablet dissolved in 0.9% saline, administered in the conjunctival sac or intranasally). Alternatively, 3% hydrogen peroxide can be administered (2.2 mL/kg, PO to a maximum of 45 mL/dog), which can be repeated once if emesis did not occur [13,23]. In cats, emesis can be tried with xylazine (0.44 mg/kg, IM). Gastric lavage should be considered in animals that did not vomit and have recently ingested large, toxic doses as well as those in which neurological signs prevent the induction of emesis.

Activated charcoal (AC) (1–3 g/kg PO, q6–8h, 2–6 doses total) should be administered after induction of emesis. Repeated administration of AC is generally recommended as many NSAIDs undergo enterohepatic recirculation. The first dose of AC should contain a cathartic (e.g. sorbitol) to promote gastrointestinal transit time, followed by AC without a cathartic for consecutive dosing, to avoid dehydration and hypernatremia.

Recent research found that a single dose of AC is as effective as either multiple doses of AC or AC with sorbitol in reducing serum carprofen concentrations in moderately overdosed dogs [24]. This may mean that repeat doses of AC in NSAID intoxication are unnecessary, but until further research evaluating other NSAID drugs is performed, it would seem prudent to continue with repetitive AC dosing.

Fluid therapy with forced diuresis plays a key role in the intoxicated patient. Intravenous, balanced isotonic crystalloids (e.g. lactated Ringer's solution, Plasma-Lyte 148, Normosol-R) can be used at 1.5–2 times normal maintenance rates (see Chapter 167). This will aid in excretion of the drug, helps to vasodilate the renal vessels, which is particularly important in NSAID toxicosis, and prevents dehydration. Careful monitoring of packed cell volume, total protein, electrolyte abnormalities, and fluid balance during treatment is important.

Gastrointestinal support should be provided with H₂ blockers such as famotidine, cimetidine or ranitidine as well as proton pump inhibitors such as omeprazole, esomeprazole or pantoprazole. Misoprostol (3 µg/kg PO q8–12h) is a synthetic PGE₁ analogue that was found to be beneficial in preventing gastrointestinal mucosal injury caused by aspirin [25] and might also be beneficial in NSAID intoxication to prevent injury. The use of metoclopramide should be avoided because it acts as a dopamine antagonist on a renal level and may decrease renal blood flow [26].

Intravenous lipid emulsions (ILE) have been used successfully in two recent case reports to treat intoxications with ibuprofen and naproxen in dogs [27,28] (see Chapter 128). The most commonly accepted mechanism of action of ILE is the “lipid sink” theory, where ILE sequesters lipophilic compounds into a newly created intravascular lipid compartment which results in decreased free drug concentrations. The lipophilicity of a drug is related to its log P value, which is a ratio of unionized solute concentrations dissolved in two solutions. Since most drugs are ionizable at a certain, adjusted pH, log P values may not always accurately predict the drug's lipophilicity. Drugs are considered lipophilic if their log P > 1.0; the higher the log P value, the more lipophilic the drug. The following dose recommendations are published in veterinary medicine for the administration of 20 % ILE: initial bolus of 1.5–4 mL/kg (~0.3–0.8 g/kg), IV over 1 minute, followed by constant-rate infusion (CRI) of 0.25 mL/kg/min (0.05 g/kg/min) IV over 30–60 minutes. If the animal continues to be clinical, intermittent boluses at 1.5 mL/kg q4–6h might be necessary with an optional follow-up CRI of 0.5 mL/kg/h (0.1 g/kg/h) until clinical signs improve [29].

Extracorporeal therapy (ECT) recommendations are not well defined (see Chapter 129). The high

protein-binding property and low volume of distribution of many NSAIDs favor the use of charcoal hemoperfusion followed by conventional hemodialysis if the animal has significant clinical signs or has ingested a large amount

of the drug. Total plasma exchange followed by charcoal hemoperfusion has also been utilized for NSAIDs that are strongly protein bound [30,31].

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Grape, Raisin, and Lily Ingestion

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Grape, Raisin, and Currant Nephrotoxicity Pathogenesis

Grapes, raisins, and currants have been reported to cause acute kidney injury (AKI) in dogs. Affected dogs have been exposed to fresh grapes from grocery stores or vines in private yards, grape crushings, or fermented grapes from wineries [1]. Red seedless grapes were involved in most cases, but AKI has also been reported with golden seedless types. The raisins involved were mostly commercial sun-dried raisins of various brands, including both dark and golden seedless varieties. The estimated ingested amount of raisins causing toxicity ranges between 0.1 and 1.3 oz/kg (2.8–36.4 g/kg) and the estimated quantity of grapes causing toxicity ranges between 0.7 and 5.3 oz/kg (19.6–148.4 g/kg) [2].

The exact toxic substance within grapes, raisins, and currants is unknown. When tested, samples of grapes and raisins were found not to contain mycotoxin or ochratoxin A [2]. Dogs developing AKI were found to have moderate to severe renal tubular degeneration, mineralization of the tubular epithelium and basement membrane, and tubular obstruction caused by proteinaceous and cellular debris [2]. Another report showed similar findings, but the tubular basement membrane remained intact [3].

Presenting clinical complaints included vomiting (100% of dogs), lethargy, anorexia, diarrhea, ataxia, and weakness. Symptoms typically develop within 24 hours of exposure.

Lily Nephrotoxicity Pathogenesis

Acute kidney injury has been reported in cats following ingestion of *Lilium* and *Heimerocallis* species of lily plants (Box 134.1) [4–7]. There are numerous plants that

are called “lily” but do not belong to these two species, such as the peace lily (genus *Spathiphyllum*). These other species of plants may result in additional toxic effects, such as oral and gastrointestinal irritation, vomiting, or cardiac effects, or may be non-toxic. Confusion arises in the identification of lily plants due to the existence of many hybrid species, as well as a lack of identification when flowers are received as gifts.

Owners should be directly questioned about possible lily exposure for any acutely azotemic cat. One study found that less than 30% of cat owners knew that lilies were toxic, so they may not willingly provide such important history [7]. All parts of the lily plant, including the petals, stamen, leaves, and pollen, are toxic to cats [5]. Just chewing on the petals or ingestion of a single flower has resulted in nephrotoxicity. The exact toxin is unknown, but has been demonstrated to be water soluble [5]. Easter lily flowers were shown to contain 16 different steroidal glycoalkaloids, which may be the nephrotoxic compounds, but this has not been confirmed *in vivo* [8]. Experimentally induced lily toxicity resulted in moderate to severe proximal tubular epithelial cell necrosis, edema, and tubular obstruction [5]. Pancreatitis has also been observed in some cats [6].

It should be noted that many cats (87% in one report) develop transient or no clinical signs following lily exposure [7]. Vomiting, lethargy, and hypersalivation are the

Box 134.1 Nephrotoxic lilies

Asiatic lily	Japanese show lily	Tiger lily
Calla lily	Leopard lily	Trumpet lily
Daylily	Panther lily	White lily
Easter lily	Stargazer lily	Yellow lily

most common clinical signs, typically observed 1–5 days post exposure, with many cats showing these symptoms within 1–3 hours after ingestion [6]. Neurological abnormalities, including seizures and ataxia, have been reported in almost 40% of cats [9]. One report suggested that seizures often occurred following handling of cats, such as after physical examination [5].

Physical Examination

Physical examination may reveal abdominal pain, abnormal mentation, hypothermia, and dehydration. Abdominal pain was present in nearly 30% of dogs with grape and raisin toxicity. Renomegaly and renal pain may be present. It should be noted that many cats with lily nephrotoxicity have a normal examination and appear remarkably bright and asymptomatic despite severe uremia. It is important to note the size of the urinary bladder during initial examination.

Initial Diagnostics

Initial diagnostics should include complete blood count, serum chemistry with electrolytes, acid–base status, urinalysis (sample should be submitted for culture to rule out pyelonephritis), and blood pressure.

Grape and raisin toxicity commonly results in hyperphosphatemia (90%) and hypercalcemia (62%), as well as an increased $\text{Ca} \times \text{P}$ product (95% of dogs). Hypo- and hyperkalemia are frequently encountered. Thrombocytopenia (mean $50 \times 10^3 \text{ PLT}/\mu\text{L}$) was found in nearly 30% of dogs. Isosthenuria, proteinuria, and glucosuria are found in the majority of dogs [2].

Common findings of lily nephrotoxicity include moderate to severe azotemia, isosthenuria, glucosuria, proteinuria, and often cylindruria. A common, but not pathognomonic, finding is a *more markedly elevated serum creatinine concentration compared to a more moderate blood urea nitrogen*. Cats may have serum creatinine concentrations of 15–30 mg/dL, whereas the BUN is typically < 250 mg/dL, resulting in a decreased BUN:Cr ratio. One study found that of cats presenting within 48 hours after lily exposure, only 20% had elevated BUN and 4.5% had elevated creatinine concentrations on initial labwork [10]. Metabolic acidosis resulting from uremic toxins and elevated serum lactate is often encountered. Hyperkalemia may be present and should prompt the clinician to inquire about urine output, as many cats with lily nephrotoxicity develop oligoanuria (see Chapter 95). Hypokalemia may be present in polyuric animals. Increased hematocrit and serum total protein may indicate dehydration.

Management of Non-Azotemic Animals Shortly After Exposure

Management recommendations vary depending on the degree of renal injury. Gastric decontamination through emesis, lavage, and activated charcoal is highly recommended for dogs following grape, raisin, or currant exposure (Box 134.2) (see Chapter 127). Induction of emesis more than 2 hours following ingestion may be warranted because *Vitis* fruits remain in the gastrointestinal tract for some time. It is unknown if activated charcoal binds to the nephrotoxic substances; in this case, repeated doses may be beneficial. Fluid therapy should be administered for a minimum of 48–72 hours and serum chemistry values monitored for at least 72 hours for indications of AKI [11].

For lily nephrotoxicity, asymptomatic cats and those with only mild azotemia within the first 48 hours following exposure should be managed with gastric decontamination and diuresis. Vomiting should be induced if exposure was recent (within 8–12 hours) to try to minimize the quantity of toxin absorbed. Alpha-2 adrenoceptor agonists or hydrogen peroxide can be used to induce emesis (see Chapter 127) [10]. Gastric lavage could be considered for cats ingesting a large amount of plant material, unless contraindicated. Oral activated charcoal may be considered to help reduce gastrointestinal absorption, but it is unknown if this is actually effective since the kinetics of the unknown nephrotoxin are still yet to be documented. Diuresis can be produced by administering normal saline intravenously at twice

Box 134.2 Initial gastric decontamination recommendations (see Chapter 127 for further details)

Inducing emesis

- Apomorphine (0.02–0.04 mg/kg IV or IM). It can also be administered by placing it directly behind the eyelid in the subconjunctival sac.
- Xylazine can be used in cats with limited effectiveness (0.44 mg/kg IM or SC).
- Dexmedetomidine 7–10 mcg/kg IM, SC

Charcoal

- Dosage varies with individual products.
- Powdered activated charcoal and water (2–5 g/kg of body weight (1 g activated charcoal in 5 mL water)). If sorbitol is added as a cathartic, it is given at a dose of 3 mg/kg and mixed with the activated charcoal. Repeat administration of activated charcoal every 4–6 hours for 2–3 days may be beneficial.

maintenance rates and continued for 48 hours (see Chapter 167).

Patients should be monitored very closely for lack of urine output, weight gain, and other signs of hypervolemia (serous nasal and ocular discharge, tachypnea, dyspnea, peripheral edema, etc.) as this may indicate the patient is oligoanuric. These patients are best managed as described below. The water solubility of the nephrotoxin suggests that it is amenable to removal via hemodialysis [12]. Although this may be considered as an adjunctive means of toxin removal, its efficacy is unknown, as is the intensity and duration of dialysis necessary to ensure sufficient toxin removal (see Chapter 129).

Managing Patients with Established Acute Kidney Injury

Dogs with grape/raisin nephrotoxicity may be polyuric or oligoanuric. Oligoanuric acute kidney injury is the most common result of significant lily nephrotoxicity. Affected cats may remain anuric for 1–2 weeks before starting to produce urine again. The return of urine production is often gradual and not typically associated with a massive polyuria phase, as observed with postobstruction diuresis and recovery from leptospirosis. Oligoanuric animals should be given intravenous fluids only if hypovolemic or dehydrated, with the volume of fluid administered being calculated to correct these abnormalities. Subsequent intravenous fluid therapy should be performed very cautiously, as patients are quite prone to iatrogenic hypervolemia when anuric. Hypervolemic patients should not receive intravenous fluids, and pharmacological conversion to polyuria may be attempted when extracorporeal renal replacement (ERRT) is not an option (see Chapter 129).

Hyperkalemia may be managed by administering intravenous insulin + dextrose, beta-2 agonists, sodium bicarbonate, and sodium polystyrene. Intravenous calcium is indicated for treating arrhythmias resulting from hyperkalemia, but the serum potassium concentration still needs to be corrected (see Chapter 109). Due to the severity of azotemia and prolonged duration of oligoanuria, extracorporeal renal replacement therapy or

peritoneal dialysis should be considered. An esophagostomy tube can be used to provide enteral nutrition, medication delivery, and accessibility for enteral water. Jugular venepuncture or catheterization should be avoided in all candidates for ERRT. Hypertension should be managed with amlodipine (PO or rectal) to reach a target systolic blood pressure < 160 mmHg (see Chapter 63).

Nutritional support should be initiated as early as the patient will tolerate, with preference given to the enteral route. Parenteral nutrition can be considered in patients which have severe or protracted gastrointestinal symptoms, but vascular access may be difficult, particularly in patients that also require ERRT. Prescription renal diets are indicated, with the diet containing the lowest amount of potassium per 100 kcal likely being most helpful in the management of hyperkalemic patients. Due to the catabolic nature of AKI and ERRT, animals typically require more than their calculated metabolic energy requirements to prevent loss of fat and muscle mass. Phosphate binders can be administered with meals and antinausea medications and antacids given as needed.

Prognosis

Approximately 25–60% of dogs will remain asymptomatic following grape or raisin exposure [2,11]. Dogs which developed AKI reportedly had a 53% survival rate. The median time until resolution of azotemia in surviving dogs was 16 days for BUN and 30 days for creatinine, although some dogs took months until normalization occurred. Eighteen percent of surviving dogs failed to regain normal renal function [2]. ERRT was used to successfully manage a dog with currant nephrotoxicity, allowing management of uremia until return of renal function occurred [13].

The prognosis for cats which have been given supportive care shortly after exposure is good, up to 100% survival in one study [10]. Cats developing AKI have reportedly had a grave prognosis, 50–100% mortality in several studies [4,6,9,14]. Successful resolution of AKI has been reported following management with ERRT [15]. Survival rate for cats treated with dialysis is reportedly 50% [16].

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Recreational Drug Intoxications

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Cocaine

Cocaine is an illicit drug with profound sympathomimetic and psychostimulatory effects. Its use is prevalent, making it the second most problematic illicit drug after heroin [1]. Derived from the leaves of the alkaloid coca plant and processed into a powder, it can be insufflated (snorted), injected, or smoked in free-base form (crack). Solid white powder forms contain 12–16% cocaine salts that are cut with adulterants (lidocaine, benzoaine, caffeine, amphetamines) [2].

Despite its prevalent use in people, cocaine toxicity is uncommonly reported in dogs, and only one case report in a cat [3]. A recent retrospective study in dogs with presumptive cocaine intoxication found neurological abnormalities to be the most common presenting sign, followed by cardiovascular effects, and all dogs in the study survived to hospital discharge [1]. Due to the complex pharmacological properties of cocaine and its derivatives, it is still considered potentially life-threatening. Working police dogs may be at higher risk of exposure, and the use of a muzzle has been advocated to help minimize intoxications [4].

Mechanism and Toxicokinetics

Sympathomimetic effects are due to reuptake inhibition of norepinephrine (NE), serotonin, and dopamine. Stimulation of endogenous catecholamine release causes direct effects on the myocardium and CNS. Neuroendocrine system dysregulation occurs with effects on appetite, sleep, alertness, and body temperature.

Cocaine is rapidly acting and readily crosses the blood–brain barrier. Plasma concentrations peak within 15–20 minutes of exposure. Metabolism is through hydrolysis by plasma and hepatic esterases and 10–20% is excreted unchanged in the urine.

- Oral LD₅₀ in dogs: 6–12 mg/kg and 3.5 mg/kg for IV/SC
- LD in cats: 7.5 mg/kg IV, 16 mg/kg SC

Clinical Signs

Hyperexcitability, hypervigilance, muscle tremors, ataxia, seizures, mydriasis, hypersalivation, tachycardia, tachyarrhythmias, hypertension, hyperthermia, and vomiting. Kidney injury may occur from rhabdomyolysis.

Differential Diagnoses

Stimulants such as amphetamines, methamphetamine, serotonergic drugs, and caffeine. Other causes of seizures and/or tremors include mycotoxins (“garbage gut”), strychnine, or metaldehyde. Additionally, pheochromocytomas may have similar clinical signs.

Diagnostics

Urine multidrug test kits for humans can be used as a point-of-care diagnostic tool, although they must be interpreted with caution (Table 135.1). Currently, there are no validated veterinary urine drug-screening tests. A positive test result is identified by the presence of a color change observed within each channel. The major limitation with these test kits is the possibility of false-negative results, which may occur in peracute cases or when drug concentrations are below the minimal detection limit. A positive test for cocaine may be seen for 2–3 days following exposure.

Minimum database is performed as a screening test. Urinalysis may reveal markers of acute kidney injury (myoglobinuria, granular casts, glucosuria, proteinuria) (see Chapter 94).

Treatment

No specific antidote exists and treatment is supportive (see Table 135.1). Decontamination through emesis is performed in cases when large quantities have been consumed, but must be avoided when neurological signs

Table 135.1 Treatment overview of recreational drug intoxication.

Treatment	Dosage and remarks
*Decontamination	Emesis: apomorphine 0.03 mg/kg IV Adsorption: activated charcoal Gastric lavage (intubation required)
Anxiolytics	Diazepam or midazolam 0.25–0.5 mg/kg IV Acepromazine 0.01–0.05 mg/kg IV, IM, SC, transmucosal Chlorpromazine 0.5–1 mg/kg IV
Anticonvulsants	Short-acting: diazepam or midazolam IV or intranasal Long-acting: phenobarbital 8–16 mg/kg IV loading dose or 2–4 mg/kg IV q12h; levetiracetam 20–40 mg/kg IV q8h
Antiarrhythmics	Lidocaine 2–8 mg/kg IV to effect in dogs; 0.25–0.5 mg/kg in cats (caution!) Propranolol 0.02 mg/kg IV slowly (maximum 1 mg/kg) Esmolol CRI
Reversal agents	Flumazenil 0.05 mg/kg IV Naloxone 0.01–0.04 mg/kg IV or IM
Antiemetics	Maropitant 1 mg/kg SC (off-label in cats) Ondansetron 0.1–0.2 mg/kg IV q8–12h

*Contraindicated with CNS depression.

CRI, constant-rate infusion; IM, intramuscular; IV, intravenous; SC, subcutaneous.

are present due to seizure potential and aspiration risk (see Chapter 127). Gastric lavage may be considered if the quantity ingested is potentially lethal. Activated charcoal with cathartic (sorbitol) can be given once, but repeated dosing is likely ineffective due to rapid absorption. Endoscopy or surgery can be considered to retrieve intact bags of cocaine, although caution must be taken to avoid their rupture.

Central nervous system (CNS) stimulation must be minimized to reduce mania and avoid seizure precipitation. A quiet, dim-lit room is ideal, but the patient must be in an area where ongoing monitoring is feasible. Monitor blood pressure and ECG and treat life-threatening arrhythmias as indicated (see Chapter 53). Hyperthermic patients should be actively cooled using water baths, ice packs, and fans (see Chapter 147). Take care to avoid overcooling (stop at 103–103.5°F). IV fluids are used to promote renal excretion of the drug. Give antiemetics as needed.

Prognosis

Prognosis depends on quantity ingested and severity of signs. Outcome can be good with supportive care.

Multiple organ dysfunction may develop and cardiac arrest is possible (see Chapter 159).

Methamphetamine

Methamphetamine (“meth”) is a highly addictive psychoactive stimulant. Its abuse as a recreational drug in people is widespread across the country. Crystal meth, the precipitated rock form, is used for smoking. Powdered meth can be insufflated, ingested, or injected IV. Effects are similar to cocaine, with much more potency [5].

Methamphetamine toxicity is almost certainly underreported due to the legal implications associated with its possession. Crude home laboratories are common sites for manufacturing methamphetamine from precursor drugs like ephedrine. Dogs may have unguarded access to such areas, creating exposure risk.

Mechanism and Toxicokinetics

Sympathomimetic stimulant effects are through inhibition of monoamine oxidase (MAO), increased catecholamine release, and direct dopamine and serotonin receptor agonism. Distribution is mainly to the kidneys, liver, and lung. Metabolism is via hepatic hydroxylation and deamination followed by renal excretion.

- Oral LD₅₀ in dogs: 9–100 mg/kg [5]

Clinical Signs

Multisystemic effects include serotonin syndrome, hyperactivity, restlessness, hypersalivation, ataxia, tremors, seizures, altered mentation, and hyperthermia. Morbidity from cardiac arrhythmias, hypertension, and disseminated intravascular coagulation (DIC) may lead to death.

Diagnostics and Treatment

Urine can be tested for methamphetamine. Supportive treatment is indicated based on clinical signs. Urinary acidification increases rate of excretion.

Differential Diagnoses

Central nervous system stimulants, cocaine, Ma Huang (ephedra), MDMA, and other “designer drugs.”

Prognosis

Respiratory, renal, and liver failure can cause death in severe cases.

Table 135.2 Sources of marijuana.

Preparation	THC source	Average THC concentration
Cigarette ("joint")	Crude plant material (dried)	3%
Seedless ("sinsemilla") Hashish	Resin from tops of flowering plant	≥10%
Hash oil		≥20%
Medical-grade butter	Extract from boiled plant	≥[THC] in plant
Synthetic cannabinoids	Synthetic herbal incenses	High potency

THC, delta-9-tetrahydrocannabinol.

Marijuana

Derived from the *Cannabis sativa* hemp plant, marijuana refers to tobacco-like dried preparations of leaves, flowers, seeds, and stems. Marijuana is the most common illicit drug in the United States and its availability has increased greatly over the past decade [6], now being legal for personal use in some states. Toxicity is due to the psychoactive compound delta-9-tetrahydrocannabinol (THC). "Hashish" refers to the highly concentrated resin from the flowering portion of the plant. Dogs are extremely susceptible to the effects of THC.

Marijuana has a wide safety margin. Toxic effects correlate with absorbed THC concentrations, which vary by preparation and cultivation technique. Medical-grade THC butter used in baked goods contains the most concentrated forms of the drug (Table 135.2).

Mechanism and Toxicokinetics

Intoxication is most commonly via oral exposure, but second-hand smoke inhalation is theoretically possible. THC absorption following ingestion is slower and more erratic than with smoking. Oral absorption can be increased with concurrent ingestion of fatty foods, such as brownies, or edibles infused with THC butter. Onset of clinical signs in dogs generally occurs within 1–2 hours following ingestion.

Delta-9-tetrahydrocannabinol is highly lipophilic with a large volume of distribution to the liver, brain, kidneys, and adipose tissue. Following ingestion, THC is converted in the liver and lung to 11-hydroxy-delta-9-THC, the primary metabolite. Excretion is 85% biliary via enterohepatic recirculation and 15% renal. Elimination half-life from adipose stores is approximately 30 hours [6].

Oral LD of THC in dogs is >3g/kg, approximately 1000 times the dose where behavioral or neurological effects are seen. An average joint contains 15–30mg of THC [6]. Estimating toxic doses is challenging due to variable drug purities and lack of witnessed exposure in many cases.

The two major cannabinoid receptors are CB₁ and CB₂. The CB₁ receptor is located primarily within the CNS. The CB₂ receptor is found in peripheral tissues. CB₁ receptor activation inhibits multiple neurotransmitters (acetylcholine, glutamate, GABA, norepinephrine, dopamine, 5-HT). Both inhibit adenylyl cyclase and increase potassium channel conductance [7]. All clinical effects of THC are thought to be due to activity at CB₁ receptors. CB₂ receptor effects are less well elucidated. Evidence suggests roles in inflammation, immune modulation, and analgesia, making it a therapeutic target for medically prescribed marijuana.

Clinical Signs

Delta-9-tetrahydrocannabinol can induce a wide range of non-specific clinical signs that vary in severity and duration, depending on the dose and route. The most common clinical signs in dogs are ataxia, depression, altered mentation, urinary incontinence, hypersalivation, mydriasis, vomiting, tremors, nystagmus, vocalizing, bradycardia, hypo- or hyperthermia, sensitivity to light and sound, and coma and death in severe cases. A recent retrospective study reported that nearly half the dogs presented with urinary incontinence, a finding that may be more common with exposure to medical-grade marijuana [8]. Additional effects include direct gastrointestinal irritation, particularly with large amounts of plant material. Patient factors, such as age, size, and co-morbidities, can influence severity of toxic effects. Signs can persist from 1–3 days in dogs (average 24 hours) [6].

In the event of concurrent chocolate ingestion, stimulatory effects from caffeine and theobromide may confound the classic clinical findings associated with marijuana. Dogs may be at risk for developing foreign body obstruction after consuming plastic bags full of marijuana [6].

Differential Diagnoses

Hallucinogenics, CNS stimulants or depressants, other recreational plants and drugs.



Figure 135.1 Example of a multichannel urine dipstick drug screening test with a positive result for THC.

Diagnostics

Urine can be tested for cannabinoids. However, dog urine may contain altered THC metabolites not detected via human drug-screening kits, making their use controversial [8] (Figure 135.1). Sample handling can also cause false-negative test results, as THC can bind to rubber stoppers and glass. While results of urine drug tests must be interpreted with caution, it is generally accepted that a positive test most likely indicates true THC toxicity and a negative test does not exclude the possibility of exposure [9].

Confirmatory testing through gas chromatography mass spectrometry is considered the gold standard for detection in people, but it is of questionable value in dogs. Stomach contents may be evaluated for cannabinoids. Consultation with a toxicology laboratory is recommended prior to specimen submission.

Treatment

There is no specific antidote for marijuana. Treatment objectives center around supportive care. As with

other intoxicants, decontamination is the most effective way to minimize further drug absorption. Emesis induction may prove unrewarding due to the significant antiemetic effects of THC. Some dogs may vomit due to direct effects of the drug, resulting in autodecontamination.

Activated charcoal is an effective adsorption agent for a plethora of toxic compounds and may be given to reduce enterohepatic recirculation of THC. Case selection is paramount, as risks of treatment should never outweigh benefits. Aspiration of charcoal can result in severe morbidity or mortality. It is important to remember that the majority of marijuana toxicity cases are not fatal, even without specific gastrointestinal intervention.

Antianxiety medications are used to sedate acutely agitated patients. IV fluids can be given to treat volume deficits from significant vomiting. Patients may be debilitated in severe cases, requiring intensive nursing care, IV fluids, and airway management. Sternal positioning with elevation of the head may minimize risk of aspiration and atelectasis. Antiemetics may be indicated for ongoing vomiting or nausea.

Recently, the use of intravenous lipid therapy has been proposed for treatment of the highly lipophilic THC (see Chapter 128). The exact mechanism is unknown, but it likely works in several ways [10], although a full description is beyond this chapter's scope. Intralipid therapy is often well tolerated, but can be associated with adverse effects. While it cannot be advocated as part of routine treatment, it may be considered in severe cases of high-potency THC ingestion, such as medical-grade butter. Currently, there are no prospective studies evaluating its utility in dogs with THC toxicity.

Prognosis

Prognosis is very good in most cases, with full recovery made within 24–72 hours. Recovery may be prolonged in animals exposed to very large doses of THC. Two canine deaths have been reported following ingestion of medical-grade butter [8].

Conclusion

Exposure to recreational drugs is possible in dogs, and much less so in cats (Table 135.3). Thoughtful questioning as to possible exposure may result in a greater likelihood of gaining knowledge of possible exposure. In most accidental exposures, there are no legal ramifications, but it may be worthwhile to have a practice policy and consult with local officials.

Table 135.3 Summary of recreational drugs and their effects.

Generic name/street name	Mechanism of action	Clinical signs
MDMA (ecstasy, Molly)	SSRI; stimulates serotonin release	CNS stimulation, hallucinations
GHB (date rape drug)	Synthetic GABA derivative; modulates dopamine signaling	CNS depression
Flunitrazepam (Rohypnol)	Benzodiazepine; opens chloride channels on CNS GABA receptor	Muscle relaxation, sedation, disorientation, hallucinations
LSD (acid)	Serotonin receptor partial agonist; increases glutamate release; binds dopamine and alpha-adrenergic receptors	Hyperexcitability, hallucinations, vomiting, disorientation, mydriasis, tachycardia, depression, compulsive scratching in litter box, increased grooming (cats)
Lysergic acid amide substances (LSAs)	Hallucinogenic seeds from morning glory and Hawaiian baby rose plant; serotonergic	Similar to LSD
Ketamine (Special K)	Dissociative agent; antagonizes glutamate at NMDA receptor by blocking calcium influx	CNS stimulation, ataxia, hallucinations, nystagmus, aggression, cataplexy
PCP (angel dust)	Dissociative agent, similar to ketamine; prolonged effects	CNS stimulation or depression, tremors, tachycardia, arrhythmias, hypo- or hypertension, hyperthermia, rhabdomyolysis, renal failure
Opioids (opium, heroin, oxycodone, morphine, codeine, meperidine, hydromorphone, fentanyl)	Opioid receptor agonist/antagonist effects; varies with drug	CNS depression (dogs) and stimulation (cats), emesis, hypoventilation, ileus

CNS, central nervous system; GABA, gamma-aminobutyric acid; GHB, gamma-hydroxybutyric acid; LSD, lysergic acid diethylamide; MDMA, methylenedioxymethamphetamine; PCP, phencyclidine; SSRI, selective serotonin reuptake inhibitor.

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Household Toxins*Lindsey Nielsen, DVM, DACVECC**Veterinary Emergency and Specialty Centers of New Mexico, Albuquerque, NM, USA***Decontamination**

One of the most effective ways to limit the clinical effects of toxins on patients is to perform decontamination processes as indicated. The type of toxin, time from exposure, and type of exposure can all influence which decontamination procedures are undertaken. Decontamination techniques are discussed in detail in Chapter 127.

Common Household Toxin Exposures**Foods****Xylitol**

Xylitol is a sugar alcohol used as a sugar substitute or sweetener in sugar-free products. It is most commonly found in chewing gum, but can also be found in products like baked goods or even some peanut butters. Ingestion of over 0.1 g/kg of xylitol by dogs causes a massive increase in insulin secretion, leading to a subsequent hypoglycemia for 12–48 hours following ingestion [1]. In addition to hypoglycemia, ingestion of >0.5 g/kg of xylitol will cause subsequent hepatic necrosis and fulminant liver failure anywhere from 9 to 72 hours following ingestion [2].

Inducing emesis should be attempted for those cases presenting within a few hours of ingestion of the product, although most commonly the xylitol is rapidly absorbed within 30 minutes of ingestion (see Chapter 127) [3]. Following decontamination attempts, most dogs should be hospitalized for glucose monitoring with dextrose supplementation when indicated. For those exposed to >0.5 g/kg, administration of liver protectants (e.g. SaME, Denosyl) and antioxidants should be initiated. Xylitol toxicity has not been described in cats.

Chocolate

Chocolate is a very common toxin exposure frequently experienced by dogs, especially around holidays when chocolate is particularly common. Chocolate is among the top five toxicities seen in veterinary hospitals according to the Pet Poison Hotline [4]. The toxic components of chocolate are methylxanthines, with caffeine and theobromine causing the most clinical signs [5]. These components can cause a range of clinical signs, worsening with increasing amounts of chocolate ingested or type of chocolate. Baker's chocolate and dark chocolate have much higher concentrations of methylxanthines compared to milk chocolate, so it is important to confirm the type of chocolate ingested. Chocolate calculators are available to help determine toxicity. "White" chocolate is not chocolate at all, so is considered non-toxic.

Initially, gastrointestinal signs such as vomiting and diarrhea can occur, but this can progress to agitation, hyperactivity, ataxia, tremors, seizures, tachycardia, arrhythmias, hypertension, hyperthermia, and even death. Clinical signs typically begin within 6 hours of ingestion and can last for up to 72 hours. Pancreatitis is also possible following chocolate ingestion due to the high fat concentration of most chocolates.

Ideally, treatment should begin with decontamination if the patient is not neurologically affected (see Chapter 127) (Figure 136.1). This should be followed with repeated doses of activated charcoal, intravenous fluid management to enhance urinary excretion of the toxic metabolites, and close monitoring of the cardiac and neurological status of the patient. When abnormalities arise, most arrhythmias can be treated with beta-blockers, such as metoprolol if available, propranolol or esmolol. Propranolol may delay excretion of methylxanthines which is why metoprolol is preferred if available [6]. Most seizures can be controlled with diazepam, although



Figure 136.1 A dog being decontaminated after eating an entire bag of Halloween candy.

seizures are quite uncommon. Fortunately, most chocolate toxicity is limited to gastrointestinal signs and tachycardia, and most dogs recover uneventfully, with “death by chocolate” being very rare without co-morbidities or massive ingestion. Cats do not appear to like chocolate, so chocolate toxicity is unheard of in this species.

Onions and Garlic

Members of the *Allium* genus, such as onions, leeks, chives and garlic, have sulfur-containing compounds that when ingested in large amounts can cause red blood cell hemolysis, Heinz body formation, and methemoglobinemia [7]. Gastrointestinal signs such as vomiting and diarrhea are common, as are signs of weakness, tachypnea, and tachycardia from the anemia. Decontamination is recommended, followed by monitoring for development of anemia and symptomatic therapy for any gastrointestinal signs that develop, which may not occur for up to 5 days [8]. It should be noted that a large quantity of onions is required for clinical disease to develop. Transfusions may be required. Also, due to the differences between feline and canine hemoglobin, cats may be more sensitive to the toxic effects of *Allium* species than dogs [8]. Cat exposure has been particularly linked to human baby foods, which may have garlic or onion powder added. Dogs are most frequently exposed by ingestion of fried onions or onions mixed with meat products.

Bread Dough

Unrisen or raw bread dough can be perceived as a tasty treat by most dogs and even rarely by some cats, but when ingested, the yeast in the dough will begin to grow and ferment within the stomach. The rapid expansion of the yeast can cause abdominal distension and, more rarely, respiratory and vascular decompensation. Emesis induction is usually unsuccessful, and therefore decontamination is often achieved with gastric lavage. If the yeast ferments, ethanol will be produced and this can result in signs of alcohol intoxication, including ataxia and disorientation, with severe cases developing profound CNS depression that could require aggressive supportive care, including mechanical ventilation [9]. Recovery is usually uncomplicated and signs are resolved within 24 hours.

Outdoor Products

Many products people use in their yards for pest management can be toxic to animals. Rodenticides are a common culprit, and more information on their ingestion can be found in Chapter 130. Other common pest control products can pose a toxic threat to pets as well.

Metaldehyde

Metaldehyde is the active ingredient in snail and slug control products that can cause severe neurological derangements in animals. Most animals will develop severe muscle tremors and hyperesthesia as well as associated tachycardia and hyperthermia. Some patients may go on to develop depression, intractable seizures, respiratory failure, and death. Emesis can be attempted within 30 minutes following exposure, although the toxin is rapidly metabolized, and many patients are already showing clinical signs on presentation to the clinic [10]. Decontamination can be attempted via gastric lavage, followed by repeated doses of activated charcoal. Additional treatment is symptomatic, including diazepam for seizures, methocarbamol for tremors, and anesthesia with gas inhalants or propofol for those most severely affected until the metaldehyde is metabolized [11]. Full recovery in severely affected patients can take up to 3 days, though most patients are recovered within 24 hours.

Mulch and Fertilizer Products

Luckily, the majority of these products are not appetizing, but some can be and can contain components that can cause gastrointestinal upset and other problems. Many fertilizers contain nitrogen, phosphorus, and potassium, but some can also contain more harmful products like insecticides, cocoa, iron, or zinc [12]. Because of the wide variation in components of each product, having the client bring the packaging material or contacting poison control in each individual exposure may be helpful. Most

will only cause mild gastrointestinal upset and ingestion can be treated symptomatically.

Strychnine

Strychnine is a poison historically found in various gopher baits and rodenticides used to kill ground squirrels. Its use is rare today, as it has been replaced by other pesticides. This is a highly potent poison and ingestion of only a few tablespoons can be lethal in both dogs and cats. Strychnine blocks the inhibitory actions of glycine in the central nervous system. This causes a disinhibition of motor neurons and interneurons, leading to exaggerated and overactive neuronal activity causing muscle spasms, hyperexcitability, seizures, hyperthermia, tetanus, and eventual death from respiratory paralysis [13]. The poison is rapidly absorbed and clinical signs can be seen within 15 minutes of exposure, making emesis induction difficult and often ineffective [14]. The remainder of treatments are geared towards supportive care and symptomatic treatment with diazepam, methocarbamol, and IV fluid therapy. For those severely affected, anesthesia and mechanical ventilation may be required until the toxin is cleared from the body, which can take up to 72 hours.

Cleaning Products

Most cleaning products are aversive and do not taste palatable, so ingestions are rare, but can be severe when they do occur. Additionally, exposure to the skin as well as eyes and mucosal surfaces can also pose threats to pets.

Soaps and Detergents

These products can be found in most of the hand soaps, body washes, and shampoos used by humans, as well as many cleaning products such as laundry or dishwashing detergents. When ingested, they can cause mild gastrointestinal signs including hypersalivation, vomiting, or diarrhea, or irritation of the skin or eyes [15]. Most of these signs are self-limiting but may require symptomatic therapy. If a patient has an ocular exposure, flushing the eye with sterile saline for 5 minutes is recommended (see Chapter 127).

Alcohols

Alcohols, including those found in beverages, medications, bread dough, windshield cleaner, and rubbing alcohol, are all rapidly absorbed through the gastrointestinal, inhalation, and dermal routes. The rapid absorption makes decontamination difficult, and supportive treatment of clinical signs that occur is often the treatment of choice. Patients can develop vomiting, ataxia, hypothermia, hypoglycemia, acidosis, respiratory depression, coma, and death [16]. Hemodialysis is an option to more rapidly eliminate the ethanol from those that have a severe toxicosis (Chapter 129) [17].

Acids

Many household cleaning products contain acids, which can be extremely toxic for pets both locally and systemically. The acids will cause local coagulative tissue necrosis and pain in those areas where exposed [14]. When exposed orally, this will cause pain, dysphagia, vomiting, and ulceration of the oral cavity and esophagus. Dermal exposure will cause irritation or ulceration. Ocular exposure can be severe, causing corneal ulceration or melting.

Acids are some of the few toxins where decontamination is not advocated due to the risk of worsening corrosive injury. Initially, administering water or milk to the patient may dilute the product and limit the effects of exposure. Following this, treatment is mostly symptomatic and geared towards pain management. For dermal or ocular exposures, flushing with copious amounts of water for over 15 minutes is recommended (see Chapter 127).

Alkalis

Alkalis are also found in many household cleaning products, including some cationic detergents, and many plumbing products. These agents will cause severe corrosive injury without associated pain, which is why clinical signs may not immediately be apparent. Clinical signs that do develop are often related to the underlying mucosal damage caused to the gastrointestinal tract, which can be severe enough to cause perforation [18]. Emesis should not be induced and charcoal is not effective in these patients. Supportive care and investigation for the extent of esophageal and gastrointestinal damage that has occurred should take place.

Foreign Objects

Many owners have experienced the stress that comes with a playful and inquisitive puppy ingesting a foreign object, which often poses more of a threat by potentially causing a gastrointestinal obstruction. However, some common household objects can also pose a toxic threat to the pets that ingest them.

Pennies

Pennies minted in the United States after 1982 are made primarily of zinc and coated with a thin layer of copper [19]. After a penny is ingested by an animal, the gastric juices will cause zinc to leach out of the coin and enter the systemic circulation, where it will cause zinc toxicity in the form of intravascular hemolysis [20]. Dogs with evidence of intravascular hemolysis should be radiographed to exclude penny ingestion.

Treatment includes removal of the penny so that the patient is no longer being exposed to zinc, which can be achieved by emesis induction, endoscopic removal or

surgical removal. Following removal of the coin, treatment for the subsequent anemia with blood products and supportive care is advocated. Pancreatitis has been reported following zinc toxicity.

Batteries

Ingestion of batteries can pose several threats to pets. When chewed, they can release their contents, which are often alkaline in nature, causing alkali burns. When swallowed whole, they can cause foreign body obstructions that commonly require surgical intervention to remove.

Treatment of battery exposures often involves first treating for the possibility of alkali exposure by giving the patient water to delay the chance of internal corrosive damage to the gastrointestinal tract [21]. Feeding a bulky diet may help the battery pass through the intestinal tract without causing damage, but if there is any question or concern about the object not passing, surgical or endoscopic removal should be undertaken.

Magnets

In addition to potentially causing a foreign body obstruction, when multiple magnets are ingested by a pet they can attract each other from differing segments of bowel and can lead to pressure necrosis of the intestinal tract and subsequent septic peritonitis [22]. Magnet ingestion should be taken seriously, and if multiple magnets have been ingested, surgical intervention should be considered.

Conclusion

There are hundreds of potential toxic threats that a pet may be exposed to in the household. A basic understanding of decontamination and the results of exposure to the more commonly encountered household toxins can help the emergency clinician to provide the best care for the poisoned pet.

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J. Skin and Soft Tissue Disease

Life-Threatening Dermatological Emergencies

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Dermatological Emergencies

Dermatological disorders are a leading cause for pet owners to seek veterinary advice. While the incidence and prevalence of all dermatological diseases are unknown, recent surveys of dogs and cats indicate that clinical signs of alopecia, dermatitis, and otitis are in the top five reasons that prompt a visit to the veterinarian [1]. Dermatological disorders were the third most common problem at primary care practices in England, with a prevalence of 10.4% [2]. While many emergency veterinarians and specialists in emergency and critical care would not consider pruritus or alopecia as an emergency, some pet owners do. Pet owners may also visit the emergency service because of convenience which is common in human medicine [3,4]. Secondary pyoderma and dermatitis can cause systemic inflammatory response syndrome and associated organ dysfunction [5].

Methicillin-Resistant Staphylococcal Infections (MRSI)

The rise of bacterial resistance has been a major issue in both human and veterinary medicine for decades [6,7]. Staphylococcal infections have become notorious for their resistance to multiple antibiotics (MRSA), cause of nosocomial infections, and zoonotic ability. MRSA can be caused by a variety of bacteria; most noted in humans is *Staphylococcus aureus*, while dogs and cats are typically associated with *Staphylococcus pseudointermedius* (MRSP) and *Staphylococcus schleiferi* (MRSS) [8,9]. MRSI are found in the environment and on the surfaces of furniture, and are nasal cavity commensals in healthy persons (MRSA: 29–38%), healthy dogs (MRSP: 1.5–2%) and cats (MRSP: 4%) [10–12]. Humans are typically considered the source of a MRSA infection in pets and pets can serve as a reservoir for people [13].

Commensal MRSIs were noted in 14.5% of oral swabs of healthy, adult cats [14].

The antibiotic resistance of MRSIs is achieved through bacterial acquisition of the *mecA* gene which encodes a penicillin-binding protein (PBP2a) that has much lower binding affinity for beta-lactams. While most dogs and cats with MRSI pyodermas do not become systemically ill, the infections are difficult to treat since other classes of antibiotics are also rendered ineffective [15]. Methicillin-resistant *Staphylococcus pseudointermedius* growth was still present in 62% of cultures from dogs treated for pyoderma and 28.3% of dogs developed MRSP who were previously MRSP culture negative after treatment [16]. In emergency facilities, exposure to MRSIs may be more likely due to high caseload, increased numbers of patients with immunosuppression, and improper disinfection of the facility between cases.

Clinical signs of MRSIs include skin abscess, otitis externa, wounds, and pyoderma which are all common emergencies; 25% of bacterial dermatitis cultures were positive for MRSI in one study of 435 dogs [17]. Most cases of MRSI-associated dermatopathies consist of localized lesions characterized by papules, erosions, crusts, and exudates (Figure 137.1). However, there have been reports of necrotizing fasciitis with associated symptoms of sepsis (tachypnea, fever, depression), erythema multiforme (Figure 137.2), and non-healing abscesses in cats [18–20].

Differential diagnoses include superficial non-methicillin-resistant pyoderma, demodicosis, cutaneous fungal infection (*Malessezia*), cutaneous drug eruption, vasculitis, and pemphigus foliaceus. It is important to realize that MRSIs can look like almost anything which causes dermatitis.

Definitive diagnosis is based on culture and sensitivity. Since methicillin is no longer a commonly used antibiotic, oxacillin is used for sensitivity testing. Additional methods of diagnosis include PCR (gold standard) and



Figure 137.1 MRSA infection in a dog. Reproduced with permission of Kimberly Coyner.

latex agglutination testing to detect PBP2a. Disk diffusion combined with latex agglutination had the best specificity and sensitivity for MRSA [21]. If a *Staphylococcus* sp. is confirmed resistant to oxacillin, it is typically resistant to all beta-lactams. One should be suspicious of MRSA if a patient with a non-healing wound, folliculitis or abscess presents after completing a course of antibiotics, especially beta-lactams. Other risk factors of MRSA include use of fluoroquinolones, intravenous catheterization, having more than 10 veterinary staff employed, and postsurgery site infection [22,23].

Successful treatment of MRSA requires ruling out other causes of dermatitis and effective antimicrobial medication. The most commonly prescribed antibiotics for MRSP are chlormaphenicol and doxycycline. Other antibiotics which may be effective include aminoglycosides, minocycline, rifampin, and fluoroquinolones. The use of fluoroquinolones is not typically recommended for a number of reasons. Most importantly, these antimicrobials have the ability to create high-level MRSA mutants which are resistant to

many classes of antibiotics [24]. If fluoroquinolones are used, they should be limited to veterinary-labeled products because of their bioavailability and the fact that non-veterinary forms may not be well absorbed [25,26]. It is paramount that antibiotic selection is determined based on sensitivity testing. Parenteral antibiotics used in human medicine include the streptogramins (daptomycin, tigecycline, quinupristin, dal-fopristin) which are administered intravenously. Use of these antimicrobials in veterinary medicine is not well documented [27].

Most infections will resolve within a month to 8 weeks of systemic antibiotic use. Like other chronic infections (i.e. fungal), antimicrobial treatment should extend for 2–3 weeks after clinical signs resolve. The time for the pyoderma to resolve is more likely to be due to the chronic nature of the dermatopathy, not the virulence of the MRSA [28].

Burns

Cutaneous thermal injuries or burns are not commonly reported in small animals [29]. The incidence and prevalence of burn injuries were not noted in the veterinary literature. Common causes of burns affecting dogs and cats include electric heating pads, open flames, mufflers of motor vehicles, hot water bottles, improperly grounded electrosurgical units, animal dryers, boiling liquids, sun exposure, and even garden hoses lying in the sun that contain residual water [30–33]. Other types of burns include chemical and radiation exposure which will not be discussed in this section. Due to haired skin, thermal injuries are sometimes overlooked. Heating pad and hot water bottle thermal injuries can take time to declare. Most importantly, other injuries to the respiratory system, cardiovascular system, kidneys, and neurological system may accompany thermal injuries, especially in cases of smoke exposure and carbon monoxide toxicity [34].

Cutaneous burns are classified based on surface area affected and depth of affected tissue. The “Rule of Nines” is a classification system used in human medicine, and sometimes in veterinary medicine, which describes percentage of total body surface area (TBSA) burned. In burned persons, the body is divided into affected zones with a corresponding percentage of surface area. Burns to the head, each forelimb and neck comprise 9% of TBSA. Burns affecting the dorsal trunk, ventral trunk and each hindlimb account for 18% of TBSA [35]. Local burns are those that injure <20% of TBSA and typically do not cause SIRS. Severe burn injury affects >20–30% of TBSA and usually leads to systemic derangements in homeostasis, causing SIRS (see Chapter 159).



Figure 137.2 MRSA and secondary EM. Reproduced with permission of Kimberly Coyner.



Figure 137.3 Five-day-old, third-degree burn injury post drain placement. Reproduced with permission of Kimberly Coyner.

Depth of burned tissue is classified as “degree” of injury. First-degree burns or superficial burns involve the epidermis, causing hyperemia and pain. Second-degree or partial-thickness burns affect the epidermis and upper portions of the dermis. These deeper burns are characterized by pain and blistering with the hair remaining intact. Third-degree or full-thickness burns encompass the epidermis and entire dermis (Figure 137.3). Fourth-degree burns have even deeper tissue injury, with not only the epidermis and dermis affected, but also extension to muscle, tendon and bone [36]. Neither method of burn classification has been validated in small animals, but they are generally accepted ways of characterizing burns.

Patients with severe burns to the muzzle, nose, and eyes may have smoke inhalation. Visualization of blisters in those areas, burn-induced alopecia, soot, black-tinged sputum, singed whiskers and erythema with blisters in the oropharynx are indicators of smoke inhalation. Confirmation using co-oximetry or comparison of pulse oximetry to arterial blood gas, and elevated central venous oxygen partial pressure can support the diagnosis.

Associated respiratory disorders include hypoventilation, bronchospasm, obstruction, and ARDS [37]. Cardiac arrhythmias and hypotension can result from carbon monoxide and cyanide toxicosis. Acute kidney injury may ensue from hypotension secondary to cardiovascular derangements and hypovolemia associated with cutaneous burns fluid loss (see Chapter 94). Hypoxia and cyanide will affect the neurological system, causing altered mentation such as stupor and coma, tremors, ataxia, and seizures [38].

The local response of the skin to thermal injury is characterized by cytokine activation by immunocytes, ischemia, and loss of cell membrane integrity. Increased

cell membrane permeability, caused by cytoskeleton disruption and loss of hydrostatic forces, is the most important reason for tissue necrosis. Epidermal and deeper cells closest to the heat source undergo coagulation and vascular thrombosis, suffering the most damage. Surrounding tissues are affected by blood stasis and edema from capillary leak syndrome. These factors and hypoperfusion result in ischemia; however, these tissues may be salvageable [39].

Immediately after a severe burn injury, systemic inflammation develops and remains in place for months, causing ARDS, capillary leak, myocardial dysfunction, and poor perfusion (see Chapter 159). Edema from hypoalbuminemia and vasoactive substances such as thromboxane along with inducible nitric oxide (iNOS) worsen hypoxia. Cytokines and other inflammatory proteins produce marked hyperalgesia of the injury site. Levels of inflammatory mediators (interleukin-1 and -6, tumor necrosis factor alpha) are used as markers of burn severity in humans. High levels are associated with severe pain, hypermetabolism, and tissue catabolism [40]. Hyperglycemia and insulin resistance have been documented in human burn injury. Persistent, significant hyperglycemia is associated with bacterial and fungal sepsis with higher mortality rates in burned persons. Tight glycemic control with insulin can blunt the proinflammatory response but can also cause hypoglycemia and increased mortality [41,42].

Treatment of burn injuries is three-fold. First, life-threatening complications such as carbon monoxide poisoning, cyanide toxicity, ARDS, pain, and hypovolemia must be assessed for and treated with oxygen, mechanical ventilation (if indicated), analgesics, and judicious intravenous fluids (see Chapter 139). Monitoring of central venous pressure trends, especially in patients with ARDS, can assist in guiding fluid rates. Patients in shock and/or with SIRS need intravenous fluids (crystalloid 25 mL/kg over 15 min for dogs; 15 mL/kg over 15 min in cats then reassess vital signs and blood pressure) for optimized oxygen delivery (see Chapter 167) [43]. Severe burn patients will lose a significant amount of protein, water, and electrolytes from their wounds. These patients will have higher than maintenance (3–5 mL/kg/h) requirement of isotonic crystalloid [44]. Colloids (Vetstarch®, Hetastarch®) are alternatives to isotonic crystalloids for patients with hypoalbuminemia and capillary leak syndrome (see Chapter 168). However, colloids may also extravasate, worsening interstitial edema. Colloids have come under scrutiny for worsening and causing acute kidney in critically ill people but these complications have not been reported in small animals [45].

Oncotic pressure measurement can help guide dosage of intravenous colloids, which are generally provided at

rates of 10–20 mL/kg/day [46]. Use of different isotonic crystalloids with different sodium content, correction of hypokalemia with added potassium chloride, and supplementation of magnesium (MgSO_4 0.1–0.15 mEq/kg loading, 0.75–1 mEq/kg/day replacement) are based on serial monitoring of electrolytes (see Chapters 110 and 173) [47].

Monitoring of complications such as hypotension, hypoxia, and arrhythmias should be undertaken (see Chapter 53) [48]. Laboratory and cage-side testing of cell count, biochemical profile, acid–base balance, coagulation parameters, D-dimer or fibrin degradation products, lactate, ionized calcium, urine output, and central venous pressure should be performed. The burn itself should be immediately cooled with water or isotonic saline for at least 10 minutes. Ice water and ice packs must not be used as they will cause worsening vasoconstriction and necrosis [49]. Debridement of necrotic tissue and cleaning of the wound with adequate systemic and local analgesia is performed once vital signs are normalized and fluid therapy is under way (see Chapter 166).

Analgesia, both systemic and local, is important for adequate wound care and limiting the stress response (see Chapter 193). Opioids that are pure mu-agonists such as fentanyl (3–10 $\mu\text{g/kg/h}$), morphine (0.5–1 mg/kg SC q4h), and hydromorphone (0.025 mg/kg/min) are all good choices. Addition of lidocaine (1–3 mL/kg/h), ketamine (2–5 $\mu\text{g/kg/min}$), and gabapentin (7–10 mg/kg PO) to the opiate will provide neuroleptanalgesia, and decrease the “wind-up” phenomenon caused by NMDA stimulation.

Protecting the wound from infection, removal of necrotic tissue and providing adequate moisture are crucial for proper healing. Strict aseptic technique must be followed during debridement, cleaning, and bandaging of burns. Wounds should be assessed, cleaned, undergo debridement and bebandaged daily. Topical antiseptic solutions such as 0.25% chlorhexidine or dilute povidone-iodine are used to clean the wound and flush away dead skin. After cleaning and debriding the wound, topical silver sulfadiazine or polysporin ointment is applied, followed by a three-layer bandage. Wound closure should not be attempted for a minimum of 3–7 days so that the full extent of the injury can be ascertained [48]. Systemic antibiotics are reserved for cases with documented wound infection, sepsis, pneumonia, and leukopenia or other immunosuppression. In general, potentiated penicillins (ampicillin 15–22 mg/kg IV q6–8h; amoxicillin-sulbactam 13.75–20 mg/kg IV q8–12h) and first-generation cephalosporins (cefazolin 22 mg/kg IV q6–8h) are used if one of the aforementioned conditions is complicating the burn-injured patient (see Chapter 200).

Dogs and cats with severe burns of high degree will likely need supplemental nutrition because of their hypermetabolic state and loss of protein. Enteral feeding

using tubes placed in non-burned skin with high caloric diets such as Clinicare and critical care diets (A/D by Hills and Recovery by Royal Canin) are prescribed at resting energy rate ($70 \times [\text{body weight (kg)}]^{0.75} \pm \text{illness factor multiplier}$).

Frostbite

Frostbite is a term used to describe injury to tissues exposed to cold [50]. There are very few reports of cold-induced injuries affecting small animals and the incidence is likely much lower than burn injury. One brief description of chilblain syndrome (an acraly located eruption that occurs with exposure to cold) has been reported in service dogs, housed in unheated outdoor kennels, experiencing pain, erythema, and swelling of tail tips [51]. Most other references found were experimentally induced cold injury to animals or anecdotal reports on the Veterinary Information Network.

Dogs' extremities are well adapted to cold temperatures, characterized by arteriovenous anastomoses and vein-artery-vein triads which act as countercurrent heat exchangers [52]. Tissue injury is caused by formation of ice crystals, resulting in mild forms of erythema to full-thickness epidermal necrosis, similar to burns. Frostbite does have some important differences from burn injury, in that inflammation is less accentuated but persists longer and the extracellular matrix is rarely destroyed [53]. In humans, frostbite is separated into two major categories of superficial and deep, with four different degrees of severity. Superficial frostbite (types I and II) have a clinical appearance of redness, swelling, and numbness which progress to blisters, erosions, and loss of sensation. Deep frostbite (types III and IV) lesions are noted as hemorrhagic blisters, black/necrotic and edematous with no sensation to the affected areas [54].

During marked reduction in temperature, exposed tissues initially suffer vasoconstriction, with the most severe constriction occurring at 15 °C. If the temperature continues to drop and reaches 10 °C, the vasoconstriction is interrupted by vasodilation in an attempt to prevent complete loss of perfusion. This is known as the “hunting response.” As the cold temperature persists, endothelial damage with formation of microthrombi follows. Edema formation, mediated by mast cell histamine release, further disrupts oxygenation of the tissues [55].

Similar to burns, small animals with frostbite should be assessed for concurrent injuries such as fractures and hemorrhage. If hypothermia (body temperature < 35 °C) is present, a number of systemic changes occur that can affect survival. Hypothermia results in catecholamine release which causes vasoconstriction, tachycardia, and

hypertension (see Chapter 148). Severe hypothermia (body temperature $<30^{\circ}\text{C}$) causes arrhythmias such as atrial fibrillation and refractory ventricular arrhythmias [56]. Additionally, delayed drug metabolism, impaired platelet function, immunosuppression, and sludging of blood occur [57].

Treatment depends on the severity of injury, degree of hypothermia, if present, and time point of the injury. Initially, the patient should be placed in a protected environment, not allowing re-exposure to cold. Alternation of freezing and thawing worsens the injury, causing severe thrombosis and ischemia. Rapid rewarming of an affected area is not recommended (unless the patient is hypothermic) due to reperfusion injury. Slow rewarming of the affected area should be performed using warm air current of $22\text{--}27^{\circ}\text{C}$ [58]. In cases of acute frostbite, affected areas may be bathed for 15–30 minutes in water at a temperature of $37\text{--}39^{\circ}\text{C}$. Rapid rewarming for acute frostbite resulted in better clinical outcomes in dogs [59]. Wound management involves protecting deeper, exposed tissues from infection and removal of necrotic tissue. Analgesia, as discussed in the burn section, must be adequate and used judiciously.

Vasodilators, thromboprophylaxis, thrombolytics, hyperbaric oxygen, and NSAIDs have been studied experimentally with animal models and clinically in humans with frostbite. Vasodilators (prostaglandin E1) combined with slow rewarming of affected areas were noted to limit the degree of tissue damage in animal models [60]. Thrombolysis with tissue plasminogen activator within

24 hours of injury helped preserve tissue and lessened amputation rates in people (see Chapter 71) [61].

Drug Eruption

Dermal drug eruptions or cutaneous drug eruptions (CDE) are idiosyncratic reactions to any medication (topical, parenteral, or enteral). CDEs are a very important issue in human medicine, affecting 7% of the general population and 10–15% of hospitalized persons. Emergency room visits by persons affected by drug allergy made up 33.5% in one study [62]. Dermatopathies associated with drug reactions cost an estimated \$136 billion annually [63].

In veterinary medicine, older reports noted an incidence range of 1.6% of all cats and 2% of all dogs presenting to a university hospital [64,65]. It is likely that the incidence is higher, since reporting of CDE is not mandatory. Compounding this is the fact that immune-mediated dermatopathies like toxic epidermal necrolysis, pemphigus foliaceus, and erythema multiforme can develop secondary to drug exposure [66]. Both immune-mediated hypersensitivity reactions of all types (I–IV) (Table 137.1) and non-immunological mechanisms such as altered arachidonic acid metabolism, complement activation and “danger” particles like cytokines and cell debris are attributed to the pathogenesis of CDE. Another means of immune activation is thought to occur through haptens and prohapens

Table 137.1 Hypersensitivity reactions.

Hypersensitivity reaction	Common cutaneous lesions	Common lesion location	Immunoglobulin, cytokine and immunocyte activity	Pathophysiology	Associated systemic effects
Type I	Angioedema, urticaria, erythema	Trunk Muzzle Periocular	IgE-antigen complex binds to mast cells and basophils	Degranulation Release of histamine, leukotrienes, kinins, eosinophilic chemotactic factor	Anaphylactic shock Bronchoconstriction Upper airway obstruction
Type II	Vesicles, bullae, erosions, mucocutaneous ulcers	Extremities and mucocutaneous junction	IgM and IgG cytotoxicity	Antigen-antibody binding results in direct cytotoxicity and complement activation	Immune-mediated anemia Immune-mediated thrombocytopenia
Type III	Urticaria, ulceration, alopecia, pitting or firm edema, hemorrhagic bullae, wheals, papules	Pinnae, footpads, mucocutaneous junction	IgG	Immune complexes deposit in endothelium of vessels	Systemic lupus erythematosus Glomerulonephritis
Type IV	Vesicles, bullae, papules, plaques and erythematous macules	Trunk, axilla, inguinal region, foot pads, pinnae	T-cell, interleukins, tumor necrosis factor-alpha	Antigens bound to T-cells resulting in tissue necrosis and activation of macrophages	

which are small drug molecules bound to proteins. These complexes invoke major histocompatibility complex to stimulate T-cell-mediated self-injury [66].

Many classes of drugs are known to cause CDE, with antibiotics representing a majority of reactions in dogs and cats. Sulfonamides, penicillins, cephalosporins, and topical antiparasitic agents are just a few of the many drugs associated with CDE. Table 137.2 lists the clinical findings and associated medications of cutaneous drug reactions and Figures 137.4, 137.5 and 137.6 are of a dog with CDE from cephalexin. Differential diagnoses include primary immune-mediated dermatopathies such as discoid lupus erythematosus, pemphigus complex (pemphigus foliaceus, pemphigus vulgaris, pemphigus erythematosus, bullous pemphigoid), vasculitis, demodicosis, panniculitis, and pyoderma. CDE can appear as almost any dermatopathy and other differential diagnoses are based on specifics of the lesions [67].

Cutaneous drug eruptions should be considered in dogs and cats with commonly described lesions



Figure 137.4 Cephalexin reaction 1. Reproduced with permission of Kimberly Coyner.

(mucocutaneous, erosive, ulcerative, vesicular, and necrotic), a history of medication use, vaccines given and topical treatments performed. Reactions to both

Table 137.2 Reactions, associated conditions and medications implicated in cutaneous drug reactions.

Reaction and associated conditions	Medications
Pruritus	Antibiotics
Facial excoriations	NSAIDs
	Opiates
	Methimazole
Sweet's syndrome: neutrophilic dermatitis	NSAIDs: carprofen, firocoxib
Erythematous plaques and nodules	
Systemic signs: pyrexia, thrombocytopenia, vasculitis, pain	
Lupus-like reactions	Sulfonamides
Erythema, depigmentation, crusts, erosions, ulcers	Hydralazine
Common locations: foot pads, pinnae, mucocutaneous junction	Vaccines
Pemphigus-like reactions	Trimethoprim-sulfamethoxypyridazine
Pemphigus foliaceus:	Cephalexin
Papules, crusts, alopecia,	Amoxicillin-clavulanic acid
Common locations: periocular, mucocutaneous, foot pads, muzzle and nose	Oxytetracycline
Pemphigus vulgaris:	Pencillin
Vesicles, bullae, erosions	Promeris (amitraz and metaflumizone)
Common locations: axilla, inguinal region, mucocutaneous, oral cavity	
Fixed drug eruption	Diethylcarbamazine
Erythema (well-circumscribed), edema, bullae, ulceration	5-Fluorocytosine
	Levothyroxine
	Cephalexin
	Amoxicillin-clavulanic acid

NSAID, non-steroidal anti-inflammatory drug.



Figure 137.5 Cephalaxin reaction 2. Reproduced with permission of Kimberly Coyner.

oral and topical medications can take days to months to develop so a thorough history of all medications must be recorded. Most cases will present 1–3 weeks after starting the medication or topical treatment. A strong suspicion of CDE is based on history and physical exam findings [67]. Additional diagnostic testing, especially in patients with systemic signs such as fever, tachycardia and tachypnea, should include complete cell count, minimum database, acid–base, lactate level, and urinalysis. Vasculitis, EM, and TEN are associated with SIRS and many secondary immune-mediated drug reactions can result in thrombocytopenia, anemia, nephritis, and hepatopathy.

Unfortunately, definitive diagnosis is only accomplished by rechallenge with the suspected medication; however, this can be dangerous and/or deadly [68]. Aspiration with cytology and biopsy with histopathology will provide diagnoses of erythema multiforme, toxic



Figure 137.6 Cephalaxin reaction 3. Reproduced with permission of Kimberly Coyner.

epidermal necrolysis, and pemphigus. In many cases, cytology and dermohistopathology are non-specific, but will assist in ruling out other differentials. Antibody testing to measure IgE reactions associated with type I immune hypersensitivity along with antidrug IgG and antitissue antibodies may be supportive of CDE.

Patients with systemic signs will need intensive monitoring and treatment. Intravenous fluid therapy to correct dehydration and support cardiac output should be instituted with isotonic crystalloids and/or colloids (see Chapters 167, 168, and 169). Colloids may be indicated for patients with hypoproteinemia and low colloidal oncotic pressure. Analgesia, nutritional support, vital sign monitoring, urine output, organ function, and cell counts should be provided and monitored as for any critically ill small animal. Criticalists should pay close attention to electrolyte, acid–base balance, and worsening lesions in patients suspected to have EM, TEN, and vasculitis. Protection against secondary infection and exposure should be accomplished by topical wound flushing (dilute chlorhexidine [14]) and bandage application. Soiled bandages or bandages with “strike-through” of wound effusion should be changed as necessary while providing adequate analgesia.

Definitive therapy is to discontinue the offending medication, cleanse any remaining topical product, and supportive care. Use of anti-inflammatory medications such as glucocorticoids is controversial [66]. Small animals with angioedema and pruritus may benefit from glucocorticoid administration, especially in the late phase of anaphylaxis. Long-term treatment of drug-induced pemphigus is often necessary. Different immunosuppressive agents such as cyclosporine and azathioprine are used in cases of EM and TEN whose dosages are mentioned in the respective sections of this chapter. Human IV immunoglobulins have been used in cases of drug-resistant pemphigus and CDE [69]. When using immunosuppressive medications, thoroughly monitor for nosocomial infection, MRSA, and sepsis.

Prognosis is good for most cases, except those with multiple organ dysfunction and extensive necrosis associated with TEN.

Vasculitis

Vasculitis is defined as inflammation of the blood vessels, caused by an abnormal immune response [70]. It is an uncommon disorder, noted in only 0.4% of cats seen for dermatopathies [3]. Vasculitis may be associated with infectious agents such as babesiosis, Rocky Mountain spotted fever, histoplasmosis, and feline infectious peritonitis, and with non-infectious disease such as lymphoma [71]. Vessel inflammation may be localized to an



Figure 137.7 Vasculitis ulcerative lesion. Reproduced with permission of Kimberly Coyner.

internal organ, disseminated systemically or only affect areas of the skin [72]. Most cases of cutaneous vasculitis in small animals are idiopathic (approximately 50%) and others have been associated with vaccination, food allergy, and medications. Implicated medications include those in Table 137.2 which can cause CDE. Vasculitis has been reported secondarily to human serum albumin, carbamazepine, and fenbendazole [73,74].

Types I, II, and III hypersensitivity reactions are the pathogenic processes involved with vasculitis. Type I reactions are believed to be important initially, but are not likely to be the major pathogenic process [70]. Complement activation and neutrophil degranulation during type II reactions result in endothelial necrosis, interstitial edema, and altered blood flow. Immune-antibody complexes associated with type III reactions occlude blood vessels, attract activated leukocytes which release



Figure 137.9 Vasculitis affecting foot pads. Reproduced with permission of Kimberly Coyner.

cytokines that stimulate more inflammation and formation of reactive oxygen species. Vessel damage from any hypersensitivity process causes extravasation of fluid and blood, leading to tissue ischemia [75].

Clinical findings in small animals with cutaneous vasculitis may be isolated to the skin or be associated with systemic signs. Skin lesions include urticaria, ulcers, alopecia, edema that is pitting or firm, hemorrhagic bullae, wheals, and papules (Figures 137.7 and 137.8). Many lesions will be associated with pitting edema so palpation and testing for blanching with pressure are important during physical examination [70]. Ischemic changes of necrosis and ulcers commonly affect the extremities, pinna tips, nasal mucosa, footpads, and oral mucosa [67] (Figures 137.9 and 137.10). Dogs and cats with systemic signs of vasculitis are commonly painful. The pain is diffuse and most severe during the initial phase of the



Figure 137.8 Vasculitis erosive and edematous lesions. Reproduced with permission of Kimberly Coyner.



Figure 137.10 Vasculitis affecting pinna. Reproduced with permission of Kimberly Coyner.

disease. Fever, anorexia, neuropathy, polyarthropathy, gastroenteritis, polyuria, and lethargy are other systemic signs that can accompany the cutaneous signs [70]. History of oral medication use, vaccines, topical product application, food sensitivities, and ectoparasites such as ticks should be thoroughly investigated.

Diagnosis of vasculitis is accomplished by histopathological examination of biopsied tissue. Histological classification differentiates cutaneous vasculitis as leukocytoclastic, characterized by nuclear pyknosis and karyorrhexis, and non-leukocytoclastic. The dominant immunocytes are noted, with neutrophilic infiltrate being found in the majority of cases [76]. Differential diagnoses include diseases that can cause DIC such as neoplasia, sepsis, cold agglutinin disease, autoimmune disorders, infectious disease associated with vasculitis, neoplasia such as cutaneous lymphoma, EM, and TEN [77]. A complete blood count, biochemical profile, urinalysis, coagulation panel, serology or PCR for infectious diseases should be performed in cases where vasculitis is suspected. Dogs and cats with critical illness and extensive dermal lesions should also have vital signs, acid–base, ionized calcium, magnesium, and fluid balance (CVP, body weight, and urine output) monitored as needed.

Treatment entails a specific plan for the individual based on clinical findings, laboratory data, severity of disease, and underlying cause. Current medications associated with CDE and vasculitis should be stopped. Lesions should be clipped, gently cleaned with antiseptic solution and their extent marked to note any progression.

Immunomodulation is required in most cases of idiopathic vasculitis and even in some neoplastic, food-allergic and infectious cases. Glucocorticoids are used initially, especially in cases of disease progression, at lower doses of 0.5–1 mg/kg of prednisone. Lower dosages are less likely to have side-effects of delayed wound healing, infection, and sepsis [70]. Other immunomodulating drugs that can be considered, especially in patients that cannot tolerate glucocorticoids or those with treatment failure, include cyclosporine, azathioprine (1–2 mg/kg), and chlorambucil (0.1–0.2 mg/kg EOD). Doxycycline (5–10 mg/kg BID) and niacinamide (22 mg/kg q8–12h) are antibiotics which have immunomodulating effects of altering neutrophil and eosinophil chemotaxis [78]. Pentoxifylline (10–30 mg/kg PO q8–12h) is recommended for cutaneous vasculitis because of its hemorrheological properties which assist in tissue oxygenation. It requires long-term dosing and is rarely helpful as a single agent.

For patients that do not respond to immunomodulation using the aforementioned medications, sulfasalazine (25 mg/kg TID) should be considered in those cases without recent exposure to it.

Prognosis is dependent on the extent of the lesions, lesion progression, and degree of systemic involvement. Classification of vasculitis combining histological lesions and clinical presentation does not currently exist in veterinary medicine [70].

Erythema Multiforme

Erythema multiforme (EM) is a rare, immune-mediated dermatopathy. One retrospective study noted a 0.4% incidence of EM in dogs and 0.11% incidence in cats [79]. In humans, the majority of EM cases are triggered by herpesvirus and EM has five different variants, some self-limiting while others cause severe illness. Approximately 10% of human EM cases are thought to be drug induced [80].

The etiology of EM in small animals has been attributed to drug reactions in 19–59% of cases [81]. Drugs implicated include (1) antibiotics such as sulfonamides, penicillins, and cephalosporins, (2) levamisole, and (3) levothyroxine. Foods with beef and soy protein, neoplasia and infection with *Staphylococcus*, and parvovirus have been reported as triggers of EM. Approximately 23% of EM cases in small animals are idiopathic [79].

The pathogenesis of EM is not well known in small animals. In human EM, T-helper lymphocytes are involved in the immune response, mediated by cytokines such as interferon-alpha in cases of herpes viral EM and tumor necrosis factor-alpha in cases of drug reactions. One study of EM and graft-versus-host disease in dogs identified activated CD4 and T-lymphocytes but implicated cytokines remain unknown. Activated lymphocytes target keratinocytes, causing apoptotic cell death [82].

Lesions and disease of EM are classified as “EM minor” and “EM major.” EM minor lesions affect one or less mucosal surfaces and less than 50% of TBSA. EM major lesions affect at least one or more mucosal surfaces (Figure 137.11). Both forms commonly affect the trunk, axillary, and inguinal regions. Pinnae and footpads can also be affected, similar to vasculitis. Most lesions have a similar appearance to cutaneous drug eruptions such as vesicles, bullae, papules, plaques, and erythematous macules [67] (Figure 137.12). Classic “target lesions” characterized by centrally clear necrosis with surrounding erythema are most frequently noted in cases of EM major. In a few instances, EM may have a more chronic form, causing thick crusts and plaques. Recurrence of EM lesions and chronic EM in dogs is most often noted affecting face and ears, mostly without target lesions [81].

Similar to cutaneous drug reactions, the differential diagnoses for EM include vasculitis, pemphigus, TEN, demodicosis, dermatophytosis, bacterial folliculitis,



Figure 137.11 Erythema multiforme mucocutaneous lesion. Reproduced with permission of Kimberly Coyner.

and drug eruption. One of the most important aspects of diagnosis is to differentiate EM from urticaria. Small animals with edema and lesions that last less than 12 hours most likely have urticaria and not EM [82]. Target



Figure 137.12 Erythema multiforme crusts and plaques. Reproduced with permission of Kimberly Coyner.

lesions, while not pathognomonic, are commonly noted in EM cases.

Diagnosis of EM is clinicopathological and confirmation can be obtained through histopathology. Patients with EM major are likely to have systemic signs of fever, lethargy, and anorexia. Organ dysfunction, DIC, and sepsis can occur also. Unfortunately, there are no clinical criteria to diagnose EM in small animals like the algorithms used for humans. Therefore, histopathology is commonly employed to obtain a definitive diagnosis; however, histopathological lesions of EM are very similar to TEN, making diagnosis difficult [81].

Erythema multiforme treatment entails first differentiating it from urticaria and removal of any inciting causes such as oral medications and bathing if a recent topical treatment is believed to be the culprit. Many cases of EM minor are self-limiting, especially if a causative agent is discontinued. Recurrent EM and idiopathic EM likely require immunosuppression using prednisone (1–2 mg/kg/day). Additional or alternative immunomodulators (Table 137.3) may be needed if a desired response is not obtained. Patients with SIRS, hypotension, and organ dysfunction may require intravenous crystalloids, colloids, and even plasma to replace fluid, albumin, and electrolyte losses from skin lesions (see Chapter 159).

Any small animal that is suspected of having EM should have a baseline minimal database. Patients with systemic signs, especially SIRS, should have additional clinicopathological diagnostics monitored routinely, including but not limited to venous blood gas, electrolytes, ionized calcium, magnesium, and lactate. Vital sign monitoring of heart rate, blood pressure, central

Table 137.3 Immunomodulators for life-threatening dermatopathies.

Immunomodulator	Dose	Dermatopathy
Prednisone	0.5–1 mg/kg/day	Vasculitis
Prednisone	1–2 mg/kg/day	Vasculitis, EM, TEN
Prednisone	2–4 mg/kg/day	Unresponsive EM, TEN
Cyclosporine	5–10 mg/kg/day	Vasculitis, EM, TEN
Azathioprine	1–2 mg/kg/day	Vasculitis, EM, TEN
Chlorambucil	0.1–0.2 mg/kg q48h	Vasculitis
Mycophenolate mofetil	20–40 mg/kg/day, divided TID	Vasculitis, EM major, TEN
Human intravenous gamma-globulin (hIVIG)	2 g/kg	TEN, EM major

EM, erythema multiforme; TEN, toxic epidermal necrolysis; TID, three times a day (*ter in die*).

venous pressure, and urine output should be considered in critically ill dogs and cats. Prognosis for EM minor cases is fair to good, with many small animals having lesion resolution in a matter of weeks. Persistent cases affecting senior dogs and those with EM major typically require life-long immunosuppression, with lesion relapses occurring commonly after medications are withdrawn. Dogs and cats that have extensive mucocutaneous lesions with systemic illness and associated complications of DIC and organ dysfunction carry a poor prognosis [67].

Toxic Epidermal Necrolysis and Stevens–Johnson Syndrome

Toxic epidermal necrolysis (TEN), which is similar to Stevens–Johnson syndrome (SJS), is another rare, immune-mediated skin disease that affects small animals and humans [83]. TEN/SJS was previously considered to be more severe variants of EM. TEN/SJS is now considered a separate disorder from EM and is commonly associated with various drugs such as sulfonamides, penicillins, cephalosporins, NSAIDs (-oxicams), and phenobarbital. Topical flea dips with D-limonene were noted to cause TEN in dogs and cats. There are also many isolated reports invoking rare triggers of TEN, including vaccines, commercial shampoos, and neoplasia. Very few cases of TEN/SJS are idiopathic [82].

The pathogenesis of TEN/SJS, similar to EM, is characterized by keratinocyte apoptosis. TEN/SJS has more extensive cell necrosis than EM and is caused by lymphocyte-mediated cytotoxicity. The major mediators of TEN/SJS are cytotoxic T-lymphocyte release of granulysin and natural killer (NK) cell activation [84]. In TEN/SJS, lesions progress from clusters of dying cells to full-thickness necrosis with less inflammation noted than in EM. Early TEN/SJS lesions have histological characteristics of burns [85]. The exact mechanism of how medications cause sensitization and resulting cell death is unknown. Experimentally, small moieties of certain drugs interacting with host peptides become antigenic and there is evidence of drug moieties directly interacting with T-cell receptors [86].

Lesions of TEN/SJS are acute and characterized by erythema and systemic signs of pain, pyrexia, and anorexia. As lesions develop, they progress from vesicles to bullae, developing ulcerations and erosions with the hallmark sign of epidermal detachment (positive pseudo-Nikolsky sign: pressure causes separation of erythematous skin versus normal skin) (Figures 137.13 and 137.14). Typical distribution involves the trunk, extremities, muzzle/face, and mucocutaneous junctions [67,82].



Figure 137.13 Toxic epidermal necrolysis food pad slough. Reproduced with permission of Kimberly Coyner.

Differential diagnoses for TEN/SJS include EM, burns, systemic lupus erythematosus, bullous autoimmune diseases (pemphigus), vasculitis, superficial suppurative dermatitis of miniature schnauzers, and epitheliotropic lymphoma. Histological examination of skin biopsies which describe full-thickness coagulation necrosis of the epidermis is the only method of obtaining a definitive diagnosis [67].

Toxic epidermal necrolysis and SJS are quickly progressive and require emergency intervention. Therapy is similar to EM and burns because the extensive dermal necrosis results in extensive fluid, protein, and electrolyte losses. Supportive care, as outlined in the burn section of this chapter, should be instituted immediately, including intravenous fluid resuscitation, support of colloid pressure, provision of analgesia, wound care, and



Figure 137.14 Toxic epidermal necrolysis target lesions. Reproduced with permission of Kimberly Coyner.

nutritional support. Any current medications that the animal is being given should be stopped.

Corticosteroids are the mainstay of therapy, but there is controversy regarding their use. It appears that they are most beneficial early on so a rapid clinical diagnosis is important [87]. Human intravenous immunoglobulin (hIVIG) was found to be effective in one cat and two dogs with TEN; however the expense and risks of using

a potential human antigenic source must be considered. Additional therapies include plasmapheresis, N-acetylcysteine, pentoxifylline, and possibly TNF-alpha inhibitors (infliximab) but small animal research using these treatments is limited [82].

Unfortunately, the prognosis for TEN/SJS is poor. Mortality rates in humans approach 30–50% and are much higher in small animals, approaching 100% [66].

Table 137.4 Treatment and supportive care of selected dermatological emergencies in dogs and cats.

Therapy	Drug	Dosage*	Indication for use	Disease/ condition
Immunosuppressants	Prednisone	1–2 mg/kg PO q24h ⁹	Immunosuppression	EM, TEN, CV
	Cyclosporine**	5–10 mg/kg PO q12–24h	Reserved for idiopathic cases of EM/TEN	
	Azathioprine	2.2 mg/kg PO q24h ⁹ (d)		
	Dapsone	1 mg/kg PO q8h ¹⁹ (d)		
	Sulfasalazine	20–40 mg/kg PO q8h ¹⁹ (d)		
Antibiotics	Amoxicillin-clavulanic acid	13.75 mg/kg PO q12h	Prevent secondary infection/septicemia in patients with compromised epidermal barrier	EM, TEN, burns
		22–30 mg/kg IV q8h		
	Ampicillin-sulbactam	22 mg/kg PO q12h ¹²		
	Cephalexin	20 mg/kg IV q8h		
	Cefazolin	5 mg/kg PO, IV q24h		
	Enrofloxacin			
Crystalloids	Plasmalyte	90 mL/kg/h: shock, dog	Hypovolemic/ maldistributive shock	TEN, EM, burns
	0.9% NaCl	60 mL/kg/h: shock, cat		
	LRS	Weight (kg) × % estimated dehydration: replacement	Dehydration	
	Normosol	60–66 mL/kg/day: maintenance	Maintain effective circulating volume	
Colloids	Hetastarch	5–15 mL/kg: shock, dog	Hypovolemic/ maldistributive shock	EM, TEN, burns
	Pentastarch	5–10 mL/kg: shock, cat		
	Dextran-70	10–20 mL/kg/d: maintenance	Hypoproteinemia, low colloidal oncotic pressure	
Opioids	Fentanyl	2–5 µg/kg/h IV or transdermal patch	Analgesia	EM, TEN, burns
	Hydromorphone	0.05–0.2 mg/kg IV q4–6h		
	Buprenorphine	0.005–0.02 mg/kg IV, buccal (c) q6–12h		
Nutrition	Enteral (nasoesophageal, nasogastric, esophageal)		Supportive care, promote wound healing	EM, TEN, burns
	Parenteral (PPN, TPN)			
Other	Pentoxifylline	10–15 mg/kg PO q8h ^{10,12}	Immunomodulation, anti-inflammatory, antithrombotic	CV
	Human IVIG	1 g/kg IV over 4h ^{11,12}		EM, TEN
				Immunomodulation

c, cats only; CV, cutaneous vasculitis; d, dogs only; EM, erythema multiforme; IV, intravenous; IVIG, intravenous immunoglobulin; PO, by mouth (*per os*); PPN, partial parenteral nutrition; TEN, toxic epidermal necrolysis; TPN, total parenteral nutrition.

* Superscript numbers correspond to references cited in the text.

** Bioequivalent to Neoral.

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Severe Soft Tissue Infections

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Introduction

Infections of the skin and soft tissues are common in dogs and cats, and vary widely in their clinical severity. The phrase “severe soft tissue infections” (SSTIs) generally refers to those infections which involve deeper tissues (fascia, muscle) and have the potential to produce substantial tissue damage or systemic compromise if not aggressively treated. “Necrotizing” infections are SSTIs that exhibit clinical and/or histopathological features of necrosis [1]. The most well recognized of the necrotizing soft tissue infections (NSTIs), necrotizing fasciitis (NF), is a rapidly progressive infection that involves bacterial tracking along fascial planes, with local tissue destruction resulting from secretion of cellular and bacterial proteases. A variant of NF is Fournier’s gangrene (FG), which involves the tissues of the perianal area [2,3]. NF and other SSTI can also be associated with toxic shock syndrome, in which massive cytokine release triggered by bacterial antigens leads to a systemic inflammatory response with multiple organ involvement. Early recognition and prompt intervention are essential components of limiting the sequelae of SSTIs/NSTIs [4].

Etiology

In humans, NSTIs are classified as type I (polymicrobial), type II (monomicrobial) or type III (caused by anaerobes such as *Clostridium*) [2,4]. Type I infections are most common and may include infection with methicillin-resistant *Staphylococcus aureus* (MRSA), although MRSA has also been reported as a cause of monomicrobial infections in recent years [2,4–6]. Type II infections are most often caused by group A streptococci, such as *Streptococcus pyogenes*, and can be associated with streptococcal toxic shock syndrome.

Polymicrobial, streptococcal, and anaerobic NSTIs have all been described in dogs and cats [7]. However, streptococcal necrotizing infections in small animals are usually caused by beta-hemolytic streptococci of Lancefield group G (e.g. *Streptococcus canis*) rather than by group A streptococci, as in humans [8,9]. In a retrospective study of 47 dogs with SSTIs, the most common bacterial species isolated in antemortem cultures were beta-hemolytic streptococci (monomicrobial in 9/13 cultures), *E. coli*, and staphylococci (including methicillin-resistant), with lower numbers of anaerobes (*Clostridium*, *Peptostreptococcus*) and a variety of other aerobes (*Pseudomonas*, *Serratia*, *Klebsiella*, *Enterococcus faecalis*, *Pasteurella*, *Enterobacter cloacae*).

In cats, *S. canis*, *Acinetobacter baumannii* (suspected nosocomial), and *Prevotella bivia* have been cultured in cases of NF, the former two associated with septic shock [10–12]. A polymicrobial infection with *Enterococcus faecium*, *Staphylococcus epidermidis*, and *E. coli* has been described in a cat with FG; the *S. epidermidis* was resistant to oxacillin and all other beta-lactams tested [13].

Pathophysiology

Streptococcus canis is a commensal organism, and many of the other organisms that cause SSTIs also arise from the patient’s endogenous flora. In some cases, the development of established infection can be attributed to a loss of the skin barrier and/or altered systemic host defenses (i.e. a pre-existing chronic wound or immunosuppressive condition). However, an early observation in human medicine was that NSTIs could also develop following seemingly minor trauma (“trivial accidents”) in otherwise healthy individuals [6].

In the above-mentioned study by Buriko et al. [7], 19% of dogs with NSTIs had a potentially immunomodulating

condition (hyperadrenocorticism, hypothyroidism, IMPA, meningitis/vasculitis, IMHA, Evans' syndrome, neoplasia, or chronic UTI) at presentation; 13% were administered steroids and 17% were administered NSAIDs prior to the onset of clinical signs. Seventeen percent had a history of recent skin barrier compromise (injections, surgery at the affected site or a distant site, vehicular trauma with minor abrasions). Three other dogs had a history of blunt trauma, boarding with no obvious history of trauma, or grooming with razor burn [7]. An inciting factor was not identified in the remaining cases.

Other potential predisposing or inciting factors for NF described in dogs and cats include tooth extraction [14], minor dog bites or superficial pyoderma [9], and prior radiation therapy (with development of clinical signs after a small wound was noted in the irradiated area [15]). One cat developed NF emanating from a site of intravenous catheter replacement (suspected nosocomial infection) [12]. Additional cases following boarding with no witnessed trauma, or cases in which no inciting factor could be identified, have also been reported [9,16].

Because of the occurrence of some NSTIs without an obvious portal for inoculation, several recent investigations in human medicine have focused on molecular characterization of the processes by which necrotizing streptococcal infections are established and propagated. One hypothesis suggests that under certain circumstances, any disruption of normal musculoskeletal anatomy can lead to hematogenous seeding of the affected tissue by streptococcal organisms [17]. The intermediate filament vimentin, which can act as a tether for streptococci, has been found to be upregulated in injured skeletal muscle cells *in vitro* [18], and in mice, minor blunt trauma followed by intravenous delivery of group A streptococcal organisms led to homing of the streptococci to the injured area [17]. Subsequent bacterial proliferation in subcutaneous tissue and fascial planes results in elaboration of proteases, by both bacteria and host leukocytes; in addition, the antiphagocytic streptococcal M protein and other virulence factors activate local coagulation pathways and produce regional thrombosis and vasoconstriction. The result is widespread fascial digestion and ischemic and liquefactive necrosis of surrounding subcutaneous tissue, muscle, and skin [19].

Although the details of these processes have not been verified in dogs and cats, they are presumed to be similar based on similar clinical and histopathological findings. Group G streptococcal isolates have also been found to express some of the same bacterial superantigens as group A streptococci; these superantigens (pyrogenic exotoxins) bind to MHC II molecules on antigen-presenting cells and T-cell receptors, triggering generalized cytokine release and producing the signs of toxic shock syndrome [20].

Clinical Features (Table 138.1)

Physical examination findings in dogs and cats with SSTIs/NSTIs include heat, swelling, or erythema of the affected area, often with pain out of proportion to the apparent extent of tissue injury [8,9]. Bullous lesions (common in humans, uncommon in dogs) and skin sloughing may occur as the disease advances [8,16]. Dramatic progression may occur within 12–24 hours of initial presentation. Lesions may be found on the limbs (most common), ventral thorax and abdomen, flanks, dorsum, muzzle, or prepuce, or in the inguinal area (or perianal area in the case of FG) [7,9].

Other common initial physical examination findings in affected dogs include fever (63%), tachycardia (70%), and tachypnea (81%); hypotension or mental dullness may also be present, particularly in dogs with sepsis or toxic shock syndrome [7]. Initial laboratory assessment may reveal leukocytosis or leukopenia (with or without a left shift), mild thrombocytopenia, hypoalbuminemia, mild to moderate elevation of AST or ALP, mildly prolonged PTT, and elevated FDPs [7]. Additionally, hyperbilirubinemia and hypoglycemia (presumed associated with sepsis) have been reported in a dog with NF [16]. Similar physical examination and clinicopathological findings have been reported in cats with NF or FG [10–13].

Diagnosis (see Table 138.1)

The possibility of a severe or necrotizing soft tissue infection should be entertained for any skin or soft tissue lesion for which pain seems disproportionate to clinical appearance, as well as for lesions which progress very rapidly or those with potential signs of necrosis such as blistering, crepitus, discoloration, or tissue sloughing. Imaging may be helpful in increasing the index of suspicion or directing sample collection. In humans, MRI is the preferred imaging modality for differentiation of necrotizing from non-necrotizing infections; characteristic findings in NSTIs include hyperintensity of deep fascia and muscles on T2-weighted images. Computed tomography has been reported to be 80% sensitive based on detection of abscesses and fascial thickening [6]. However, advanced imaging is not commonly performed initially in dogs because of expense and the need for sedation.

Radiography and ultrasound findings have been described in 47 dogs with SSTIs/NSTIs; 23 of these dogs had radiographs performed of the affected area, and 16 had ultrasound examination. On radiographs, none of the dogs had bony involvement or gas visualized in the soft tissues (the latter is a specific but not sensitive sign

Table 138.1 Summary of recommendations for recognition, diagnosis, and treatment of severe and necrotizing soft tissue infections.

Suggestive historical and PE findings	<p>Localized erythema, swelling, and warmth with pain out of proportion to clinical appearance</p> <p>Bullae, discoloration, or skin sloughing</p> <p>Rapidly progressive lesions</p> <p>History of recent trauma, injections, procedures, or immunosuppression</p>
Diagnostic plan	<p>Collect CBC, biochemistry, urinalysis, infectious disease testing as applicable to assess for:</p> <p>Evidence of SIRS/sepsis</p> <p>Concurrent conditions or organ dysfunction</p> <p>Imaging:</p> <p>Ultrasound of affected area</p> <p>Consider advanced imaging (CT/MRI)</p> <p>Radiographs may be performed but are likely to be low-yield.</p> <p>Collect microbiological samples.</p> <p>If open wound, obtain cytology and culture from leading edge (tissue swab or biopsy). If skin is intact, consider:</p> <p>Ultrasound-guided aspiration of affected tissue for cytology and culture</p> <p>Local anesthesia with skin incision, “finger test”, and sample collection</p>
Treatment plan	<p>Appropriately support blood pressure and vital signs</p> <p>Opioids preferred for analgesia; avoid NSAIDs (controversial)</p> <p>Initiate parenteral antibiotic therapy</p> <p>Clindamycin + penicillin + either (1) an aminoglycoside, (2) a third-generation cephalosporin, or (3) meropenem</p> <p>Consider prior antibiotic therapy and potential adverse drug reactions</p> <p>Avoid fluoroquinolones as monotherapy</p> <p>Consider early surgical debridement</p> <p>Excision of all necrotic tissue, probing of wound pockets</p> <p>Repeated debridement or limb amputation if necessary</p> <p>Consider NPWT, skin grafts once infection is resolved</p> <p>Refractory cases of streptococcal toxic shock unstable for surgery: consider IVIG</p> <p>Continue supportive care (Rule of 20)</p>

CBC, complete blood count; CT, computed tomography; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drug; NPWT, negative pressure wound therapy; PE, physical examination; SIRS, systemic inflammatory response syndrome.

of necrotizing infections in humans). Ultrasound identified a subcutaneous fluid pocket in 69% of dogs in which it was performed, and subcutaneous edema in all. Fine needle aspiration of the affected area was performed in 23 dogs (some under ultrasound guidance) and revealed evidence of subcutaneous bacterial infection in 62% [7]. Therefore, although ultrasound findings are neither sensitive nor specific for necrosis, imaging and aspirates may facilitate the assignment of a bacterial etiology to a rapidly progressive skin lesion and aid in acute management, and aspirates of affected tissue (preferably with ultrasound guidance to identify pockets) should be considered in all dogs with potential necrotizing infections.

The definitive diagnosis of NSTI is often made during surgical exploration of the diseased tissue. The “finger test” describes the ease with which tissues can be digitally separated along fascial planes; the characteristic lesions associated with necrotizing infections are a positive finger test, fascial edema, gray non-contracting muscle, and a thin, murky, foul-smelling “dishwater” discharge [6,8]. The finger test can be performed through a small incision with local anesthesia if a necrotizing infection is being considered and uncertainty exists regarding the need for surgical debridement [8].

Histopathologically, necrotizing infections are associated with polymorphonuclear cell infiltration, edema of the dermis and subcutaneous fat, and thrombosis of nutrient vessels to skin and muscle, in addition to liquefactive necrosis of fascia and tissues [6,8,21].

Treatment (see Table 138.1)

Treatment of SSTIs/NSTIs should include early initiation of broad-spectrum antibiotic therapy with activity against likely pathogens, source control (generally consisting of early, aggressive, and potentially repeated surgical debridement), and pathogen identification by culture, with appropriate tailoring of antimicrobial treatment [4] (see Chapter 200). Tissue cultures should be taken from the leading edge of a lesion if possible, as the central portion may contain contaminants [8]; blood cultures can also be considered if sepsis is suspected.

Once cultures are obtained, empirical antibiotic therapy directed against streptococci, other skin flora (including methicillin-resistant staphylococci), gram-negative organisms, and anaerobes should be initiated. In one recent human study, a combination of clindamycin, a penicillin, and gentamicin was adequate against the causative pathogen(s) in 95% of necrotizing infections, based on susceptibility testing [22]. Because protein synthesis inhibitors such as clindamycin may inhibit exotoxin synthesis by streptococci, and because a proportion of streptococci isolated in the study by Buriko et al. [7] were penicillin resistant, a similar regimen incorporating clin-

damycin might be appropriate as empirical therapy in dogs and cats. The risks of nephrotoxicity induced by aminoglycosides must be weighed against their potential benefits when using them in animals with possible sepsis-induced hypoperfusion or renal compromise. Alternatives to aminoglycosides in animals with known or potential renal compromise are third-generation cephalosporins or carbapenems (i.e. meropenem); it should be remembered that carbapenems, like other beta-lactams, are not effective against methicillin-resistant staphylococci.

Fluoroquinolones, although they provide good gram-negative coverage, may not be ideal as a first-line treatment for NSTIs. First, they have been shown to induce bacteriophage-mediated lysis of streptococci *in vitro*, with increased expression of superantigens [23], although the significance of this finding *in vivo* remains unknown. Second, in the study by Buriko et al. [7], over 50% of organisms isolated in antemortem culture were resistant to fluoroquinolones.

Surgical exploration and debridement should be considered early, as antibiotic access to necrotic tissues may be limited by thrombosis and poor local perfusion, and both reduction of bacterial load and exposure of tissues to oxygen may be beneficial in resolving infection [6,8] (see Chapter 166). Debridement should include removal of all questionable tissue and blunt probing of wound pockets in all directions [6,8]. Once debridement has been completed, the surgical site may be initially managed as an open wound, with antibacterial dressings and frequent bandage changes. Repeated debridement (every 24–48 hours) may be necessary, depending upon wound appearance and progression; in some cases, amputation of the affected limb has proved necessary to halt the spread of infection into adjacent tissues [6,8,16]. Negative pressure wound therapy (NPWT) has been shown to be beneficial in NSTIs in human medicine, and there are several reports of the use of NPWT to enhance healing after debridement in dogs and cats [24,25]. Skin grafts may also be considered once infection is resolved and a bed of healthy granulation tissue has formed [25]. Although surgery is indicated in most cases of SSTI, there have been three reports of successful treatment of FG in cats with conservative therapy [26].

Other aspects of patient care, including analgesia, correction of fluid, acid–base, and electrolyte abnormalities, nutrition, and recumbency care, are also integral components of treatment (see Sections 5 and 7). Animals with toxic shock syndrome and abnormal vascular responsiveness may require pressors to maintain appropriate perfusion. For analgesic therapy, opioids are an appropriate choice, with mu-agonists preferred because of the severe pain usually associated with SSTIs. The use of NSAIDs is controversial; they have been postulated to facilitate more rapid spread of NSTIs in humans because of interference with neutrophil chemotaxis,

and in mice, the NSAID ketorolac was associated with a marked increase in the number of group A streptococci in injured muscle when given 1 hour before injury [17]. However, more recent prospective human studies and a retrospective study in 47 dogs have not found an association between NSAID use prior to diagnosis and progression of disease and/or survival [7,27].

Other therapies that have been suggested to be beneficial in NSTIs include hyperbaric oxygen therapy (HBO) and intravenous immunoglobulin (IVIG). In humans, no prospective, randomized clinical trials have been conducted to evaluate the use of HBO, and delaying other treatment in favor of HBO is not advised [2,3]. However, there are reports of successful treatment of SSTIs using antibiotic therapy and IVIG in cases in which surgery was precluded by hemodynamic instability of the patient or extensive tissue involvement [28], and IVIG administration was associated with faster resolution of MODS in a small randomized study [29]. Proposed actions of IVIG in SSTIs include binding and neutralization of streptococcal or staphylococcal exotoxins and superantigens [6,28].

Hyperbaric oxygen therapy has been described in a dog with NF [16], but so far, as in human medicine, insufficient information exists in veterinary medicine to determine whether or not it has the capability to reduce morbidity and mortality associated with NSTIs. Administration of IVIG has not been formally described in dogs or cats with NSTIs, but could be considered in suspected streptococcal or staphylococcal SSTIs with toxic shock where surgical debridement must be delayed or is not possible.

Prognosis

In the study by Buriko et al. [7], the overall mortality rate for dogs with SSTIs (of which 85% were NSTIs) was 53%. The majority of deaths in this study were euthanasias, but a similarly guarded prognosis has been reported for SSTIs in human medicine (overall mortality of 25–30%, increasing to 70% in the presence of toxic shock syndrome [6]). Predictors of mortality in humans include white blood cell counts greater than 30 000/ μ L, creatinine > 2 mg/dL, heart disease at hospital admission, and clostridial infection [30]. Delay in surgical debridement has also been identified as an independent negative prognostic factor in humans with NSTIs [31].

In dogs, although a number of clinicopathological variables, initial respiratory rate, and the proportion of patients undergoing initial surgical debridement have been found to differ between survivors and non-survivors of SSTIs, all of these findings were limited by the retrospective nature of the study and small sample size, and further studies are necessary to better characterize prognostic factors in dogs and cats with SSTIs/NSTIs [7].

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K. Environmental Emergencies

Smoke Inhalation Toxicity

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Introduction

House and building fires are common occurrences in the United States, especially in large cities. Smoke inhalation in pets trapped within a house fire can have a multitude of different problems and presentations. Inhaled smoke and debris may contain respiratory irritants and toxins, and can cause heat damage to the skin, eyes, and the upper airway. In humans, inhalation injury is a greater contributor to overall mortality than the percentage of body surface area affected by burns [1]. Early recognition, intervention, and stabilization of smoke inhalation victims is necessary as these patients can rapidly progress to respiratory failure and life-threatening complications.

Pathophysiology of Smoke Inhalation

Smoke is a heterogeneous mixture of chemicals and particulate matter in which the components are specific to each fire. The detrimental components of smoke include thermal heat, particulate matter, systemic toxins, and respiratory irritants [2,3]. The main clinical consequences of smoke inhalation include acute upper airway obstruction, bronchospasm, small airway occlusion, predisposition for pulmonary infection, and respiratory failure [2,3].

The thermal heat of smoke is damaging to the sensitive mucosa of the nose, oral cavity, and oropharynx. Thermal damage is commonly localized to the upper airway since the body is able to dissipate heat rapidly past the nasal pharynx. If the temperature of the smoke is hot enough to cause thermal injury to the lower airway, patients typically succumb to upper airway obstruction due to extensive edema prior to exhibiting clinical signs from the lower airway thermal burns [3].

The size of the particulate matter determines whether it is deposited in the upper or lower airway. The toxins associated with these particles may be water soluble and may dissolve within airway mucus and cause damage to the mucosa for 48 hours post inhalation [4]. The adherence of these toxins along with thermal injury predisposes the respiratory lining to acute inflammation, increased vascular permeability, and extensive edema. The damaged mucosal cells will produce large volumes of protein-rich exudate and inflammatory cells. Cytokines IL-1-alpha, IL-6, IL-8, and TNF-alpha are released and trigger neutrophilic migration to the airway lumen, furthering the inflammatory cycle and resulting in damage of the respiratory columnar cells and mucociliary apparatus. The combination of mucosal damage, loss of protective mechanisms, and reactive oxygen species results in distal migration of upper airway material and bacteria towards the lower airways, predisposing patients to bacterial pneumonia [2,3,5]. Obstruction of the bronchi, bronchioles, and terminal bronchioles with this debris can occur and further exacerbate respiratory distress. Damage to the upper airway, including the trachea and mainstem bronchi, can result in necrosis 3–5 days post exposure. The resulting pseudomembranous casts often slough and then obstruct the lower airways, resulting in surfactant disruption, lung lobe collapse, and further respiratory dysfunction [2,3,6].

One of the major complicating factors in patients with smoke inhalation is acute respiratory distress syndrome (ARDS). ARDS can develop as a response to smoke inhalation and can be further exacerbated and worsened by the damage to the upper respiratory tract and epithelial sloughing as previously described. The formation of nitric oxide (NO) synthase by the respiratory epithelial cells and alveolar macrophages resulting in formation of NO (a potent vasodilator) has been implicated in

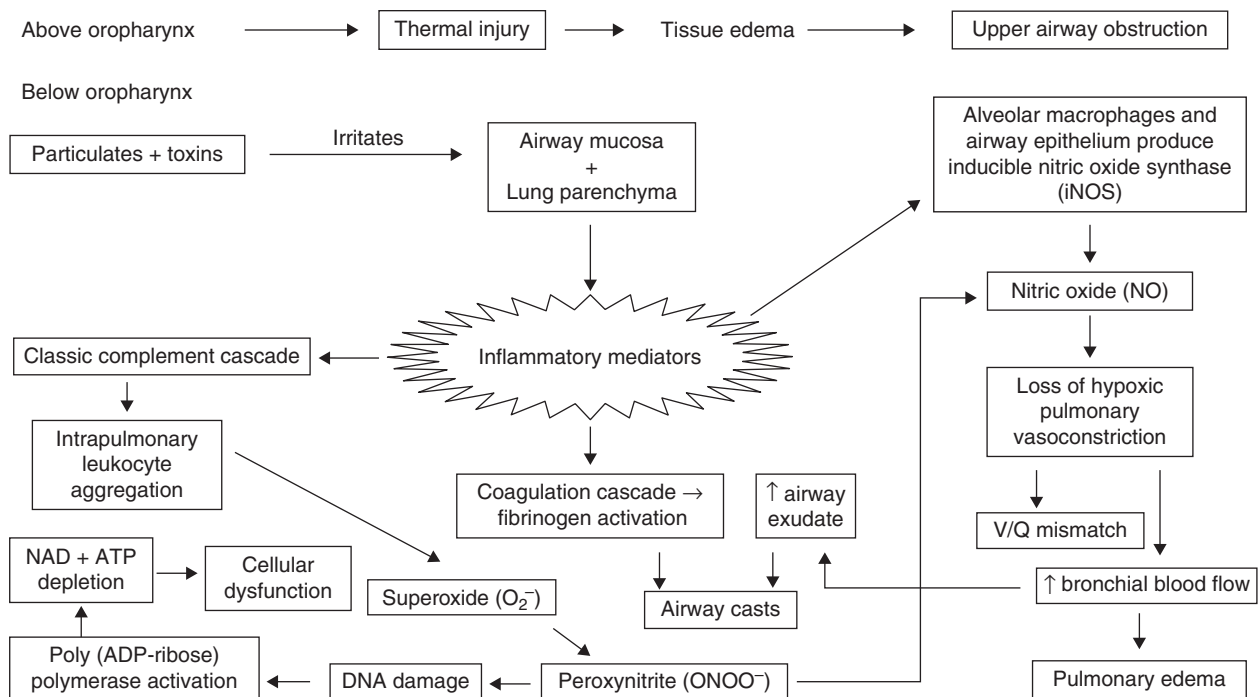


Figure 139.1 Pathophysiology of smoke inhalation induced-respiratory tract inflammation and pulmonary edema. Reproduced with permission of the College of Intensive Care Medicine of Australia and New Zealand.

increasing bronchial blood flow and decreasing hypoxic pulmonary vasoconstriction, resulting in V/Q mismatch. NO can also combine with the superoxide (O_2^-) produced by activated neutrophils to form peroxynitrite ($ONOO^-$). Peroxynitrite leads to DNA damage and subsequent activation of poly (ADP-ribose) polymerase which utilizes large amounts of ATP and NAD, resulting in energy depletion and cell death [3,7].

The pathophysiology of smoke inhalation is described in Figure 139.1. The combination of edema, increased blood flow, increased vascular permeability, vasodilation, and energy depletion can lead to ARDS and respiratory failure. The severity of lung damage and inflammation may predispose to pulmonary infection. Approximately 50% of human patients with smoke inhalation injury will develop a secondary infection [2,3,8].

Carbon Monoxide and Cyanide Exposure

Inhaled carbon monoxide (CM) and hydrogen cyanide (HC) can exacerbate respiratory and systemic collapse in smoke inhalation patients. The severity of intoxication from CM is dependent on the duration of exposure, concentration of inhaled CM, and underlying health status of the patient [2]. CM is rapidly absorbed across the alveolar membrane and has an affinity for

hemoglobin that is 200–250 times greater than that of oxygen [2,3,6,9]. CM binds hemoglobin tightly to form carboxyhemoglobin (CO-Hgb), resulting in a functional anemia in which red blood cells are unable to facilitate oxygen carrying and release. This causes a left shift of the oxygen-hemoglobin dissociation curve and secondary cellular hypoxia. CM also competitively inhibits intracellular cytochrome oxidase enzyme systems, specifically cytochrome p450, which disrupts aerobic metabolism and cellular respiration. CM toxicity is associated with the induction of lipid peroxidation, direct cellular damage, reperfusion injury, and central nervous system demyelination [2,6,10].

While literature in the veterinary field is limited, a recent case series found that dogs with higher CO-Hgb concentrations had a significantly longer duration of hospitalization, altered mental status, abnormal respiratory sounds, increased respiratory effort, and hypothermia [11].

Carbon monoxide toxicity may result in both acute and delayed neurological abnormalities. Delayed neurological sequelae are more common in people that are more symptomatic at presentation. Delayed onset of neurological signs in these people manifests as memory loss, confusion, ataxia, and seizures 2–40 days post exposure [12]. Delayed neurological signs have been described in veterinary medicine [2,10,13,14].

One case report describes a dog that presented comatose secondary to CM toxicity from smoke inhalation with initial recovery, but re-presented 5 days later for progressive neurological signs including tetraparesis and mental dullness. This dog recovered completely with intensive supportive care and had no evidence of neurological abnormalities at a 34-month follow-up [10]. Another case series describes multiple animals from the same household hospitalized for CM toxicity from smoke inhalation. All but one animal recovered initially from CM toxicity. Two weeks after exposure, hearing deficits were found in all remaining animals, but resolved by 6 weeks post incident [14]. In a case series of three adult Chihuahuas hospitalized after smoke inhalation, the patients showed initial improvement but later developed seizures. Despite intensive hospitalization and supportive care, all three dogs died and multiple intracranial lesions were found on histopathological examination that were consistent with CM exposure [13]. Another case series describes 21 dogs caught in a kennel fire; those with neurological signs had significantly increased CO-Hgb levels and all five of the dogs that presented with neurological deficits had CO-Hgb levels >24% [11].

Thermal combustion of nitrogen-containing polymers produces HC. HC is rapidly absorbed upon inhalation and inhibits cellular use of oxygen. Once absorbed, cyanide combines with Fe^{3+} in the mitochondrial cytochrome a3 complex and inhibits electron transport and cellular respiration [15]. The inhalation of CM and HC results in synergistic effects that rapidly inhibit the body's ability to utilize oxygen. This leads to tissue hypoxia, acidosis, and a decrease in cerebral oxygen consumption [16–18].

Physical Examination Findings

A clinical diagnosis of smoke inhalation should be based on the patient's history and physical examination. Indications of smoke inhalation include singed nasal vibrissae, oropharyngeal blistering, facial burns, a smoke smell to the fur, and dark, soot-filled sputum [6,9,19]. Patients should be immediately assessed for respiratory difficulty (both upper and lower airway). Lung auscultation may reveal increased breath sounds, wheezes secondary to bronchoconstriction, or crackles. The patient should be evaluated for hypoventilation secondary to either poor pulmonary or chest wall compliance. Patients may present initially with only mild clinical signs that may worsen over 24–36 hours.

Smoke inhalation and associated CM toxicity can result in significant cardiovascular abnormalities such as hypotension, cardiac arrhythmias, and dehydration. Neurological assessment should evaluate for signs of head trauma as well as evidence of neurotoxicity.

Agitation, confusion, ataxia, decreased mentation, loss of consciousness, and seizures are highly suggestive of CM or cyanide toxicity [6,19–21]. Intracranial signs are supportive of hypoxic events to the brain which can lead to intracranial edema, swelling, and an increase in intracranial pressure.

A thorough eye exam should be performed as exposure keratopathy and corneal ulceration are common secondary to smoke exposure. A patient with suspected smoke exposure should have their eyes liberally irrigated to minimize continued topical exposure of toxicants and irritants. Significant burn injury is a rare finding in smoke inhalation patients. In two retrospective studies, only one of 27 dogs and one of 22 cats had a major burn injury. The most common dermatological abnormalities seen in animals that presented to the emergency department following smoke inhalation were minor injuries such as singed fur and skin lacerations [22,23]. It is possible that patients with more severe burns and inhalation injury died at the scene.

Diagnostics

Patients with respiratory difficulty should have diagnostics such as pulse oximetry and arterial blood gas analysis performed, but results should be interpreted carefully if CM or cyanide toxicity is suspected. A standard two-wavelength pulse oximeter will provide a falsely elevated peripheral saturation of oxygen (SpO_2) reading due to the inability to differentiate between oxyhemoglobin and CO-Hgb [8,10,19,21,24]. An arterial blood gas (PaO_2) only reflects the dissolved oxygen which should be unchanged in CM or cyanide toxicity. To evaluate the amount of CO-Hgb in patients with CM toxicity, a CO-oximeter is required. The blood of normal cats and dogs should have <1% CO-Hgb [25,26]. Elevations of this value, along with clinical presentation and history, should be used to make a diagnosis of CM toxicity. If the CO-Hgb is normal but a patient presents with neurological signs, metabolic acidosis, high lactate concentration despite adequate perfusion parameters, and a reduction in the arterial-venous oxygen gradient, then cyanide toxicity should be considered.

Thoracic radiographs may be performed, but often parenchymal abnormalities will be absent initially, but may appear over the first 24 hours following smoke inhalation. Radiographic abnormalities associated with smoke inhalation include a diffuse interstitial pattern, focal alveolar pattern, and lung lobe collapse secondary to obstruction of the main stem bronchi with debris [22,23].

Laryngoscopy is often useful to evaluate the upper airway and determine the extent of edema and damage. In

human patients, bronchoscopy is a standard diagnostic tool and patients are graded to determine the extent of injury and prognosis [16]. Bronchial lavage is also useful to obtain a sample for culture and susceptibility testing, and to remove excessive debris.

Bronchoscopy is of limited use in veterinary medicine due to the need for general anesthesia if a tracheostomy tube is not in place.

Treatment

Immediate treatment with supplemental oxygen is imperative for supporting arterial oxygen content and increasing the elimination of CM (see Chapter 181). Rapid clinical improvement is common with the addition of supplemental oxygen, and it is becoming increasingly common for first responders to administer oxygen as soon as possible. At 21% inspired oxygen, the half-life of CM is 5 hours. The half-life decreases to 1 hour at 100% oxygen and 20 minutes with 100% hyperbaric oxygen therapy at 2.5–3 times atmospheric pressure [9,12,19]. The use of hyperbaric oxygen therapy has theoretical benefits, but the results of a Cochrane review evaluating seven randomized controlled trials failed to show sufficient evidence to justify its use in the treatment of CM toxicity [27]. While the use of hyperbaric oxygen therapy is rare in veterinary medicine, oxygen supplementation given via mask, oxygen cage, endotracheal intubation, or other methods is adequate in most cases.

Ensuring an adequate airway is a priority after the administration of supplemental oxygen. Severe edema may be seen initially, but can also develop rapidly. Ensuring a functional and open airway is vital. If there is concern, either intubation with positive pressure ventilation or a tracheostomy tube should be considered (see Chapter 180).

Mechanical ventilation may be indicated for both persistent hypoxia despite supplemental oxygen or hypoventilation due to poor pulmonary compliance and chest wall injuries. Low tidal volume mechanical ventilation with associated permissive hypercapnia has been shown to reduce ventilator-induced lung injury [3,28]. Positive pressure ventilation along with positive end-expiratory pressure (PEEP) helps decrease atelectasis and maintain adequate oxygenation and increase compliance of damaged lungs (see Chapter 188).

Intravenous fluid resuscitation with a balanced isotonic crystalloid should be instituted, if indicated, to support the cardiovascular system and maintain hydration (see Chapter 167). While smoke inhalation patients typically need only maintenance rates of fluids, if dermal burns are present the patient's fluid requirements may be significantly increased [19]. See Section 5 for further details.

If HC is highly suspected and the patient has not improved significantly with supportive care, then antidotes such as amyl nitrate and sodium thiosulfate may prove beneficial. These antidotes oxidize hemoglobin to methemoglobin, which preferentially binds cyanide to create cyanomethemoglobin and allows free cyanide to be converted to thiocyanate by the liver and metabolized [7]. Since treatment of cyanide requires the formation of methemoglobinemia, the use of this antidote is controversial as it may worsen hypoxemia. Hydroxocobalamin (vitamin B12a) administration may also be considered since it binds cyanide to form cyanocobalamin which is excreted via the urine [3].

Supportive treatments include the use of beta-2 agonists to reduce bronchoconstriction-induced airflow resistance and improve dynamic compliance. Beta-2 agonists such as terbutaline (0.01 mg/kg IV, SC, IM, PO) or inhaled albuterol decrease histamine release, leukotriene levels, and TNF-alpha concentrations, thereby conferring an anti-inflammatory effect. There is also evidence that beta-2 agonists may improve fluid clearance within the respiratory tract and promote mucosal repair [3,29–31].

Even though it is reported that 50% of humans treated for smoke inhalation develop bacterial pneumonia, preventive antibiotics are not recommended (see Chapter 200) [8,19]. If a patient develops clinical signs of pneumonia and culture and susceptibility tests are not available, empirical antimicrobial therapy covering the most common isolates, *Staphylococcus aureus* (cefazolin 15 mg/kg IV q12h) and *Pseudomonas* (ceftazidime 30 mg/kg IV q6h or amikacin 15 mg/kg IV q24h), should be instituted (see Chapter 37) [6,19].

Nebulization of epinephrine and corticosteroids is reported to help minimize edema of the upper airway. Use of systemic steroids has resulted in higher infection and mortality rates in clinical animal studies [6,32,33]. In children, a significant decrease in the incidence of reintubation for pulmonary failure, decreased atelectasis, and decreased mortality was shown following nebulization with heparin and N-acetylcysteine [34]. Future treatments attempting to target nitric oxide synthase and inflammation in an attempt to restore hypoxic vasoconstriction in the lungs may prove beneficial, in addition to the use of nebulized antioxidants such as gamma-tocopherol (vitamin E) [3,35–37]. A recent study in dogs looked at high-volume lung lavage to reduce toxin exposure and minimize inflammatory mediators and found an improved short-term outcome [38].

Prognosis

In humans, the mortality rate of patients admitted for smoke inhalation without concurrent dermal burn injury

is <10% [39]. The overall survival rate of dogs and cats suffering from smoke inhalation without accompanying severe dermal burns has been variable. In a case series looking at dogs presenting to an urban veterinary hospital for smoke inhalation, 11/27 cases were deemed more complicated, and of those, 8/11 either died or were euthanized [22]. In a case series looking at cats presenting to that same institution, only 5/22 were deemed complicated, and there was a survival rate of 20/22 [23]. The majority of the cats and dogs that did well had significant improvement within 24 hours of admission [22,23]. These studies may provide an overly optimistic prognosis

as the only patients that were included were ones that made it to the hospital for treatment.

After treatment for smoke inhalation, the potential for delayed complications continues. Delayed neurological signs have been discussed already and chronic respiratory conditions, such as bronchitis, bronchiectasis, pulmonary fibrosis, and atelectasis, are possible. However, long-term studies have not been performed in veterinary patients. As the exact outcome of patients with smoke inhalation is unknown, it is important to have appropriate client communication as well as long-term follow-up, if indicated.

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Porcupine Quilling

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Introduction

Porcupines are rodents indigenous to much of the northern parts of the United States and throughout Canada [1]. They are the second largest rodent in the US, second only to the beaver. They live in wooded areas and dens, where they eat leaves, twigs, berries, and other vegetation. Porcupines are strong tree climbers. They are nocturnal, near-sighted, and non-aggressive, and have evolved to use their modified hairs (quills) as protection against predators. Quills are hollow and barbed, and range in length from less than 1 cm to 8–9 cm. Shed quills are replaced, and quills in newborn porcupines (porcupettes) harden within a few days. The quill itself is an engineering marvel, with small barbs that help the quill to slide into the tissue of the attacker, but prevent easy withdrawal [2]. This characteristic has recently been exploited to create a suture, aptly named Quill™ [3].

Importantly, the quills are not actively thrown at an attacker, but when the porcupine is threatened, the quills will stand up and will be more easily dislodged. Thus, the porcupine is never the aggressor, but rather the victim in dog:porcupine interactions [4]. Interestingly, porcupine quills have antimicrobial properties, as self-quilling in falls is not uncommon in porcupines [5]. Free-roaming large-breed dogs often encounter and attack porcupines [4] (Figure 140.1). Cats are rarely, if ever, quilled. Keeping a dog leashed will prevent porcupine quillings, but this may be harder to do in more rural areas.

Prehospital Care

Owners of dogs that have been quilled should be advised to bring them to the veterinarian for removal. Quill removal is painful and, in all but the most minor quillings, should be performed under sedation or general anesthesia. If immediate removal is not possible, dogs should be prevented from rubbing at the quills as



Figure 140.1 A bloodhound with a minor quilling after a porcupine encounter.

this will push them in deeper and make them harder to remove, as well as more likely to migrate.

Quill Removal

After sedation or anesthesia, quill removal is performed by gently grasping the quill at its base with a hemostat and pulling it out. Intubation may be challenging or impossible with severe quillings as the quills may be lodged in the larynx (Figure 140.2). The hemostat may be rinsed in a bowl of water, which serves to contain the quills as well for easier clean-up (Figure 140.3). Removed quills are still sharp. After all visible quills have been removed, the head, neck, chest, and front limbs should be carefully palpated for migrating quills. Small incisions may be required to retrieve these quills.



Figure 140.2 A pit bull terrier type dog with a severe quilling, including quills in the larynx. Note the quill through the tongue, as well as the catheter in the saphenous vein. It may be easier to restrain a severely quilled dog for a hindlimb catheter in order to prevent the restrainer from being injured by the quills.



Figure 140.3 Hemostats and a bowl of water used to help remove quills.

Discharge Instructions

Dogs may be discharged as soon as recovered. Analgesics, such as NSAIDs, are often prescribed. Due to the antimicrobial nature of quills, infection is rare but a short course of antimicrobials may be prescribed if removal is accompanied by multiple incisions (see Chapter 200).

Owners should be advised that dogs will not avoid porcupine encounters in the future and additionally, that some quills might remain.

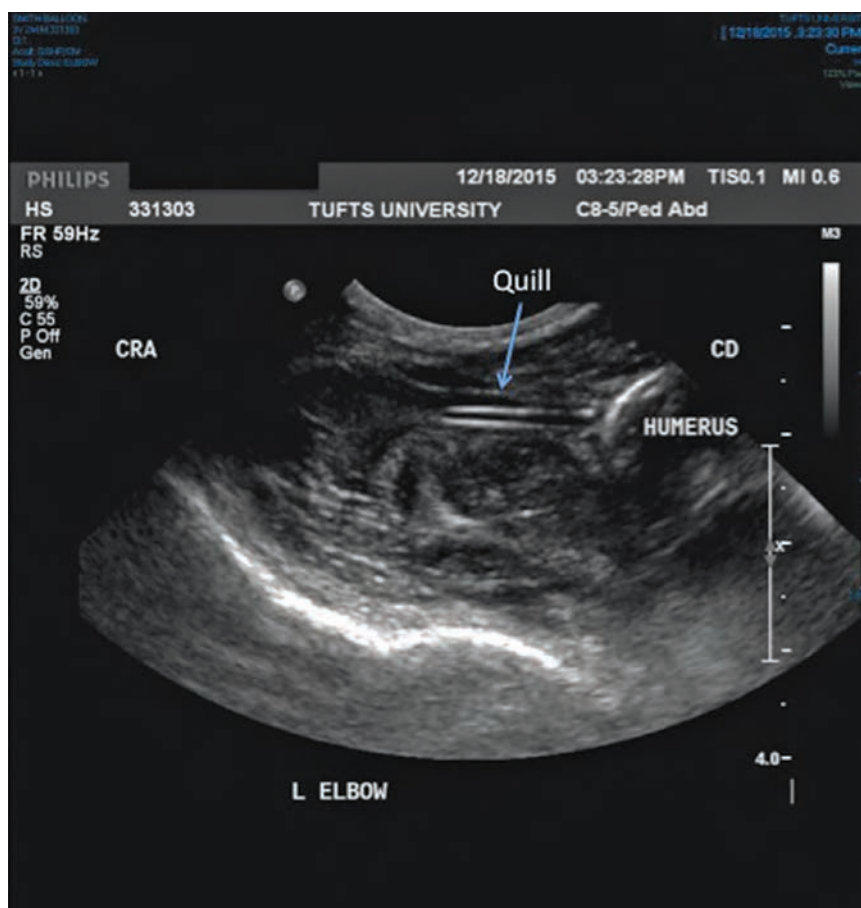
Rabies has not been reported after a quilling. One study identified that raccoons found with quills imbedded were more likely to be rabid, but this appears to reflect rabies infection in the raccoon, as rabies encephalitis caused the raccoons to attack porcupines, rather than the other way around [6]. A rabies booster vaccine is therefore not necessary after a dog attacks a porcupine, unless there is some other reason for considering rabies infection, such as a true porcupine attack during daylight hours. In the most recent report on rabies surveillance, there were no reported rabies infection in porcupines [7].

Complicated Quillings

Complicated quillings are defined as the presence of migrating quills that cause significant morbidity or even mortality [8–12]. Complicated quillings should be suspected in dogs that show signs of lameness, altered mentation, difficulty breathing, or swellings within a few days to several weeks after the quilling. Quills have been reported in the eyes, central nervous system, joints, and thorax [8–12]. Intrathoracic quills are associated with pneumothorax in some cases, usually within days of the initial quilling.

Treatment of quill-associated pneumothorax is surgical exploration and removal of the quill and any damaged lung parenchyma. Quills have also been found and removed from the heart and pericardium. Quills are hard to find with diagnostic imaging, although experienced and patient radiologists may be able to localize some migrating quills, particularly with ultrasound [9] (Figure 140.4). Complicated quillings are more common with severe quillings and those quillings that are not promptly addressed.

Figure 140.4 Ultrasound image of a quill in the front leg of a German short-haired pointer. This dog was non-weight-bearing lame 2 weeks after a severe quilling. Image courtesy of Dr. Heather Spain.



Conclusion

Most quillings are uncomplicated, and treated successfully in emergency rooms. Severe or complicated

quillings may be much more challenging and require careful evaluation and planning.

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Crotalinae Snake Envenomation*Raegan J. Wells, DVM, MS, DACVECC**Phoenix Veterinary Emergency and Referral, Phoenix, AZ, USA***Introduction**

Snake envenomation is a clinically significant cause of presentation to veterinary hospitals for small animal patients. Approximately 162 snake taxa are native to the United States, about 27 of which are front-fanged venomous taxa, with the majority of these belonging to the family Viperidae, subfamily Crotalinae. Pit vipers (Crotalinae), including rattlesnakes (*Crotalus* spp), copperheads and water moccasins (*Agkistrodon* spp), and pygmy rattlesnakes and massasaugas (*Sistrurus* spp), are responsible for approximately 99% of the venomous bites sustained in the US [1]. Crotalinae envenomation in the United States will be discussed, but general concepts of treatment and disease can be applied to victims in any region. Practicing veterinarians should orient themselves to the venomous snakes indigenous to the region in which their patients may have exposure.

A good deal of dogma surrounds snake behavior, characteristics of envenomation, and resultant clinical signs in victims. A common misconception is that young pit vipers cannot control the amount of venom injected with a bite, therefore resulting in a larger dose of venom. All pit vipers control the amount of venom injected during a bite, with the volume injected dependent upon the size of the snake's venom glands and the nature of the bite. Studies evaluating the flow and volume of venom injected with various types of bites (predatory or defensive) have confirmed that there is a percentage of bites without measureable venom delivery, and there may be a trend toward lower volumes injected with defensive bites [2].

While the mechanics of pit viper venom delivery is fascinating, the clinical reality is that most veterinary patients will present with clinical signs of envenomation. The decision to treat these symptoms will be directed by the severity of clinical signs and available resources.

Snake envenomation can occur at any time of year, depending upon the activity of the snakes and exposure of veterinary patients. In very warm climates, such as the Sonoran Desert, crotalinae envenomation occurs year round [3].

Crotalinae Envenomation

There is relatively more information available on Crotalinae envenomation in dogs compared to cats. The published mortality rates for Crotalinae envenomation are low, ranging from 1.8% to 24% in dogs and 6% to 18% in cats [3–14]. Non-survivors typically suffer envenomations to the head, including the eye and tongue, which may provide a more direct route to the central nervous system or predispose to asphyxiation. Dogs that have suffered distal limb envenomations and acutely died are suspected to have experienced intra-arterial envenomation. Envenomations to the trunk may lead to profound clinical signs, including hemoperitoneum and acute respiratory muscle paralysis [6,15]. Relatively speaking, cats appear more susceptible to profound muscle weakness [6,14]. Dogs with advanced age and increased time from envenomation to treatment are risk factors for death [3]. It is well accepted that Crotalinae envenomation has an overall low mortality rate, but patient suffering and morbidity may be profound, requiring significant and costly therapies. Nearly any body system may be affected following envenomation.

Crotalinae venom is a complex mixture of water, proteins, and peptides. Most of the proteins are enzymatic, while the peptides exert organ toxicity [4,5,16]. The classically described enzymes include hyaluronidase, which facilitates rapid spread of the venom by breakdown of the connective tissues; phospholipase A2, which leads to cytotoxicity, including the characteristic echinocytosis

and spherocytosis observed as well as anticoagulation via anti-Xa activity; thromboxane, which is at least partially responsible for the thrombocytopenia often observed; as well as snake venom metalloproteinases (SMVPs) which contribute to platelet dysfunction, leading to clinical hemorrhage [16–18].

Crotalinae venoms can cause profound and complicated alterations in the coagulation system, leading to both thrombosis and hemorrhage. These proteins can be broadly classified as FV and FX activators, activators of prothrombin, thrombin-like enzymes, anticoagulant factor IX/X binding proteins, activators of protein C, thrombin inhibitors, fibrinolytic enzymes as well as plasminogen activator (see Chapter 70) [19]. Some venoms contain potent neurotoxins, such as the Mojave venom that causes presynaptic inhibition and may lead to progressive paralysis. These toxins have been identified in the venoms of the Mojave rattlesnake (*C. scutulatus*), western diamondback (*C. atrox*), prairie rattlesnake (*C. viridis*) and southern pacific rattlesnake (*C. helleri*) and pose a significant risk of life-threatening neurological complications associated with envenomation [6]. Myotoxins have been identified in a number of venoms, placing patients at risk for widespread myonecrosis and profound neuromuscular weakness. The most salient point is that nearly any body system may be affected.

Clinical Signs of Envenomation

The classic clinical signs of Crotalinae envenomation involve pain, swelling, regional ecchymosis, and one to two small puncture wounds. It is reported that the Mojave rattlesnake may have pure neurotoxins, therefore making identification of a wound difficult.

Most animals presenting for evaluation following envenomation will exhibit local disease at the bite site, in addition to systemic clinical signs. Dogs often suffer bites to their muzzle, with extremity as the next most common site. Cats will often suffer bites to multiple regions of their body. These patients may present anywhere along the spectrum of compensatory to decompensatory shock (see Chapter 152). Bites to the tongue or mouth may swell rapidly, leading to upper airway obstruction. Hyperglycemia and hypokalemia may be appreciated as a consequence of catecholamine surge. Cardiac arrhythmias are common and should be monitored for (see Chapter 53). Pigmenturia may occur due to hemolysis, rhabdomyolysis or both (see Chapter 66). Anemia may occur due to hemorrhage, hemolysis or both. Thrombocytopenia may be observed, with or without prolonged bedside coagulation times (PT, aPTT) (see Chapter 67). Hyperlactatemia is common,

and likely due to both tissue damage and hypoperfusion. Widespread hemorrhage may occur, leading to hematemesis, hematuria, melena, epistaxis, pulmonary infiltrates or any combination thereof. Neurotoxicity may lead to seizures, nystagmus, or paralysis. Hypoventilation is a risk factor for patients with profound weakness and/or central nervous system involvement. Patients may exhibit any combination or degree of severity of these clinical signs.

Patient Evaluation and Stabilization

An extensive human snake bite severity score has been proposed for use in applying objective assessment to veterinary envenomations [20]. Computation of this score requires measurement of coagulation times and platelet count, so it may not be a practical tool for widespread application in veterinary medicine.

A practical approach to assessment of envenomation is to complete a thorough physical examination. Further measurements may be directed based upon abnormalities noted during physical examination. Additional monitoring to consider includes measurement of systolic blood pressure, electrocardiogram, venous blood gas and electrolytes, a complete blood count with blood smear for evaluation of manual platelet count, echinocyte and spherocyte assessment, chemistry panel to assess renal and hepatic function, urinalysis to assess for pigmenturia, and coagulation times. If client or hospital resources are limited, then an abbreviated laboratory evaluation may consist of a blood smear to evaluate for red blood cell abnormalities and platelet count, venous blood gas and electrolytes, packed cell volume and total protein, measurement of blood urea nitrogen and/or creatinine, and a urine specific gravity with visual inspection for pigmenturia. Cystocentesis is contraindicated due to risk of hemorrhage. Circumferential measurement of the bite site is painful and unlikely to confer any significant advantage to the patient, and is not routinely performed by the author.

Patients should receive a triage assessment immediately upon arrival to the hospital (see Chapter 2). If clinical signs of pain, any form of shock or any other abnormalities are noted, rapid venous access should be obtained while the remaining baseline evaluation of perfusion parameters is assessed. Hypovolemic shock should be treated with isotonic balanced electrolyte fluids, in titrated aliquots of blood volume (see Chapter 153). Analgesia should be provided, ideally with a reversible opioid agonist such as hydromorphone or fentanyl (see Chapter 193). Opioid administration is safe and should not be withheld for fear of exacerbating neurological symptoms.

Finally, neutralization of the circulating venom with antivenom is the ideal treatment for patients with clinical signs of Crotalinae snake envenomation. Advances in antivenom manufacturing have occurred in recent years, providing the clinician with safer and more effective options. Veterinarians must familiarize themselves with the venoms in their region, evaluate their patient's clinical signs and then decide if antivenom administration is necessary. It is important, however, to remember that neutralization of circulating venom is the most direct method to reverse or halt progression of clinical signs and minimize patient suffering.

Antivenoms

There are currently two Crotalinae antivenoms approved by the United States Department of Agriculture (USDA) for use in veterinary medicine: Antivenin (Crotalidae) Polyvalent (ACP) and Venom Vet™. Other antivenoms that have been demonstrated safe and effective in the peer review literature include CroFab™ and an F(ab')₂ polyvalent Crotalinae antivenom produced by Veteria Labs, in Mexico (Table 141.1) [3,10,11,14,21].

One antivenom product has predominated veterinary medicine for years: Antivenin (Crotalidae) Polyvalent (ACP), an equine origin antivenom comprised of whole immunoglobulin G (IgG) molecules. Newer antivenoms have been developed from enzymatic digestion of the whole IgG to cleave off the antigen (venom) binding region, termed fragment antigen binding (Fab) region, from the fragment crystallizable (Fc) portion. The creation of a smaller product lacking the Fc portion is believed to increase the volume of distribution and possibly result in a less antigenic product [22–25]. These Fab-based antivenoms include Crotalinae Polyvalent Immune Fab (CroFab™), an ovine origin single Fab-based molecule antivenom, and Fab dimer (F(ab')₂) equine origin antibody-derived antivenoms (Table 141.1). The Fab-based antivenoms tend to have a relatively short half-life and move outside of the intravascular compartment faster than other antivenoms and may necessitate re-administration if re-envenomation occurs. Compared to the Fab monomer, F(ab')₂ antivenoms have a longer half-life and remain in the vascular compartment longer. They also have 2 antigen binding sites per molecule, compared to 1 antigen-binding site on the Fab monomer.

Table 141.1 Commonly available Crotalinae antivenom formulations.

Immunoglobulin type	Formulation	Supplied as	Venoms used in production	Approval status as of March 2018
IgG – equine	Antivenom	Lyophilized powder	<i>Crotalus atrox</i> , <i>C. adamanteus</i> , <i>C. terrificus</i> , <i>Bothrops asper</i>	USDA approved for use in veterinary medicine
Longest T _{1/2}	Crotalinae Polyvalent (ACP)	Slow reconstitution		
150 kDa	Distributed by Boehringer Ingelheim Vetmedica	Room temperature storage		
2 venom-binding sites				
Fab – ovine	CroFab®	Lyophilized powder	<i>Crotalus atrox</i> , <i>C. adamanteus</i> , <i>C. scutulatus</i> , <i>Agkistrodon piscivorus</i>	FDA approved for use in human medicine
Shortest T _{1/2}	Distributed by Protherics	Fast reconstitution		Off-label use in veterinary medicine
50 kDa		Room temperature storage		
1 venom-binding site				
F(ab')₂ – equine	Venom Vet™	Liquid	<i>C. durissus</i> , <i>C. simus</i> , <i>Lachesis muta</i> , <i>Bothrops asper</i> , <i>B. alternatus</i> , <i>B. diporus</i>	USDA approved for use in dogs
Longer T _{1/2} than Fab, shorter than IgG	Produced by Instituto Biologico, Argentino S.A.I.C.	No reconstitution necessary		
110 kDa		Refrigeration necessary		
2 venom-binding sites				
F(ab')₂ – equine	Antivenom – <i>Bothrops asper</i> and <i>Crotalus durissus</i>	Lyophilized powder	<i>C. durissus</i> , <i>C. oreganus</i> , <i>C. o. helleri</i> , <i>C. adamanteus</i> , <i>C. scutulatus</i> , <i>C. atrox</i> , <i>C. horridus</i> , <i>Agkistrodon contortix</i> , <i>A. piscivorus</i> , <i>Bothrops asper</i>	Pending USDA approval for use in veterinary medicine
Longer T _{1/2} than Fab, shorter than IgG	Produced by Veteria Labs, S.A. de C.V.	Slow reconstitution		Import permits required for experimental use
110 kDa		Room temperature storage		
2 venom-binding sites				

There is one USDA approved F(ab')₂ antivenom available at the time of writing, Venom Vet™. This product is labeled to neutralize the venom of all North American Crotalinae snakes, and is a collection of purified pooled immunoglobulins from healthy horses immunized against multiple species (Table 141.1). There are no peer-review publications describing the clinical efficacy or use of this antivenom. Another widely used F(ab')₂ antivenom is Antivenom Bothrops asper & Crotalus durissus, imported from Mexico and distributed by Veteria Labs. This antivenom has been described in multiple peer review publications, and appears to be safe and effective [3,6,9,10,13,14]. The author finds this antivenom to be effective at clinical improvement with neurotoxins and myotoxins. One vial has been shown to be sufficient to neutralize clinical signs of rattlesnake envenomation in most dogs. Dogs with lower body weight and increased time from bite to presentation require more antivenom [3]. A safety study reported that up to 6 vials could be administered intravenously within one hour safely to healthy dogs [21].

A definitive dose of antivenom has not been established. Each batch of antivenom may have different antigen-binding abilities. It is reasonable to consider starting with two vials of F(ab')₂ antivenom in very small dogs or patients presenting with severe clinical signs such as cardiovascular collapse. Once it has been determined that antivenom is indicated, timely neutralization of venom should be prioritized, so the infusion should be administered as rapidly as possible. Initial infusion rates of 0.25–0.5 mL/kg/h are recommended while monitoring for signs of reaction. If no reaction is appreciated, the rate can be increased to administer the entire dose within 30–60 minutes. Cats may be more likely to experience a reaction to antivenom infusion, so close monitoring and slower infusion rates may be warranted in this species [14].

Some patients experience severe and protracted signs of envenomation, requiring multiple repeat boluses of antivenom. In these instances, it is sometimes advised to administer the antivenom as a constant-rate infusion (CRI). The dosing is empirical, and based upon human CRI protocols for bleeding diathesis [26]. Consider 1–2 vials over 6 hours continuously. Examples include patients with ongoing severe clinical signs such as neuromuscular collapse, profound hemolysis and/or rhabdomyolysis. It is not necessary to perform intradermal testing prior to antivenom administration, nor is it necessary to administer prophylactic diphenhydramine or glucocorticoids [1,3,11].

Endpoints to consider include optimization of perfusion parameters (heart rate, blood lactate, systolic blood pressure, electrocardiogram), resolution of coagulopathy as demonstrated by normalized coagulation times

and/or platelet count, sustained resolution or significant improvement in echinocytosis and spherocytosis if noted at baseline, lack of pigmenturia and/or progressive hemolysis, control of pain, and lack of progressive swelling or tissue damage.

Additional Therapies

There is an equine plasma protein product, RTL™ (MG Biologics), marketed as snake bite protein support for dogs. This is from horses that have been vaccinated against the Mojave, eastern diamondback, western diamondback, and prairie rattlesnake. The manufacturer recommends administration at about 4 mL/kg. Each bag contains 100 mL of unpurified equine plasma. Peer review literature evaluating safety or efficacy does not exist at this time. The author cautions against offering this therapy to canine and feline patients in lieu of purified antivenom products. Potential complications include volume overload due to relatively larger dose of colloid product compared to antivenom, and risk of acute and delayed hypersensitivity reactions.

Antibiotic prophylaxis has been a controversial topic in the treatment of Crotalinae envenomation. The consensus in human medicine is that antibiotics are not indicated unless evidence of an infection develops [27,28]. Recent veterinary literature evaluating dogs with rattlesnake envenomation does not support routine antibiotic prophylaxis [3,9]. Some wounds will require treatment, likely due to secondary compartment syndrome and opportunistic infections (see Chapter 166). When indicated, single agent with the narrowest spectrum and shortest treatment duration possible, guided by bacterial culture and susceptibility, is recommended.

Routine administration of glucocorticoids is not recommended. No morbidity or mortality benefit has been documented with use of glucocorticoids in dogs envenomated by Crotalinae spp, and potential risks of use outweigh the potential benefit.

Local wound treatment with laser therapy has been promoted by some veterinarians. Peer review evidence of this therapy is lacking. It is a reasonable therapy to offer, should only be used by individuals with proper training, and should not be applied more than every 8 hours. This is an adjunctive therapy and should not be offered in lieu of standard treatments such as neutralizing antivenom, fluid therapy, and analgesia. Non-steroidal anti-inflammatory medications are not recommended, as these patients are at risk for kidney injury due to hypoperfusion, coagulopathy, nephrotoxins in the venom, and pigmenturia. Additionally, gastrointestinal ulceration is possible secondary to hypoperfusion and coagulopathy.

Some patients may require transfusion of red blood cells to treat secondary anemia due to blood loss, hemolysis or both (see Chapter 176). Hemolysis with spherocytosis may be observed, sometimes as late as 72 hours following initial envenomation. It is most likely that these patients are experiencing ongoing envenomation, and treatment with antivenom should be prioritized over immune suppression. In patients experiencing hemorrhagic complications of envenomation, treatment with fresh frozen plasma is not indicated. The mechanism of coagulopathy in most cases is not due to factor deficiency, but rather a complex syndrome of factor inhibition, activation, platelet inhibition, and endothelial dysfunction. As such, neutralization of circulating venom with antivenom is the treatment of choice.

The only reliable means of envenomation prevention is avoidance. Common attempts at envenomation prophylaxis include aversion training and use of a rattlesnake vaccine, *Crotalus atrox* toxoid manufactured by Hygieia Biological Laboratories and distributed by Red Rock Biologics. This vaccine claims efficacy against *C. atrox* venom, and the manufacturer also notes possible protection against venoms of many other Crotalinae snakes. Canine challenge studies evaluating postvaccine antibody titers in dogs or support of clinical efficacy are lacking. A retrospective evaluation of dogs suffering rattlesnake envenomation reported no measurable benefit of vaccination [3]. There is no peer review evidence supporting prophylaxis of snake bite by using avoidance training, behavioral modification, or prophylactic vaccination.

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Elapid Snake Envenomation: North American Coral Snakes and Australian Elapids (Tiger Snakes, Brown Snakes, Taipans, Death Adders, and Black Snakes)

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Introduction

Elapids are venomous front-fanged snakes found in Australia, North America, South and Central America, Asia, Africa, India, and the Middle East. Fangs are often small, resulting in minimally traumatic bites. Therefore, failure to identify a bite site does not rule out envenomation. Elapid snakes may also give a 'dry bite' without injection of venom into the patient. The authors recommend that antivenom is used when there is clinical evidence of Australian elapid envenomation in dogs and cats. Because of the potential for anaphylactic reactions to equine immunoglobulins, antivenom should not be used in the absence of definitive signs of envenomation, and epinephrine should always be available when antivenom

is going to be used. In America, prompt treatment with antivenom is recommended for dogs found in close contact with a recently found dead or mutilated coral snake.

This chapter primarily discusses elapid envenomations in Australia and North America. The basic principles of treatment of envenomation may be helpful to guide treatment decisions for elapid envenomations in other countries, with the proviso that the correct antivenom needs to be administered (Table 142.1). Worldwide veterinary-specific information about elapids is often limited; a useful source of information about the human envenomation syndromes for individual species of snakes worldwide and recommended antivenoms can be found at the following website: www.toxinology.com

Table 142.1 Australian and North American elapid snakes, toxins, and recommended antivenoms.

Genus	Species	Venom toxins	Potential clinical effects	Recommended antivenom type and starting dose
North America elapids				
Coral snakes (<i>Micruroides</i> ; <i>Micrurus</i>)	Western coral snake or Arizona coral snake (<i>Micruroides euryxanthus</i>)	Neurotoxin (dogs, cats) Hemolysin (dogs)	Paralysis (severe) Hemolysis (mild, uncommon)	Suero Antiofídico Anticoral – Liquido- Solucion inyectable- Instituto Clodomiro Picado, Universidad de Costa Rica
	North American coral snake or Eastern coral snake or harlequin coral snake (<i>Micrurus fulvius</i>)			Coralmyn, Polivalent Anticoral Fabotherapeutic, Instituto Bioclon SA de CV, Mexico
	Texas coral snake (<i>Micrurus tener</i>)			Both require special permission to import
				1–2 vials. Increase dose to 5 vials if severe signs such as paralysis and hypoventilation, if the owners can afford

Genus	Species	Venom toxins	Potential clinical effects	Recommended antivenom type and starting dose
Australian elapids				
	There are over 100 different species of elapids within Australia; only those commonly associated with envenomation in animals are discussed below			Australian polyvalent snake antivenom 40 000 units (CSL) can be used to treat envenomation by all Australian elapid species. It is extremely expensive compared to monovalent antivenoms listed below
Brown snakes (<i>Pseudonaja</i>)	Dugite (<i>Pseudonaja affinis</i>)	Procoagulant Neurotoxin	Coagulopathy (severe) Paralysis (severe)	Brown snake antivenom 1000 units.
	Eastern brown snake (<i>Pseudonaja textilis</i>)			If requires intubation and ventilation, 3000 units
	Western brown snake or Gwardar (<i>Pseudonaja nuchalis</i>)			
	Speckled brown snake (<i>Pseudonaja guttata</i>)			
Black snakes (<i>Pseudechis</i>)	Red-bellied black snake (<i>Pseudechis porphyriacus</i>)	Procoagulant (mild?)	Hemolysis (severe) Anemia (severe)	Tiger snake antivenom 3000 units
		Hemolysin	Rhabdomyolysis (severe)	(black snake antivenom 18 000 units can be used but is more expensive)
		Myotoxin	Paralysis (minimal to severe)	
		Neurotoxin		
	Mulga snake or king brown snake (<i>Pseudechis australis</i>)	Hemolysin	Hemolysis (mild to severe)	Black snake antivenom 18 000 units
		Myotoxin	Anemia	
Copperheads (<i>Austrelaps</i>)	Common copperhead or lowlands copperhead (<i>Austrelaps superbus</i>)	Neurotoxins	Paralysis (mild to severe)	Tiger snake antivenom 3000 units
		Myotoxins	Rhabdomyolysis (severe)	
		Hemolysins	Hemolysis (severe)	
		Anticoagulant	Anemia (severe)	
Death adders (<i>Acanthophis</i>)	Common death adder (<i>Acanthophis antarcticus</i>)	Neurotoxins Anticoagulant	Paralysis (severe)	Death adder antivenom 6000 units
Taipan (<i>Oxyuranus</i>)	Coastal taipan or common taipan (<i>Oxyuranus scutellatus</i>)	Neurotoxins	Paralysis (severe)	Taipan antivenom 12 000 units
		Myotoxin	Rhabdomyolysis (severe)	
		Procoagulants	Coagulopathy (severe)	
		Hemolysins	Hemolysis (mild)	
Tiger snake (<i>Notechis</i>)	Mainland tiger snake, Western tiger snake, island tiger snake (<i>Notechis scutatus</i>)	Procoagulant toxins	Coagulopathy (severe)	Tiger snake antivenom 3000 units. If requires intubation and ventilation, 9000 units
		Neurotoxins	Paralysis (severe)	
		Myotoxin	Rhabdomyolysis (severe) Hemolysis (rare, mild)	

Elapid Species Identification

North America

The venomous Eastern coral snake can be easily identified as having a black snout, and yellow, black, and red bands encircling the body. The red and black rings are wider than the interposed yellow rings (Figure 142.1). Care should be taken not to become confused with the harmless scarlet king snake in which the yellow and red rings are separated by black rings (“Red on yellow kill a fellow, red on black, venom lack”). The other species of coral snakes in the Americas and Mexico will have color pattern variations specific to the species in a particular geographic location.

Australia

Snake coloration or relying on the public’s description is notoriously inaccurate for identifying snake species within Australia, with the majority of snakes being brown in colour even if they are a member of the Black (*Pseudechis*), Taipan (*Oxyuranus*), Copperhead (*Austrelaps*) or Brown (*Pseudonaja*) snake family or one of the many mildly venomous species of snakes. The following methods are recommended to help determine which type of antivenom should be administered.

- Identification of the snake by an experienced herpetologist. Veterinarians can attempt to identify dead snakes using a snake identification key for their local area which identifies snakes according to scale counts, body shape, and color. Catching, attempting to kill or examination of live elapid snakes by inexperienced

snake handlers should be strongly discouraged due to the significant risk of life-threatening human envenomation.

- Use of the Commonwealth Serum Laboratory (CSL) snake venom detection kit (SVDK) on the bite site, urine or blood. This kit determines the most appropriate antivenom to administer. The SDVK is not suitable for use outside Australia and Papua New Guinea.
- Knowledge of elapid snakes within the specific locality together with clinical signs can help determine the most appropriate antivenom to use [1]. See Table 142.1 for clinical signs of the major venomous elapid species. However, failure to respond appropriately to antivenom should always raise concerns that the wrong antivenom has been administered.

Pathophysiology of Elapid Venoms

Elapid snake venoms are a complex combination of toxins, with the venom of many species containing multiple neurotoxins, peptides, and enzymatically active and non-active compounds [2]. Despite the prodigious amount of research into elapid venom toxins, their mechanisms of action and treatment efficacy *in vitro* and recent studies of antivenom efficacy in human envenomations, there is limited research into the clinical syndrome of envenomation in dogs and cats. Additionally, there are many mild to moderately venomous elapids whose venom has not been researched.

There appear to be significant clinical differences in the envenomation syndromes of humans and other species, with humans being less susceptible to the neurotoxin effects of envenomation in comparison to dogs and cats [3]. It is also possible that the high incidence of severe paralysis in dog and cat envenomation is due to higher amounts of venom being injected by the snake, potentially due to the unrelenting attacking behavior of dogs and cats when hunting snakes.

Neurotoxins

Neurotoxins are classed as either presynaptic or postsynaptic and exert their effects at the neuromuscular junction, causing a rapid onset of lower motor neuron (LMN) paralysis. Many venoms contain both presynaptic and postsynaptic neurotoxins. Presynaptic neurotoxins belong to the phospholipase A₂ group of toxins and cause structural changes to the nerve terminal, preventing release of acetylcholine. *In vitro* studies have shown that presynaptic neurotoxins can become irreversibly bound and unresponsive to antivenom. Postsynaptic neurotoxins (as found in the western hemisphere elapids and some Australian elapids) act as antagonists at



Figure 142.1 The Eastern coral snake, *Micrurus fulvius fulvius*, is a venomous elapid snake characterized by the red and yellow colors lying adjacent to one another. It is geographically distributed in the south-eastern part of the United States.

acetylcholine receptors, and *in vitro* studies do not support irreversible binding, so theoretically there should be a rapid response to administration of appropriate antivenom.

Clinical experience in dogs and cats with Australian brown (*Pseudonaja*) and tiger (*Notechis*) snake envenomations which contain presynaptic neurotoxins indicates that severe acute paralysis can rapidly reverse with high doses of antivenom, and irreversible binding is likely to take longer than 24 hours and potentially several days [4]. Conversely, reports of envenomations when postsynaptic neurotoxins are present in both dogs and humans (in Australasia) have revealed cases in which improvement of paralysis has been delayed post antivenom [5,6].

Higher doses of neurotoxic venom have been associated with a more rapid onset of paralysis in dogs envenomated with tiger snake venom and the same is thought to occur in other elapid envenomations [7]. Dogs and cats which are active post envenomation tend to have a faster onset of clinical signs, probably due to muscular activity increasing lymphatic flow and absorption of the venom from the bite site. Paralysis is non-painful and humans have been reported to progress to severe paralysis while sleeping in a hospital bed.

Procoagulant Toxins

Prothrombin activators which are present in some Australian elapid venoms are either classed as group C prothrombin activators (*Oxyuranus* and *Pseudonaja* venoms), similar to factor XaVa prothrombinase complex, or group D prothrombin activators (*Notechis* venom) which is similar to factor Xa and requires the presence of the patient's factor Va for the procoagulant effects to be manifested. Procoagulant toxins cause diffuse intravascular thrombosis, consuming clotting factors and then resulting in venom-induced consumptive coagulopathy (VICC) with depletion of fibrinogen, factor V and factor VIII. Coagulation testing reveals prolongation of PT and aPTT commonly beyond the limits of test detection [4,8]. VICC and cerebral haemorrhage are the most common causes of human death in Australian snake bite. Acute renal failure occasionally occurs in patients with VICC and is potentially due to renal ischemia secondary to intrarenal microthrombosis.

Normalization of the patient's clotting times post antivenom administration takes a significant period of time due to the requirement for hepatic synthesis of replacement clotting factors, commonly at least 12 hours in dogs and cats after antivenom and 24–36 hours in humans [4,8]. Current human guidelines and clinical experience with animals indicate that one vial of antivenom should be sufficient to neutralize

procoagulant toxins. Clinical signs of hemorrhage are infrequent, and fresh frozen plasma is rarely indicated and should never be given before antivenom as it may worsen thrombosis formation [9]. Because of the severe coagulopathy and the potential for life-threatening bleeding, strict confined rest is recommended until clotting times normalize [10].

Anticoagulant Toxins

Several phospholipase A₂ toxins in Australian elapids have an anticoagulant effect on blood, causing prolongation of aPTT and potentially PT. Spontaneous hemorrhage does not occur and the prolonged bleeding times improve rapidly after antivenom administration [11,12].

Myotoxins

Various phospholipase A₂ toxins in Australian elapids can cause severe rhabdomyolysis. Increases in creatine kinase (CK) are generally delayed for at least 3–6 hours post bite, and minimizing patient muscular activity and early administration of antivenom prevent the development of rhabdomyolysis; delayed administration of antivenom is still worthwhile as it potentially prevents the worsening of rhabdomyolysis. CK can be severely elevated >5000 U/L, and in some patients massive elevations >500 000 U/L can occur. Elevations in CK do not immediately resolve post administration of antivenom; instead, CK plateaus and then gradually decreases [11,13]. Myoglobinuria is common and severe myoglobinuria may cause acute kidney injury (AKI) to develop [7,13,14]. Megaoesophagus secondary to myotoxins has been reported as a complication of Australian tiger snake envenomation in dogs, with reports of resolution taking up to 5 weeks [15].

Hemolytic Toxins

Some phospholipase toxins in North American and Australian elapids cause lysis of red cells, resulting in severe anemia, hemoglobinemia and hematuria, and potentially AKI [16]. Echinocytes or burr cells and evidence of red cell damage may be visualized on blood smear examination (see Chapter 66). The risk of development of anemia from exposure to hemolytic toxins appears to be species specific, with dogs having an increased susceptibility compared to humans and cats [11,13,16]. Rare cases of immune-mediated delayed hemolytic anemia in dogs have also been reported [17]. In envenomations due to Australian tiger snake bites and US coral snake bites, hemolysis may occur without significant anemia developing. Severe hemolytic anemia can develop in bites from Australian black snakes, copperheads, and taipans.

Local-Acting Cytotoxins

Localized tissue reactions or injury around the bite site are not a significant component of North American or Australian elapid envenomations and in most cases the bite is difficult to identify in dogs and cats. Mild local tissue swelling may occur associated with envenomating bites from Australian black snakes, taipans, and copperheads. Severe local tissue injury can occur to secondary to African and Asian cobra bites, which are also members of the elapid family [18].

Clinical Signs of Envenomation

Any of the following clinical signs are an indication for antivenom administration.

Preparalytic Signs

Preparalytic signs most commonly occur within 30 minutes or less of the bite, and can include one or more of vomiting, salivation, inappropriate urination or defecation, trembling, tachypnea or collapse and then a period of apparent recovery. In dogs, preparalytic signs have been associated with an LD₅₀ dose or higher of *Notechis* venom or progression to clinical signs of envenomation [4,7].

Paralysis

Elapid venoms are primarily neurotoxic, resulting in paralysis, and in severe cases death from ventilatory failure. Any signs of LMN paralysis, even if mild, are an indication for antivenom if there is known contact with an elapid. Elapid snake envenomation should be considered as a differential diagnosis for any animal which develops rapidly progressive LMN paralysis in endemic areas.

Australia

Classically, clinical signs start with a decreased gag, weak or absent palpebral reflex, then weakness of the limbs and a mildly ataxic gait, followed by recumbency, inability to hold the head up, difficulties swallowing and ptialism due to pharyngeal paralysis, loss of all withdrawal reflexes and complete LMN paralysis with signs of respiratory distress, hypoventilation, and then finally respiratory arrest. Mydriasis is a relatively late clinical sign. Brachycephalic breeds can develop respiratory distress as an early sign when envenomated. Because of the potential for irreversible binding of neurotoxins and requirement for prolonged periods of hospitalization or ventilation, sufficient antivenom should be administered early in the course of envenomation. The onset

and speed of progression of paralysis is highly variable. Dogs occasionally require ventilation within 30 minutes of being bitten or can take 6–12 hours to develop signs with rare reports of longer time periods. Therefore, the patient must never be left unobserved when monitoring for potential snake bite.

Cats occasionally have a more delayed presentation and may be presented with signs of severe paralysis after their owners notice that the cat hasn't moved off the same piece of furniture for 12–24 hours.

Complications of paralysis include aspiration pneumonia, corneal ulcers, and detrusor atony. If ventilation is required then multiple vials of antivenom are associated with a more rapid improvement in tiger and brown snake envenomations [4].

North America

Coral snake envenomations have a similar progression of paralysis as above and also have a variable time course for onset of clinical signs of paralysis, varying from immediately post bite to 36 hours later, with the majority showing clinical signs within 2–4 hours of being bitten. Any sign of weakness or illness after close contact with a coral snake is an indication for antivenom, especially if the venous PCO₂ is increasing toward 65 mmHg.

Coagulopathy

Coagulopathy can occur with Australian elapid envenomations and is an indication for administration of antivenom (see Chapter 70). VICC is associated with severe prolongations of PT, aPTT, and ACT test beyond the limits of test detection. Clinical bleeding occurs infrequently in dogs and cats and can include bleeding from oral wounds, hematuria, hyphema, gastrointestinal hemorrhage and, very rarely in small animals, internal bleeding or central nervous system hemorrhage [4,17]. Large hematomas can occur associated with venepuncture, cystocentesis, and oral wounds; therefore jugular venepuncture should be avoided if possible and pressure bandages placed over sites of venepuncture. Occasionally, dogs and cats will not develop coagulopathy despite other clinical signs of envenomation from a species of snake known to have procoagulant toxins. Anticoagulant toxins may just cause a mild prolongation of APTT which does not progress to a severe coagulopathy.

Rhabdomyolysis

Rhabdomyolysis commonly occurs with Australian elapid envenomations at least 3–6 hours post bite and is primarily detected by recognition of myoglobinuria or elevated CK on testing. Myoglobinuria can be severe, with urine

dark brown to black in color. Humans often report significant muscle pain secondary to venom-induced rhabdomyolysis although this is more difficult to appreciate in dogs and cats. Regurgitation secondary to megaesophagus may occur in dogs and take weeks to resolve.

Hemolysis and Anemia

Severe hemolysis and anemia can develop in bites from Australian black snakes, copperheads and taipans; antivenom is indicated and blood transfusions may be required.

In envenomations due to Australian tiger snake and US coral snake bites, hemolysis may occur without significant anemia developing. Hemolysis only occurs in approximately 50% of the dogs that are bitten by North American coral snakes. The hemolysis is usually not life-threatening but pigmenturia should be treated with intravenous crystalloid solutions and is an indication for antivenom (see Chapter 167).

First Aid Advice for Owners

Because of the potential for rapid onset of clinical signs of paralysis, any owner who phones to say that their pet has been bitten or may have been in close contact with a snake should be advised to minimize activity and present their pet for immediate veterinary examination. If owners describe an already collapsed patient, provide instructions on how to perform mouth-to-nose ventilation if required en route, as the most common cause of acute death in dogs and cats is hypoxemia secondary to respiratory paralysis. A firm crepe pressure bandage can be applied to a bitten limb and has been shown to slow venom absorption; however, in dogs and cats, most bites are found on the head, neck, and thorax and in these locations pressure bandages are contraindicated.

Treatment of Envenomation in Dogs and Cats

Patients should be under constant observation because of the significant risk of rapid onset of paralysis. Dogs occasionally progress from walking to respiratory arrest within 15–30 minutes.

Asymptomatic Patients

An IV catheter should be placed (avoid the jugular vein) and blood collected to evaluate PT, aPTT or ACT, PCV, TP, hemolysis, and CK (where geographically indicated). Urine should be collected to assess for pigmenturia. In

Australia, a SVDK is recommended if signs of envenomation are present and there is an uncertainty regarding which antivenom to administer. Cystocentesis should be avoided, if coagulopathic. Neurological assessment is performed to assess for evidence of paralysis. The presence of paralysis, coagulopathy, hemolysis or anemia and known contact with an elapid snake are indications for antivenom.

When a severely envenomated patient presents, the first steps in treatment follow the ABC approach (see Chapter 2). Assess if the patient has a patent airway (suction/swab any saliva present), intubate if the patient is apneic or severely paralyzed and unable to breathe and start manual or machine ventilation with 100% oxygen if apneic or hypoventilating ($\text{ETCO}_2 > 60 \text{ mmHg}$) (see Chapter 188). Most severely envenomated dogs and cats will respond well to oxygen support and assisted ventilation, allowing time to perform diagnostics and start appropriate treatment. Bradycardia is common during severe envenomations, is not associated with hypotension and normally resolves with improvement in oxygenation. Hypotension can occur but normally resolves with appropriate correction of hypoxemia or a conservative fluid bolus.

Antivenom is administered diluted at least 1:1 in Hartmann's/lactated Ringer's or 0.9% NaCl and administered over 20–30 minutes with close monitoring for evidence of anaphylaxis occurring, unless cardiac arrest has occurred in which case it is administered as a bolus. Epinephrine should always be readily available. If anaphylaxis is suspected 0.01 mg/kg epinephrine is administered IM, and it may be necessary to repeat it in 15–20 minutes if the vital signs do not stabilize. Intravenous adrenaline should be avoided except in the situation of cardiac arrest because of the potential for cardiac arrhythmias and intracranial hemorrhage if VICC is present.

There is significant variation between the purity and potential risk of anaphylaxis between antivenoms from different countries. If dexamethasone and antihistamines are recommended by the manufacturer prior to administration, this recommendation should be followed. In Australia, antivenom is highly purified and the incidence of anaphylactic reactions in dogs and cats is 10%; when they do occur, reactions are rarely severe [4].

The patient's neurological status should be reassessed immediately after administration of antivenom. If there is deterioration in neurological status, further antivenom should be administered.

In Florida, cost restrictions usually limit the administered dose to 1–2 vials of coral snake antivenom [19]. The Costa Rican product used is purified and requires no preventative hypersensitivity treatment. In Australia, if VICC or anticoagulant coagulopathy is present, a single dose of antivenom should be sufficient to neutralize

the effects of the procoagulant or anticoagulant toxins. With VICC, the coagulopathy normally improves within 12 hours in dogs and cats although normalization of clotting times may take up to 24 hours post antivenom. Fresh frozen plasma is only recommended if it has been at least 6 hours post bite and only if life-threatening hemorrhage is suspected and antivenom has already been administered [9]. Strict confined rest is recommended until the patient's clotting times have normalized.

If myolysins are present and CK continues to rise significantly 6 hours after antivenom, and there is severe myoglobinuria, further antivenom should be administered

and intravenous crystalloid should be infused at an approximate twice maintenance dose of 120 ml/kg/day until the pigmenturia clears. The urine output should be closely monitored because of the risk of AKI developing. Pigmenturia secondary to myoglobinuria often improves rapidly once sufficient antivenom has been administered. Humans report significant muscle pain associated with myotoxins and opiate analgesia should be administered to dogs and cats (see Chapter 191).

Dogs and cats should remain under close observation until all signs of envenomation have resolved. Strict confined rest for 1–2 weeks is recommended after discharge.

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Spider and Scorpion Envenomation

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Spider Envenomation

There are more than 41 000 species of spiders in the world and although almost all of them are technically venomous, only a few of them are considered medically important. The two most important clinical syndromes associated with spider bite worldwide are loxoscelism and latrodectism. There are other venomous spiders of significant medical importance but they are confined to relatively small geographical regions and will not be addressed here. Spiders of the family Theraphosidae will be briefly discussed as they can cause significant envenomation of dogs and cats.

The actual incidence of spider bites is very difficult to determine, especially in veterinary patients where it is unlikely that a spider bite can be verified. The risk of spider bites as perceived by clinicians and the lay public far exceeds the actual risk and leads to frequent misdiagnoses [1].

Loxoscelism

Loxoscelism describes the bite of spiders from the genus *Loxosceles*, commonly known as recluse, fiddle-back or brown spiders. There are alleged cases of necrotic arachnidism due to non-*Loxosceles* spiders, but these have not been definitively diagnosed. There are more than 100 species of *Loxosceles* spider and most are found in South America. They are endemic in the central and southern United States but are not found in the states on the east or west coasts or along the Canadian border.

The classic abnormality associated with loxoscelism is dermonecrosis. The exact pathogenesis of *Loxosceles* venom is not fully understood. Key components of the venom include phospholipases and hyaluronidase [2]. The venom can trigger an intense inflammatory

response and has direct hemolytic effects. The bite itself is not painful and human patients are often unaware that they have been bitten. This makes a definitive diagnosis challenging. It is believed that most bites by *Loxosceles* spiders cause minor erythema and edema and are self-limiting. Cutaneous loxoscelism describes the development of skin necrosis and ulceration at the bite site. Skin necrosis in human patients takes 72 hours or more to become evident. A dry necrotic eschar forms and detaches after 2–3 weeks, leaving an ulcerated lesion that can take weeks or months to heal.

Cutaneous loxoscelism is associated with non-specific systemic signs in many cases such as fever and vomiting. In contrast, systemic loxoscelism is very uncommon and is associated with intravascular hemolytic anemia developing over 7–14 days. Acute kidney injury in systemic loxoscelism is rare and has been associated with a poorer outcome in human cases [1,2].

The diagnosis is generally based on the presence of a cutaneous lesion with non-specific systemic signs in a patient with an appropriate epidemiological history. This means the patient must have been in a geographical area known to have *Loxosceles* spiders for the diagnosis to even be considered. In reality, loxoscelism is exceedingly rare. These spiders hide in dry dark places and are not aggressive; most human bites occur when the spider is trapped against the person. The likelihood of them biting animals is considered very low.

There are numerous other diseases that can cause necrotic skin lesions that may be misdiagnosed as a brown recluse spider bite. These include severe soft tissue infection (streptococcal or staphylococcal infections), pyoderma, neoplasia, toxic epidermal necrolysis, erythema multiforme, purpura fulminans, and localized vasculitis (see Chapter 137). All possible diagnoses should be investigated before considering necrotic arachnidism as a likely cause.

There are no confirmed cases of loxoscelism published in the veterinary literature. There is a case report from Brazil of a dog with necrotic skin lesions “probably” due to a *Loxosceles* spider. This lesion was treated symptomatically and the lesions took 2 months to heal [3]. There are innumerable anecdotal cases of skin lesions attributed to a spider bite in veterinary medicine; many are from geographical regions that do not have loxoscele spiders. It is likely that most of these cases are a misdiagnosis and unfortunately there is no way to determine the true incidence or nature of spider envenomation in our patients at this time. Readers are directed to Isbister and Whyte for a suggested diagnostic approach to patients with necrotic, ulcerative skin lesions [4].

Recommended first aid for a brown recluse spider bite includes elevation and immobilization of the affected limb, ice packing of the bite site, and local wound care. Supportive care is provided as indicated. Other adjunctive therapies have been suggested but none has been proven to be of benefit. Most loxoscele spider bites are self-resolving without medical intervention. Cases of severe necrosis may require surgical management but this is very uncommon and is rarely life threatening (see Chapter 166). There are conflicting reports regarding the possible benefits of glucocorticoid therapy. No detrimental effects of glucocorticoid therapy have been reported and they are commonly given to human cases of spider bite. There is no loxosceles antivenom available in the United States, although *L. lateum* antivenom is available in Mexico and South America and may be of benefit if administered within 8 hours of the bite.

The prognosis for recovery from a brown recluse spider bite is excellent; severe necrosis may lead to subsequent scarring but this is a rare occurrence [1,2].

Lactrodectism

The widow spider group is the most medically important group of spiders in the world, causing the greatest number of human deaths. These spiders are from the genus *Lactrodectus* and are found worldwide. The venom of these spiders contains numerous toxins; the most clinically relevant toxin in mammalian envenomation is the alpha-latrotoxin. It has a unique selective effect on nerve endings, causing initial activation followed by depletion of neurotransmitters and subsequent flaccid paralysis. The female spider has fangs long enough to envenomate animals or people [2,5].

People often report little or no pain at the time of the bite but in 5–60 minutes local pain develops with increasing intensity. There may be local swelling or visible puncture marks but the major clinical sign is pain. About a third of human widow bite cases will have systemic signs, as outlined in Table 143.1. Pain is still the

dominant sign; acute abdominal pain, muscle cramps, and/or spasms are all reported. Weakness, malaise, blepharoconjunctivitis, rhinitis, and photophobia are the more common systemic signs reported in people suffering lactrodectism in North America. Infants commonly present screaming in pain and often appear to have an acute abdomen and rigidity without pyrexia. Death is rare in human medicine and usually occurs in young, old or infirm patients [2].

There is considerable species variability in susceptibility to black widow envenomation. Guinea pigs and horses are highly susceptible, cats are moderately susceptible, and dogs are relatively resistant to the effects of the venom [6,7]. The single well-described case of feline black widow spider envenomation in the literature reports acute distress with muscle stiffness and pain of the abdomen and pelvic limbs. These signs progressed to muscle weakness, flaccid paralysis, and respiratory difficulties. There was significant elevation in creatine kinase and aspartate aminotransferase. The cat was treated with a vial of antivenom and slowly improved over 5–6 days [8]. There are many anecdotal reports of black widow spider bites in dogs and cats. Most of the cases are unsubstantiated but the general clinical presentation is one of acute pain and cats tend to be more severely affected than dogs.

There is little first aid indicated for a widow spider bite; application of an ice pack may help relieve the local pain. The majority of widow spider bites in people do not require medical therapy. In more severe

Table 143.1 Systemic signs reported in human patients with latrodectism.

Organ system	Abnormality
Cardiovascular	Bradycardia, tachycardia, arrhythmias, hypertension
Respiratory	Bronchial secretions, bronchoconstriction, pulmonary edema
Central nervous system	Psychoses, amnesia, confusion, insomnia, hallucinations, delirium
Peripheral nervous system	Pain, lacrimation, salivation, rhinitis, priapism, mydriasis, miosis
Skeletal and smooth muscle	Hypertonia, clonic contractions, fasciculations
Gastrointestinal	Nausea, vomiting, heartburn, hypersalivation, acute abdomen
Renal	Urine retention due to sphincter tone Nephritis
Hematology	Leukocytosis, neutrophilia, lymphopenia, eosinophilia, monocytosis, hemoconcentration

envenomations, supportive care should be provided, including parenteral opioid analgesia, as indicated. Antivenom therapy has been commonly recommended for patients with systemic signs, although antivenom administration is controversial as strong evidence for its efficacy is currently lacking. A randomized placebo-controlled study of widow spider envenomation in Australia found no improvement associated with antivenom therapy [5,9]. Muscle relaxant therapy with methocarbamol or diazepam has been used to treat muscle spasms.

Other therapies suggested for latrotoxicity include corticosteroids, magnesium, and calcium administration. Evidence for the efficacy of these therapies is scarce and they are not currently recommended in human medicine [2].

Theraphosidae Spiders

Spiders from the family Theraphosidae are commonly known as tarantulas, bird-eating, spiders or whistling spiders. Envenomation by these spiders has minor effects in humans but can have fatal effects in animals, including cats, dogs, rats, mice, and birds. There are several cases of Theraphosidae envenomation reported in dogs in Australia. All nine cases reported died, including two dogs that were 40–50 kg in size. Many of the dogs died within 1–2 hours of being bitten [10,11]. There is limited information on the venom of Theraphosidae. As there are no reports of pets suffering tarantula bites from North or South America that the author is aware of, it is possible that members of this spider family from Australia are more venomous than other regions of the world. But given the increasing popularity of keeping Theraphosidae spiders as pets where dogs and cats may be exposed, it is important to be aware of the possible risks.

There are no specific treatment recommendations currently for Theraphosidae envenomation other than symptomatic and supportive care.

Scorpion Envenomation

Scorpions, like spiders, are members of the class Arachnida. They have eight legs, grasping appendages at the head known as pedipalps, and a long, segmented tail. The terminal segment of the tail is a venomous stinger known as a telson. There are over 1700 species of scorpions, although only a small number of them are considered capable of causing clinically significant envenomation. Scorpions live in tropical and temperate regions of the world and pose a significant human health issue in many areas. Some of the important genera are *Centruroides*

in North America, Central America, and parts of South America, *Tityus* in South America, *Androctonus* and *Buthus* in North Africa, *Buthus* and *Leiurus* in the Middle East, and *Mesobuthus tamulus* in India. In the United States and Mexico, stings of *Centruroides sculpturatus* (bark scorpion) are potentially fatal to small children [12]. There is very little published information regarding scorpion envenomation of dogs or cats and our understanding is largely based on the human literature.

Pathophysiology of Envenomation

Scorpion venom is a complex mixture of numerous toxic substances and there is substantial variation in composition between species. The venom can contain acetylcholinesterases, serotonin, histamine, protease inhibitors, phospholipase, hyaluronidase, and neurotoxins [7,12]. The toxins with the greatest medical importance are neurotoxins that bind to sodium, potassium, and calcium channels. Scorpion alpha-toxins bind to mammalian voltage-gated sodium channels causing membrane hyperexcitability and repetitive, uncontrolled axonal firing. The result is autonomic dysfunction and neuromuscular activity. In addition, there can be massive endogenous release of catecholamines and other vasoactive peptides, including neuropeptide Y and endothelin-1.

Clinical Effects of Scorpion Envenomation in People

Scorpion envenomation varies in severity and clinical signs, but overall the clinical consequences are a manifestation of neurotoxic excitation syndromes leading to primarily cardiovascular and neurological abnormalities.

Pain, paresthesiae, and numbness are commonly reported in the region of the scorpion sting, soon after envenomation. Most stings only have local signs but it is possible to see systemic signs with stings of the more venomous scorpions.

Stimulation of the sympathetic nervous system can result in tachycardia, hypertension, mydriasis, restlessness, and seizures. If cholinergic stimulation is significant, it can lead to bradycardia, vasodilation, miosis, salivation, lacrimation, vomiting, and priapism. Abnormal sympathetic and/or parasympathetic tone can cause cardiac arrhythmias, including atrial tachycardia, ventricular premature contractions, ST segment changes and, less commonly, bundle branch block (see Chapter 53) [13]. Generally, the more severe envenomations are associated with predominantly sympathetic signs. Myocardial ischemia and myocarditis can occur following some species of scorpion envenomation found in Africa, the Middle East, and Asia. Neuromuscular excitation in people can be manifested as visual disturbances,

abnormal ocular movements, fasciculations, paralysis, and unco-ordinated muscular activity.

A simple grading system for evaluation of scorpion stings in human patients was recently published. A slightly abbreviated version of this grading system and general treatment recommendations is shown in Table 143.2 [13].

Treatment of Scorpion Envenomation in People

The treatment approach to scorpion envenomation varies with the severity of the sting and a summary is provided in Table 143.2. It has been recommended that patients who present with grade 1 or 2 envenomation remain under observation for 4 hours in case of progression to a higher grade of severity. Antivenom therapy is controversial and results of studies to date have been variable. In North America, scorpion antivenom is considered beneficial but not cost-effective for routine use and it has been suggested that it should be reserved for severe envenomations [14]. In addition, the benefit of antivenom is questionable once severe systemic envenomation has been established. Benzodiazepines are

Table 143.2 Classification and treatment of scorpion stings for human patients [13].

Clinical Grade	Clinical Effects	Potential Treatment
Grade 1	Local manifestations only	
	Pain	Analgesia
	Paresthesia	Local anesthesia
	Numbness	
Grade 2	Autonomic excitation	Antivenom
	Hypertension	Prazosin
	Agitation and anxiety	Oral benzodiazepines
Grade 3		Antivenom
	Pulmonary edema	Oxygen therapy +/- mechanical ventilation, vasodilators (e.g. prazosin)
	Hypotension & cardiogenic shock	Dobutamine, other inotropes
	Severe neuromuscular excitation	Benzodiazepine infusion
Grade 4	Multiorgan failure including coma, seizures and end organ damage due to hypotension	Antivenom
		Mechanical ventilation
		Inotropes
		Benzodiazepine infusion
		Supportive care

used in human patients to control the neuromuscular hyperactivity and opioids are commonly indicated for analgesia. Atropine administration is often avoided as, although it can alleviate many of the cholinergic signs, it may worsen the adrenergic effects. Alpha-adrenergic receptor antagonists such as prazosin and doxazosin may be of benefit to reduce some of the cardiovascular abnormalities and prevent pulmonary edema [15].

Scorpion Envenomation in Dogs and Cats

There are numerous anecdotal reports of scorpion envenomation in dogs and some suspected cases in cats. In 2008 the Veterinary Pet Insurance company reported that scorpion stings were the fifth most common animal-induced injury to pets reported for claims.

The only published case report the author could find described scorpion envenomation (*Tityus bahiensis*) in a dog from Brazil. The presenting signs included intermittent drowsiness with bouts of vocalization and aggressiveness, tachypnea, tachycardia, and a painful region of the right thoracic limb. The animal was managed with supportive care, including a local anesthetic block around the area of the sting, and was asymptomatic by 24 hours [16].

Anecdotal reports of scorpion stings in dogs in the US are commonly described as having local signs with pain at the site of the sting but very little swelling. The *Centruroides sculpturatus* scorpion may also cause coughing. Potential reasons for scorpion envenomation to cause a cough include paresthesia of the mouth and oropharynx, as well as pulmonary edema.

Anecdotal reports of treatment of scorpion stings in dogs in the US commonly describe the use of antihistamines and glucocorticoids. There is no mention of antihistamine therapy in the treatment of human patients with scorpion stings. Given the commonly reported clinical signs of scorpion envenomation in dogs, it seems unlikely that antihistamines would be of benefit. Similarly, glucocorticoids are not used in routine therapy for scorpion envenomations in people. Studies evaluating the role of hydrocortisone in treating scorpion stings in adults and children found no benefit [17,18]. Unless there is a specific indication for their use, routine administration of glucocorticoids to treat scorpion envenomation cannot be recommended.

Analgesia is an important part of management of these cases (see Chapter 193). If severe systemic signs are present, supportive care as outlined for human patients is indicated. If severe adrenergic signs such as hypertension and tachyarrhythmias are evident, there may be a role for alpha-adrenergic receptor antagonist drugs such as prazosin (see Chapter 63). Scorpion antivenom may be beneficial in severe envenomations, but may not be

feasible in veterinary patients given the costs associated with this product.

To the author's knowledge, there are no published reports of scorpion envenomation in cats. It has been sug-

gested that cats may be more resistant to scorpion venom than dogs but there is no evidence to support this claim. It is possible that cats are more careful and agile than dogs so may not be as likely to be exposed to scorpion stings.

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Bufo Toad Toxicosis

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Introduction

The cane or giant toad, previously classified as *Bufo marinus*, now classified as *Rhinella marina*, is a large terrestrial toad native to Central and South America. While hundreds of species belonging to the *Bufo* genus are distributed throughout the tropical and temperate regions of the world, the classic toxicity is seen with the cane or giant toad; these are widely distributed through Central and South America, parts of the US such as southern Florida and Texas, and northern Australia. Other species of *Bufo* toads are more widely spread but are associated with less severe clinical signs.

The cane toad was first introduced to the states of Florida and Hawaii in North America, and Queensland, Australia, in the early 1900s as a biological pest control measure in sugar cane and other plantations. They owe their colonizing success to the lack of predators, their ability to eat other animals, including native frogs and toads, their adaptability to agricultural and urban settings, and their high fecundity. Shortly after introduction to different

regions of the world, the cane toad became a significant threat to local species and companion animals.

Bufo toads can measure 10–23 cm and females can weigh up to 1.5 kg [1], hence they are often referred to as “giant toads.” These stout and short-legged amphibians vary in color from tan to dark brown with spotted patterns; the source of their venom is two large parotid, warty-like glands located behind each eye extending from the temporal region past their shoulder area (Figure 144.1). These glands secrete a milky venomous fluid, which serves to deter predators, helping this species to survive in difficult environments.

As with many venomous animals, the composition of this venom is very complex. The venom's main two components are biogenic amines and steroid derivatives (Table 144.1) but the composition of the venom varies significantly, depending on the species of the toad and geographical differences [2,3]. The components of the venom have significant effects on the victim's neurological, cardiovascular and gastrointestinal systems, leading to the signs of toxicosis observed in both humans and companion animals.



Figure 144.1 Adult cane toad on a residential lawn in North Palm Beach, Florida. Reproduced with permission of Michael West.

Table 144.1 Components of *Bufo* venom and associated systemic effects.

	Components	Effects
Biogenic amines	Epinephrine, norepinephrine	Tachycardia, hypertension, hyperthermia, visceral vasoconstriction, bronchodilation
	Bufotenin, bufotionin, dihydrobufotenin	Hallucinogenic effects
	Serotonin, 5-hydroxytryptophan	Hallucinogenic effects, seizures, tremors, ptyalism, abdominal pain
Steroid derivatives	Ergosterol, cholesterol, gamma-sistosterol	No effects
	Bufagins and bufadienolids (e.g. arenobufagin, bufotalin, cinobufagin, marinobufagin)	Cardiac effects with digitalis-like action

Incidence

Because of the curious nature of dogs and cats, *Bufo* toads are a highly attractive, venomous threat to companion animals. According to a survey among general practice and emergency veterinarians from the United States, Canada, Australia, and the UK, 51% of the respondents chose animal envenomation as the most common toxin exposure in dogs and 9% of these cases were associated with toad toxicosis [4]. On the other hand, 40% of respondents to the survey chose animal envenomation as the most common exposure in cats, and only 1% of these cases were related to toads. *Bufo* toxicosis in dogs is most commonly reported during the warm months of the year in south Florida (March–November) with no events reported during the month of December [5]. The seasonal distribution of *Bufo* toxicosis follows a similar pattern in Australia, where the incidence of toad toxicosis drops between the months of June and September, when the temperature and rainfall averages are lowest [6]. Seasonal increases in cases of envenomation during the summer and heavy-rainfall months are correlated to the time of peak breeding activity of the giant toads, while the drop in case reports during the winter months is likely due to hibernation behavior.

Signalment

Cats are not commonly envenomated by *Bufo* toads compared to dogs, and reports of *Bufo* toxicosis in cats are not found in the veterinary literature. The reason for the

apparent low incidence of *Bufo* toxicosis in cats is likely multifactorial but it may be due to the fact that outdoor cats are less likely to receive veterinary attention when exposed to a toxin, or in this case shortly after exposure to a venomous animal, and are less likely to bite or ingest relatively large animals.

Toad envenomation can affect dogs of all breeds and ages. Small breeds represent the vast majority of dogs affected by toad toxicosis. Terriers appear to be the breed most commonly affected with *Bufo* toxicosis. In one retrospective study, 76% of dogs in Australia intoxicated by cane toads were small breed and from this group of dogs, 73.5% were considered pure- or mixed-breed terriers [6]. These findings were also observed in a previous study in south Florida, where the most common breeds affected by this toxicity included Yorkshire terriers, Jack Russell terriers, West Highland white terriers, dachshunds, and toy poodles [5]. No sex predilection was identified in these studies. Younger dogs, less than 4 years old, appeared to be more frequently affected in one study [6].

Clinical Signs of Envenomation

Absorption of the *Bufo* toxins is through the oral mucosa and upper gastrointestinal mucosa, or cutaneous wounds. Dogs and cats are exposed to the toxin after mouthing or ingesting the toad. The hallmark clinical sign of *Bufo* toxicosis is hyperemic “brick-red” mucous membranes (Figure 144.2). Hyperemic gums were recorded in 51% and 63% of dogs with suspected *Bufo* toxicosis in two retrospective studies [5,6]. Among the clinical signs of dogs affected with cane toad toxicosis in south Florida, neurological abnormalities were most frequently observed,



Figure 144.2 An 11-year-old, neutered male West Highland white terrier with signs of *Bufo* toxicosis; note the hyperemic mucous membranes. Reproduced with permission of Michael West.

followed by hyperemic mucous membranes, ptialism, collapse, tachypnea, and vomiting [5]. Another retrospective study of dogs in Australia found that increased salivation was the most common clinical sign observed followed by hyperemic mucous membranes, seizures, weakness/ataxia, cardiac arrhythmias, muscle tremors, and vomiting [6]. Dogs with mild envenomation or envenomation with other, less toxic species of *Bufo* toads are likely to present with signs of hypersalivation and red mucous membranes. Moderate to severely envenomated dogs most commonly present in status epilepticus or during the postictal phase after having seizures at home or on their way to the hospital.

In humans, *Bufo* toxicosis is associated with gastrointestinal signs and cardiotoxicity due to the resemblance of the bufogenic toxins to cardiac glycosides and digoxin toxicity [3,7]. There are reports of envenomation in people after ingesting aphrodisiacs or Asian herbal supplements containing bufogenic toxins, as well as ingestion of *Bufo* toad eggs, leading to life-threatening cardiac arrhythmias [7–9]. In one of these case reports, a 40-year-old man had positive digoxin serum concentrations after ingesting aphrodisiac pills, despite never taking digoxin [8]. Successful treatment with digoxin Fab fragments for toad envenomation has been reported in two men and in mice [10,11].

Dogs receiving lethal doses of bufogenic toxins were reported to develop ventricular fibrillation leading to 100% mortality in all untreated dogs [12]. In dogs with natural exposure to bufogenic toxins, the incidence of cardiac arrhythmias is less prevalent, approximately 21% in one study [6], and bradycardia with heart rates less than 50 beats per minute was the indication for treatment with IV atropine in another study [5] (see Chapter 53). In the authors' experience, dogs infrequently present with cardiac arrhythmias, but small dogs with severe signs of toxicity are more likely to show these signs. Smaller dogs are also more likely to be hospitalized than larger dogs according to one study [5], suggesting that a higher ratio of toxin to body weight may cause more severe clinical signs, although the correlation between body weight and development of cardiac arrhythmias has not been formally investigated. No studies have been performed looking at digoxin serum concentrations in dogs with *Bufo* toxicosis.

Diagnosis

The diagnosis of *Bufo* toad toxicosis is made purely based on history and clinical exam findings. In cases of observed exposure to the *Bufo* toad, diagnosis is straightforward. At this time there are no biochemical, hematological or biomarkers that can aid the clinician in the

diagnosis of *Bufo* toxicosis. Veterinarians practicing in areas where *Bufo* toads are endemic should be aware of the clinical signs associated with toad toxicosis in order to promptly recognize and treat the affected animal.

History taking plays a major role in the diagnosis of *Bufo* toxicosis. Dogs with cane toad envenomation have no previous history of seizures or other neurological disorders [6]; they may have had previous environmental exposure to these toads [5] and develop acute onset of clinical signs consistent with a toxicity. In one study, 18% of dogs had a history of previous exposure to *Bufo* toads ranging from one to eight encounters in the past [5]. Dogs do not appear to learn precautionary behaviors towards these venomous toads, despite previous encounters and development of toxicosis.

Treatment and Monitoring

Initial treatment of dogs and cats with *Bufo* toxicosis should be tailored towards oral decontamination and treatment of seizure activity. The owner can be instructed to start decontamination techniques at home as long as the animal is not actively seizing in order to prevent injuries to the owners. At-home decontamination should be performed with a damp towel or damp clean rag used to wipe the oral mucous membranes and prevent further absorption of the toxins. A common mistake made by veterinarians is to recommend owners to lavage the animal's mouth with a hose or running tap water, increasing the risk of aspiration pneumonia. Several dogs that have died in hospital while being treated for *Bufo* toxicity died due to aspiration pneumonia caused by owners attempting to lavage the mouth with water or by administration of products such as milk or olive oil believed to decrease toxin absorption.

If the animal is observed ingesting the toad or parts of the toad, emesis can be induced if the animal is neurologically stable. Orogastric lavage can also be attempted in the animal with neurological signs once seizure activity has been controlled. The use of activated charcoal in *Bufo* toxicosis has not been evaluated or reported in retrospective studies. Currently, charcoal or charcoal with cathartics in cases of severe envenomation is not used routinely due to the risk of aspiration pneumonia.

Treatment of seizures is described in further detail in Chapter 21. In cases of *Bufo* toad envenomation, standard doses of benzodiazepines are used to control seizures or to help control neurological signs of muscle rigidity. If boluses of benzodiazepines are not enough to control seizure activity, continuous-rate infusions of benzodiazepines or propofol can be administered. Other anticonvulsants such as phenobarbital or levetiracetam can also be administered in refractory cases. Treatment of cardiac

arrhythmias should be based on electrocardiogram findings (see Chapter 53). Atropine is the treatment of choice for bradyarrhythmias as recommended in previous studies [5,6]. In cases of tachyarrhythmias, propranolol was used in two dogs due to prolonged (>30 min) sinus tachycardia in one study [5]; the use of other drugs such as esmolol, lidocaine, amiodarone, and verapamil has also been suggested [6,13]. Treatment of *Bufo*-envenomated dogs with digoxin Fab fragments has not been reported.

Intravenous fluid therapy is commonly administered to hospitalized animals with signs of *Bufo* toxicosis (see Chapter 167). There is a lack of information regarding blood pressure, lactate levels, and other hemodynamic parameters in envenomated dogs, but clinical experience indicates that true cardiovascular shock is rare in *Bufo* toxicity, and so routine use of aggressive fluid resuscitation is not typically required. Maintenance fluid therapy at conventional rates is therefore recommended in addition to replacement of any ongoing losses. In cases of tachyarrhythmia, ECG monitoring should be performed before and during patient assessment and treatment, and those with persistent tachyarrhythmia may require treatment with antiarrhythmic agents, depending on its severity. Typically, short-acting beta-blockers are the drug of choice for the treatment of these arrhythmias (see Chapter 53). Indiscriminate fluid therapy may lead to fluid overload in debilitated animals and worsen lung pathology in cases of aspiration pneumonia.

Animals with mild signs of *Bufo* envenomation (hyper-salivation and hyperemic mucous membranes) can be

treated as outpatients after oral decontamination and owners should continue monitoring at home for development of neurological signs. For moderately to severely affected animals, hospitalization with supportive care and monitoring for seizure activity should be recommended. In the two retrospective studies mentioned earlier, 55–61% of the dogs were admitted to hospital and monitored for periods ranging between 11 and 48 hours [5,6]. Long-term monitoring is not required once the animal is discharged from hospital after recovery from envenomation.

Prognosis

Prognosis is excellent for dogs with *Bufo* toxicosis and prompt appropriate treatment. The prognosis in cats is unknown. Mortality in dogs with *Bufo* toad envenomation has been reported to be 4% [5,6]. The incidence of short-term complications such as aspiration pneumonia or long-term complications such as neurological deficits has not been reported.

Acknowledgments

The authors would like to thank Dr Michael West, associate ER veterinarian at Pet Emergency and Referral Center of Palm Beach Gardens, for the photographs and clinical input provided.

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Hymenoptera Envenomation

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Apoidea

The family Apoidea includes the social honey bees, bumble bees, and solitary bees. These insects are social and herbivorous, feeding off flower pollen and nectar. They build their nests (hives) in hollow trees or other cavities. Nests of bumble bees contain 100–200 insects and are typically not involved in mass envenomations whereas honey bee (*Apis mellifera*) hives often contain thousands of workers, with 40 000 workers in some managed colonies [1].

Africanized honey bees (AHB) are a tropical variety of honey bee that was imported from Africa to Brazil in 1956 to improve honey production [2]. This variety of bee, known for its aggressive temperament leading to mass envenomation, escaped and replaced the local honey bee variety in Brazil, reaching the United States by 1990 [3]. As of 2011, AHBs have spread to 10 US states although attacks have not been noted in all of these states [4]. AHBs are quicker to attack and will chase their victims up to 0.6 miles, as compared to European honey bees which will follow for up to 500 yards. AHBs also tend to establish a larger number of colonies in less protected locations within a particular geographic area, making them more easily disturbed [5].

Bees can only sting once, as their barbed stinger remains in the victim's skin following envenomation. After a sting, the stinger and venom sac are pulled out of the bee's abdomen, resulting in the insect's death shortly thereafter [6,7].

Vespoidea

The family Vespoidea includes the wasps, hornets, and yellowjackets. These insects are predacious carnivores, feeding on other insects and sweet substances such as

sap and nectar, that frequently forage near open food containers and garbage. Stings typically occur via a single vespid and most commonly occur in the late summer and early fall when hungry yellowjackets are attracted to the smell of human food prepared outdoors [6]. Mass envenomation may occur when a colony is disturbed. Hornets and wasps typically inhabit trees and shrubs, while yellowjackets are frequently ground dwellers. Compared to the Apoidea, vespids tend to be more aggressive and possess smooth stingers which allow them to deliver multiple stings [7,8].

Formicidea

The family Formicidea contains the ants. Those medically relevant include the black and red imported fire ant (*Solenopsis invicta* and *S. richteria*). Both are native to South America and entered the United States in the 1900s [9], where they formed hybrids with native species. The black imported fire ants are mostly confined to Alabama and Mississippi but the red imported fire ants and hybrids are highly adaptive and have spread to 12 southern states. Red fire ant hybrids appear to be cold resistant and can overwinter, allowing for northward migration into areas with a cooler climate [10].

Fire ants form mounds which can interfere with farming. They may attack livestock and other native species and increasingly are reported to attack pets and debilitated humans [11]. Imported fire ants are omnivorous, stinging and killing invertebrates as their primary food source. Fire ants can quickly swarm a victim, using pheromone cues to sting simultaneously. The fire ant initially bites its prey with its prominent mandibles and, once anchored, tucks its abdomen to sting with a non-barbed stinger. The ant then remains attached by its mandibles, removes its stinger, rotates its body, and stings again.

This is repeated 6–7 times in a circular pattern, with venom slowly injected over 20–30 seconds. This results in a slower onset and less painful sting than those delivered by bees or vespids [12,13].

Venom

Bee venom is a complex mixture of proteins and biologically active peptides. Mellitin, the major component and the main cause of pain following a sting, is a detergent, which alters cell membrane integrity. Mellitin works synergistically with the primary allergen of venom, phospholipase A2, to cause red blood cell, platelet, leukocyte, and vascular endothelial cell lysis [1,14], and is suspected to cause myelinolysis of the spinal cord [13,15]. Other venom components include mast cell degranulating factor, which causes histamine and vasoactive amine release from mast cells, and hyaluronidase, which disrupts collagen, allowing venom to spread to adjacent tissues. Bee venom also contains vasoactive amines such as histamine, dopamine, and norepinephrine, and apamin, a neurotoxin that acts on the spinal cord [13].

Wasp venoms are more heterogeneous but most contain three major allergenic peptides as well as vasoactive amines (serotonin, histamine, tyramine, catecholamines), wasp kinins, and acetylcholine. The vasoactive substances are responsible for the intense pain of wasp stings. Antigen 5 is the most allergenic component but its activity is poorly understood. Other venom components include phospholipase A and B, which cleave lipid bilayers, and hyaluronidase. Vespid venom does not contain mellitin [16].

Unlike the venom of other Hymenoptera, which are composed primarily of proteins in an aqueous solution, fire ant venom is composed of 95% water-insoluble alkaloids. These alkaloids are primarily piperidines which have cytotoxic, hemolytic, antibacterial, and insecticidal properties [13]. They do not produce an IgE-mediated reaction, but instead produce sterile pustules secondary to tissue inflammation which are almost pathognomonic for fire ant stings [17].

Lethal Dose

Stinging insects are not able to meter their venoms like some venomous snakes and deliver a relatively standard volume of venom per sting. The European honey bee is thought to inject 147 μg of venom per sting, with most wasps injecting about 17 μg of venom per sting [17]. Africanized honey bees likely inject a slightly smaller volume of venom per sting than their European counterparts. The lethal dose for bee, wasp

or hornet envenomation is approximately 500 stings per adult human [1,8,18] and is estimated to be 20 stings/kg in most mammals [1,19]. Each fire ant sting can deliver 0.11 μL of venom, with up to 20 consecutive stings being delivered before venom stores are depleted. Severe systemic reactions have been reported following 50–100 fire ant stings in humans. While fatal envenomation can occur in animals, the lethal dose is unknown [20].

Clinical Manifestations of Envenomation

Hymenoptera envenomation may result in local tissue reactions, immune-mediated responses or, rarely, venom systemic toxic effects. A local reaction, characterized by edema, erythema, and pain at the site of envenomation, occurs following all Hymenoptera envenomation as a result of the vasoactive properties of the venom. This is typically self-limiting and generally resolves within 24 hours [13].

Immune-Mediated Response

Immune-mediated response to envenomation can be divided into three subtypes: regional reaction, systemic anaphylaxis, and delayed hypersensitivity reaction. Regional reactions are thought to be IgE mediated and involve the area immediately surrounding the site of the sting. Regional reactions can be extensive and may lead to erythema and edema encompassing an entire extremity. This may not be apparent for up to 24 hours following a sting and will typically peak in severity within 48 hours, although signs may not resolve for several days and may be confused with cellulitis [13,21].

Systemic anaphylaxis, though rare, is the most life-threatening reaction to Hymenoptera envenomation (see Chapter 146). It is mediated by IgE and is characterized by all or a combination of clinical signs related to cardiovascular collapse, respiratory difficulty, or cutaneous or gastrointestinal signs. Clinical signs are due to massive release of a variety of chemical mediators, primarily histamine, from mast cells and basophils. Cutaneous signs include urticaria, erythema, angioedema, and pruritus. Respiratory signs include dyspnea, bronchospasm, stridor, and cough as a result of laryngeal and pharyngeal edema, increased mucus production, and bronchoconstriction. Circulatory compromise is characterized by hypotension and signs of poor tissue perfusion (pale mucous membranes, prolonged capillary refill time, poor pulse quality, and dull mentation) due to vasodilation and increased vascular permeability. Tachycardia or, less commonly, vagally mediated bradycardia may be seen. Arrhythmias,

myocardial ischemia, and cardiac arrest may also occur. Gastrointestinal signs may include nausea, vomiting, and diarrhea or hematochezia. Other clinical signs which may occur include weakness, syncope, lacrimation, conjunctival hyperemia, and seizures.

Clinical signs of anaphylaxis typically occur within 15 minutes of the insult and are unlikely to occur if no signs are noted within 30 minutes. The time to onset of signs is directly proportional to the severity of the signs. Depending on the severity and manifestation of anaphylaxis, death can occur within minutes [22].

Delayed hypersensitivity reactions are uncommon but can occur within days to weeks of envenomation, resulting from tissue deposition of antigen-antibody complexes. The resultant inflammatory cascade leads to complement binding and subsequent formation of anaphylatoxin, causing mast cell degranulation and histamine release which results in damage to the basement membrane. This may result in vasculitis, polyarthritis, glomerulonephritis, and myocardial lesions [13,22].

Systemic Toxic Reactions

Systemic toxic reactions occur due to the direct effects of venom and are related to the total volume of venom injected. Clinical signs can include fever, depression, ataxia, seizures, pigmenturia, hypotension, and melena or hematochezia [23]. Secondary immune-mediated hemolytic anemia and thrombocytopenia have been reported in dogs following massive bee and vespid envenomation [24–31] (see Chapter 66). Mellitin and phospholipase A2 may cause rhabdomyolysis, leading to myoglobinemia, myoglobinuria and potentially a pigment nephropathy. Ataxia, transient facial nerve paralysis, seizure, and other neurological dysfunction secondary to the effects of mellitin and apamin have been reported in dogs [13,25]. Acute respiratory distress syndrome (ARDS) may occur following massive envenomation [24,26,32]. One case report describes a dog which was mechanically ventilated for suspected ARDS secondary to massive bee envenomation; this dog ultimately recovered to discharge [33]. Coagulopathy and disseminated intravascular coagulation are also commonly reported, likely due to hepatocellular injury and release of tissue thromboplastin and endothelial cell disruption [26,34] (see Chapter 70).

Only one published case report describes massive envenomation of two dogs by fire ants in Australia. Both dogs developed acute kidney injury (see Chapter 94). One dog died, and necropsy revealed evidence of mesenteric and myocardial hemorrhage as well as renal tubular necrosis [35].

Diagnosis

Definitive diagnosis may be challenging if the incident was not witnessed, but the circumstances may raise a clinical suspicion for Hymenoptera envenomation. Depending on the type of reaction, there may be few biochemical or radiographic changes noted. Local and regional reactions are diagnosed on physical examination. Anaphylaxis is often a clinical diagnosis, but elevations in ALT and ultrasound evidence of gall bladder wall edema have been associated with anaphylaxis in dogs [36–38]. Animals presenting with delayed or toxic reactions may show evidence of hepatopathy (elevated ALT, AST, ALP, GGT, bilirubin), azotemia secondary to acute kidney injury, urinary casts, evidence of rhabdomyolysis (elevated CK, myoglobinemia, myoglobinuria), evidence of immune-mediated hemolytic anemia or thrombocytopenia (spherocytosis, anemia, thrombocytopenia, hemoglobinemia, hemoglobinuria), or coagulopathy (prolonged PT/PTT, thrombocytopenia, and elevated D-dimers). Complete blood count may also reveal an inflammatory leukogram [13].

Treatment

Local or mild regional reactions often do not require treatment but application of ice or cool compresses, and oral or injectable antihistamines (1–2 mg/kg diphenhydramine IM, PO) may be helpful [14]. Sarna lotion (camphor and menthol) can be applied topically for fire ant stings. Topical use of meat tenderizer (papain) or aluminum sulfate has not been demonstrated to be effective. Animals with multiple stings or with severe regional reactions should be hospitalized to monitor for the development of systemic toxic reactions. Human recommendations are to hospitalize patients for 24 hours following massive envenomation of >50 stings [39].

Hypotension should be treated aggressively with intravenous fluid therapy see (Chapter 167). Maintenance of normotension and adequate tissue perfusion is of utmost importance. Appropriate analgesia (see Chapter 193) should be provided and while broad-spectrum antibiotics are not typically required, they should be administered if secondary infection develops [13,22,24].

Treatment of Systemic Anaphylaxis

Anaphylaxis is a medical emergency and survival is dependent on immediate patient assessment and stabilization (see Chapter 146). Immediate administration of epinephrine (Table 145.1) given as an IV bolus is indicated, followed by CRI of epinephrine titrated to

Table 145.1 Treatment of systemic anaphylaxis [22].

Medication	Dog dosage	Cat dosage
Epinephrine	0.01 mg/kg (1 mg/mL solution) IM/IV q5–15 min Max dose: 0.3 mg < 40 kg, 0.5 mg > 50 kg CRI: 0.05 µg/kg/min if shock is present	0.01 mg/kg (1 mg/mL solution) IM/IV q5–15 min CRI: 0.05 µg/kg/min if shock is present
Isotonic crystalloid	90 mL/kg (in aliquots, to effect)	60 mL/kg (in aliquots, to effect)
Colloids (Hetastarch)	5 mL/kg bolus, up to 20 mL/kg	5 mL/kg bolus, up to 20 mL/kg
Methylprednisolone sodium succinate	30 mg/kg IV	30 mg/kg IV
Dexamethasone sodium phosphate	1–4 mg/kg IV	1–4 mg/kg IV
Prednisone sodium succinate	10–25 mg/kg IV	10–25 mg/kg IV
Diphenhydramine	1–4 mg/kg IM or PO q8–12h 0.5–1 mg/kg IV slowly (not >50 mg total)	0.5–2 mg/kg IM or PO q8–12h
Ranitidine	0.5–2 mg/kg IV, PO or SC Give IV slowly over 10 min	0.5–2 mg/kg IV, PO or SC Give IV slowly over 10 min
Albuterol	0.5 mL of 0.5% solution in 4 mL isotonic saline by nebulizer q6h, 90 µg/actuation (1–2 puffs) by metered dose q15min for 3 doses	0.5 mL of 0.5% solution in 4 mL isotonic saline by nebulizer q6h, 90 µg/actuation (1–2 puffs) by metered dose q15min for 3 doses
Aminophylline	5–10 mg/kg IM or slowly IV	5–10 mg/kg IM or slowly IV
Vasopressin	CRI: 0.5–1.25 mU/kg/min	CRI: 0.5–1.25 mU/kg/min
Norepinephrine	CRI: 0.1–1 µg/kg/min	CRI: 0.1–1 µg/kg/min
Dopamine	CRI: 2.5–10 µg/kg/min	CRI: 2.5–10 µg/kg/min
Glucagon	1–2 mg/kg followed by CRI: 5–15 mg/min	1–2 mg/kg followed by CRI: 5–15 mg/min
Atropine	0.02–0.04 mg/kg IV	0.02–0.04 mg/kg IV
Ipratropium	18 µg/actuation, via inhalation	18 µg/actuation, via inhalation

CRI, constant-rate infusion; IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

clinical response if shock is present. The airway should be secured and the patient intubated if necessary, and supplemental oxygen should be provided.

Aggressive fluid resuscitation is recommended in hypotensive patients. Bolus IV infusion of an isotonic crystalloid solution should be administered at resuscitative volumes (90 mL/kg in dogs and 60 mL/kg in cats, given in aliquots to effect). Colloids may be beneficial in providing a more sustained hemodynamic response and can be administered in bolus form.

Glucocorticoid use is controversial and a Cochrane review showed no benefit of administration during systemic anaphylaxis [40]; however, glucocorticoid use may reduce the severity of inflammation in late stages of anaphylaxis. Antihistamines (H1 and H2 antagonists) may

be administered to relieve symptoms, particularly urticaria and pruritus, and they may decrease gastric acid secretion.

Bronchodilators may be another useful adjunctive therapy. Albuterol acts to relieve bronchospasm by relaxing bronchial smooth muscle [41]. Aminophylline, in addition to smooth muscle relaxation, also increases endogenous epinephrine release and decreases histamine release via phosphodiesterase inhibition [42].

Refractory hypotension may require treatment with vasopressors such as norepinephrine, vasopressin or dopamine. Refractory bronchospasm can be treated with glucagon or inhaled ipratropium. Persistent bradycardia or previous administration of beta-blockers may necessitate treatment with an anticholinergic [22].

Treatment of Toxic and Delayed Reactions

Massive envenomation requires aggressive, rapid stabilization with IV fluids to improve perfusion as well as provision of analgesia. Depending on the clinical manifestation, ancillary therapies may include antihistamine and corticosteroid administration to reduce upper airway edema and pruritus, plasma transfusion to treat DIC

or coagulopathy, hemodialysis for severe or oligoanuric acute kidney injury (see Chapter 94), and oxygen support or mechanical ventilation for acute lung injury/acute respiratory distress syndrome (see Chapter 181). Epinephrine should be considered if there is suspicion of an anaphylactic component to the reaction. Broad-spectrum antibiotic therapy should be considered, particularly for fire ant massive envenomation [13] (see Chapter 200).

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Hypersensitivity and Anaphylaxis

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Incidence and Definitions

In the United States, 1% of all human emergency department visits are allergy related. The majority of visits are composed of acute allergic and hypersensitivity reactions, with only 1% considered anaphylactic reactions [1]. The prevalence of acute allergic and anaphylactic reactions in veterinary medicine remains unknown, but is assumed to be increasing due to the growing exposure of small animals to antigenic substances [1–3].

Hypersensitivity reactions are defined as “objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons” while an *allergy* or *allergic reaction* is a hypersensitivity reaction initiated by a specific immunological mechanism such as IgE-mediated allergies (see below) [4].

Atopy is an individual or familial tendency to become sensitized and produce IgE antibodies in response to ordinary exposure to antigens that can lead to the typical symptoms of allergies [4].

Definitions of *anaphylaxis* commonly include acute, serious, generalized or systemic allergic or hypersensitivity reactions that are rapid in onset, can be life threatening or fatal, and occur suddenly after contact with an allergy-causing substance [4–7]. The World Allergy Organization proposes a brief definition of anaphylaxis as “a serious, life-threatening, generalized or systemic hypersensitivity reaction” [8].

Classification and Pathophysiology of Hypersensitivity Reactions and Anaphylaxis

Acute allergic reactions can clinically be divided into localized and systemic hypersensitivity reactions. *Local* hypersensitivity reactions are restricted to cutaneous

abnormalities such as erythema, pruritus, urticaria, or angioedema (Figure 146.1) whereas *systemic or generalized* hypersensitivity reactions lead to signs of systemic inflammatory mediator release [9,10].

In people, *mild generalized* hypersensitivity reactions are defined as causing cutaneous reaction only, such as generalized erythema, urticaria, and angioedema [9]. *Moderate generalized* hypersensitivity reactions comprise manifestations of severe illness with respiratory, cardiovascular, and gastrointestinal involvement [9]. Symptoms can include nausea, vomiting, and dizziness, along with processes known to lead to hypotension or hypoxemia such as dyspnea and stridorous respiration [9]. *Severe generalized* hypersensitivity reactions are defined by documented hypotension (systolic blood pressure <90 mmHg) or hypoxemia (SpO₂ <92%), as well as clinical signs of neurological compromise resulting from hypotension or hypoxia, such as collapse and altered mental status [9]. Moderate and severe generalized hypersensitivity reactions are defined by features associated with hypoxemia and hypotension and therefore can be classified as *anaphylactic reactions* [9].

Immunologically, hypersensitivity as well as anaphylactic reactions are immediate (type 1) hypersensitivity reactions. Mast cells and basophils express Fc-epsilon-RI receptors on their cell surface that have a high affinity for the Fc portion of immunoglobulin E (IgE) antibodies [11]. Initial exposure to an antigen leads to increased production of IgE antibodies, which are subsequently bound to mast cell Fc-epsilon-RI receptors in sensitized individuals. After re-exposure to the same antigen, the antigen induces cross-linking of two adjacent surface IgE antibodies, leading to mast cell degranulation [11,12]. Multiple vasoactive mediators are released during mast cell degranulation, including histamine, tryptase, heparin, and cytokines [13]. Histamine effects are exerted via histamine receptors and receptor stimulation



Figure 146.1 Localized hypersensitivity reaction in a Shar-Pei following Hymenoptera sting to the paw with facial urticaria, erythema, and pruritus.

can lead to pruritus, urticaria, angioedema, conjunctivitis, and rhinitis in allergic reactions as well as the vasodilation and increased vascular permeability responsible for cardiovascular collapse in anaphylactic reactions [3,13,14]. Platelet-activating factor (PAF) has also been shown to play a major role in anaphylactic reactions. PAF is a potent bronchoconstrictor, increases vascular permeability, and enhances platelet aggregation, histamine release, and vasodilation [11].

Apart from the classic IgE-mediated immunological pathway, a second pathway of systemic anaphylaxis was recently identified in murine models of anaphylaxis. This alternative pathway is mediated by immunoglobulin G (IgG) production and binding to the low-affinity IgG receptor Fc-gamma-RIII on macrophages. Re-exposure to an antigen induces anaphylaxis by formation of IgG antigen complexes. Complexes bind to Fc-gamma-RIII and cross-linkage of the receptor causes release of PAF from macrophages. In the alternative pathway, PAF rather than histamine is primarily responsible for development of hemodynamic alterations [12]. The significance of an alternative pathway of anaphylaxis in dogs and cats is yet to be determined.

Immunological mechanisms of hypersensitivity all require initial exposure to an antigen to stimulate the antibody response, also known as sensitization. Hypersensitivity responses only occur upon re-exposure to the antigen [11].

Lastly, in addition to the immunological; forms of anaphylaxis described above, non-immunological triggers for anaphylaxis have also been described when physical factors such as heat, cold, or pharmaceuticals cause degranulation of mast cells and basophils without participation of immunoglobulins [3,13]. This mechanism does not require sensitization, so hypersensitivity or anaphylaxis can occur upon the first exposure to an antigen.

The term *anaphylactic reaction* traditionally refers to IgE-mediated events, while *anaphylactoid reactions* are mediated by IgE-independent immunological or non-immunological events. Clinically, the two entities are not distinguishable and the World Allergy Organization suggests that the term *anaphylaxis* be used in preference to anaphylactoid reaction, regardless of the pathophysiology [7].

Etiologies and Clinical Manifestations

Hypersensitivity reactions and anaphylaxis occur as a dynamic continuum and any antigen capable of activating mast cells can trigger a reaction. The most common substances reported in veterinary medicine include vaccine proteins, insect and reptile venoms and their antivenoms, blood products, antimicrobial agents, non-steroidal anti-inflammatory agents, opioids, radiographic contrast agents, food, and physical factors such as heat or cold [15–24]. Single cases of fatal anaphylaxis associated with a dexamethasone suppression test and an intraoperative anaphylactic reaction to accidental dissection of an adult heartworm during lung lobectomy have also been reported in dogs [25,26].

After initial exposure to the antigenic stimulus, hypersensitivity and anaphylactic reactions occur within minutes of contact [6,12,13]. The time to onset of clinical signs and the severity of systemic anaphylactic reactions correlate, and as a general rule, the more rapidly the symptoms manifest, the more severe a reaction will be and the more likely it is to progress to being life threatening [13]. Manifestations of hypersensitivity and anaphylactic reactions can include cutaneous, cardiovascular, respiratory, gastrointestinal, and neurological symptoms [9]. The clinical presentation and course are dictated by the organ systems primarily affected by the reaction and directly relate to the distribution of the largest mast cell population, which varies between species [10,13].

In dogs with hypersensitivity reactions, cutaneous and gastrointestinal signs predominate. Specifically, in vaccine-associated adverse events, dermal signs including facial edema, pruritus, erythema, and urticaria are the most common clinical manifestations in 68% of patients, followed by gastrointestinal signs such as vomiting, diarrhea, and anorexia in 45% of patients [19]. Young adult

small-breed dogs were found to be at greater risk for vaccine-associated adverse events and the risk has been shown to significantly increase with an increasing number of vaccines administered per visit [27]. Anaphylactic reactions following vaccine administration are less commonly observed and appear to rarely be fatal [19]. It is important to note that the clinical signs of hypersensitivity and anaphylaxis can vary with the antigen responsible.

In anaphylactic reactions, the liver and gastrointestinal tract are most commonly affected in the dog. Histamine released from the gastrointestinal tract leads to significant sinusoidal and hepatic venous congestion, which in some cases may progress to hepatic hemorrhage and hepatocellular necrosis [10,28]. This can lead to distributive shock (see Chapter 155). Increased vascular permeability can contribute to cardiovascular collapse and massive fluid shifts of up to 35% of the intravascular volume to the interstitial space can occur [3,29]. Rapid hemodynamic compromise can occur without preceding cutaneous signs. A study of canine hypersensitivity reactions reported that only 57% of dogs showed cutaneous signs during anaphylactic reactions, and that their manifestations were more subtle than in milder allergic reactions [10]. Respiratory manifestations of anaphylaxis in the dog are rare but can consist of pulmonary congestion or hemorrhage clinically manifesting as tachypnea and increased respiratory effort [28].

The most common clinical signs with vaccine-associated allergic reactions in cats include lethargy with or without fever, localized vaccination site reactions such as soreness or inflammation, vomiting, facial edema, or generalized pruritus [30]. Cats with anaphylactic reactions more commonly exhibit pulmonary and gastrointestinal signs such as open mouth breathing, tachypnea, respiratory distress, salivation, vomiting, and diarrhea [3,18]. Respiratory signs are thought to result from bronchoconstriction, laryngeal edema, and increased mucus production [31]. The risk for vaccine-associated adverse reactions in cats also increases with the number of vaccines administered per visit, but severe hypersensitivity reactions are rare [30]. Anaphylactic reactions have also been reported in cats following administration of ophthalmic medications, the most commonly reported signs being respiratory and gastrointestinal in nature [18]. Less commonly, dermatological signs such as angioedema, pruritus, urticaria, chemosis and conjunctival hyperemia, and neurological signs including ataxia have been described in cats suffering from anaphylactic events [18].

The most severe anaphylactic reactions, such as cardiovascular collapse and respiratory compromise, are most commonly observed after parenteral administration of antigen [28,29]. Oral ingestion of antigens can cause gastrointestinal symptoms as well as dermal reactions, and

topically applied antigen can cause cutaneous and ocular signs, as well as systemic signs of anaphylaxis [18,31]. Lastly, antigen inhalation commonly causes local signs of rhinitis and bronchoconstriction [31].

Diagnosis

The diagnosis of hypersensitivity reactions and anaphylaxis is clinical and based on history and recognition of classic clinical signs on physical examination. A detailed history that investigates recent exposure to potential triggers such as vaccinations, new medications, insect bites and stings can help raise the suspicion for an allergic reaction. As discussed previously, cutaneous, gastrointestinal, respiratory, cardiovascular, neurological, and ocular signs can be encountered in patients suffering from hypersensitivity and anaphylactic reactions.

Clinical criteria for the diagnosis of anaphylaxis have been formulated in people, but to date universal criteria have not been established for veterinary species. Based on the criteria reported in people and previous reports of hypersensitivity in small animals, suggested clinical criteria that make hypersensitivity and anaphylactic reactions likely in dogs and cats are summarized in Box 146.1 [6].

One study found both increased ALT and changes in gall bladder wall appearance to be significantly associated with anaphylaxis in canine patients [10]. Gall bladder wall changes found in patients with anaphylaxis include increased wall thickness >3mm and striated

Box 146.1 Suggested diagnostic criteria for hypersensitivity and anaphylaxis in dogs and cats

Known recent exposure to antigen greatly increases the diagnostic likelihood

Hypersensitivity in dogs

One or both of the following:

- Acute cutaneous signs
- Gastrointestinal signs

Hypersensitivity in cats

Any one or more of the following:

- Gastrointestinal signs
- Respiratory signs
- Cutaneous signs

Anaphylaxis in dogs and cats

Life-threatening abnormality with one or more of the following:

- Cutaneous signs
- Gastrointestinal signs
- Respiratory signs
- Cardiovascular signs

gall bladder wall (halo or double rim effect) suggestive of subserosal edema [10]. More than 100 biomarkers for mast cell and basophil activation, such as plasma histamine and tryptase concentrations, have been described, none of which are readily available in clinical veterinary medicine [32].

Treatment

The treatment for hypersensitivity reactions is largely symptomatic and dictated by the severity of the reaction. Anaphylaxis is a medical emergency and initial patient assessment should focus on circulation, airway, and breathing (see Chapter 2). Life-threatening signs of anaphylactic reactions to Hymenoptera stings (bees, wasps) in dogs are usually apparent within 10–15 minutes of venom exposure and in a small number of susceptible animals can rapidly progress to death (see Chapter 145). This is likely the case for anaphylactic reactions to a variety of antigens [15]. In veterinary medicine, no randomized controlled trials have been performed to evaluate the medications most commonly used in the treatment of anaphylaxis and the choice of treatment therefore remains controversial. Treatment recommendations are summarized in Table 146.1.

Antihistamines

Antihistamines are commonly used in veterinary medicine to treat hypersensitivity reactions. While H1 antihistamines have been shown to reduce pruritus associated

with antigen exposure in allergic reactions, treatment with antihistamines has not been proven effective in alleviating cardiovascular signs of anaphylaxis [33,34]. In a Cochrane review on the role of H1 antihistamines for the treatment of human anaphylaxis, no strong evidence was found for or against their use and no recommendations for clinical practice could be formulated [35]. Antihistamines should therefore only be considered in the treatment of mild to moderate hypersensitivity reactions or as an ancillary treatment in anaphylactic shock to relieve cutaneous, ocular, and nasal signs.

Recommended dosages for diphenhydramine, an H1 antihistamine, are 1–4 mg/kg PO or IM, in dogs and 0.5–2 mg/kg IM or PO in cats [36]. Some evidence exists that concurrent administration of H2 with H1 antihistamines can alleviate flushing, headache, and other symptoms in people [8]. It is possible that H2 receptor antagonists lead to similar relief in animals, but this has yet to be shown. Similar to H1, H2 antihistamines should be considered ancillary treatment of anaphylaxis only.

Glucocorticoids

Glucocorticoids are another drug class frequently used in the treatment of all hypersensitivity reactions. Similar to H1 antihistamines, a Cochrane review was unable to find evidence to justify the use of steroids in the emergency management of anaphylaxis, and currently their use can neither be supported nor refuted [37]. When using glucocorticoid drugs, it is important to remember that the onset of effects of this drug class takes several hours and it therefore does not relieve acute signs associated with hypersensitivity reactions [8].

The dose for oral administration of prednisone for mild hypersensitivity reactions is recommended to be 1 mg/kg and equivalent doses of parenterally administered glucocorticoids are appropriate (e.g. dexamethasone sodium phosphate at 0.1 mg/kg IV) [6].

Epinephrine

The World Health Organization and several published anaphylaxis treatment guidelines consider epinephrine to be an essential medication and recommended first-line treatment in human anaphylaxis [6–8]. The predominant clinical signs in human patients are respiratory failure, laryngeal edema, and cardiovascular collapse [38–40]. The beneficial effects of epinephrine in human anaphylaxis are believed to be due to both alpha- and beta-adrenergic effects [41]. Alpha-1 adrenergic stimulation is responsible for potent vasoconstriction of the small arterioles, which can have life-saving cardiovascular effects [41]. Furthermore, the vasoconstriction decreases mucosal edema and helps relieve

Table 146.1 Suggested drugs and dosages for treatment of hypersensitivity and anaphylactic reactions in dogs and cats.

Drug	Dose and route
Diphenhydramine	Dogs: 1–4 mg/kg PO or IM Cats: 0.5–2 mg/kg PO or IM
Dexamethasone sodium phosphate	0.1 mg/kg IV
Epinephrine	0.01–0.025 mg/kg IV 0.05 µg/kg/min IV as CRI
Albuterol	0.5 mL of 0.5% solution in 4 mL of isotonic saline by nebulizer 1–2 puffs (90 µg/actuation)
Terbutaline	0.01 mg/kg IM or IV 0.625–1.25 mg PO
Aminophylline	5–10 mg/kg IM or IV

CRI, constant-rate infusion; IM, intramuscular; IV, intravenous; PO, by mouth (*per os*).

upper airway obstruction [41]. Beta-2 effects further alleviate respiratory signs by increased bronchodilation and decreased histamine release, while beta-1 adrenergic effects increase cardiac contractility [41].

In contrast to these findings in human medicine, distributive shock in canine anaphylaxis may be due to pooling of venous blood in the hepatic circulation and the use of epinephrine as a first-line treatment is controversial [28]. In experimental models of canine anaphylactic shock, low-rate constant-rate infusions of epinephrine were considered more effective than a single bolus dose [42–44]. Subcutaneous administration is not recommended due to potent vasoconstriction and unpredictable absorption in states of anaphylactic shock [44].

Epinephrine is supplied as either a 1:1000 (1 mg/mL) or 1:10000 (0.1 mg/mL) solution. Epinephrine autoinjector (EpiPen) use is not recommended by the authors due to several concerns. Injectors are most commonly available in two fixed doses of 0.15 and 0.3 mg and therefore cannot be safely administered to patients weighing less than 15 kg. Furthermore, the needle size is limited and might preclude the intramuscular administration of the drug in obese animals. At-home administration of first aid drugs could additionally delay appropriate presentation of an at-risk animal to a veterinarian within the critical time period.

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Bronchodilators

Beta-2 agonists such as albuterol and terbutaline, as well as xanthine derivatives, can be beneficial as an additional treatment for respiratory manifestation of anaphylaxis.

Intravenous Fluids and Other Ancillary Treatments

Due to the potential of rapid extravasation of significant amounts of plasma volume and distributive shock due to venous pooling, intravenous fluid resuscitation is recommended for anaphylactic patients (see Chapter 153). Patients with refractory clinical hypoperfusion or hypotension might also require vasopressor administration (see Chapter 155).

Prognosis

The prognosis of hypersensitivity reactions is variable and depends on the allergenic trigger, severity, and progression of the reaction. Once a diagnosis of allergic or anaphylactic reaction is suspected, a detailed history should be taken and recommendations made to avoid exposure to the suspected trigger.

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Canine Heat Stroke

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Pathophysiology

Elevation of body temperatures above the normal hypothalamic set point can be due to pyrogenic or non-pyrogenic causes. Non-pyrogenic hyperthermia occurs when heat-dissipating mechanisms cannot adequately compensate for heat production, or when these mechanisms are impaired [1]. In dogs, under normal environmental conditions, more than 70% of total body heat is dissipated through radiation and convection from body surfaces. As environmental temperatures increase and approach body temperature, evaporation, primarily through panting, becomes more important for maintaining normothermia. The nasal turbinates provide a large surface area for water loss from the moist mucous membranes, and play an important role in heat dissipation. Hypersalivation increases the evaporative efficiency, although high environmental temperatures and increased humidity (>35%) will decrease its effectiveness; when humidity is >80%, this cooling measure will be negated [2,3].

Heat stroke is caused by the inability to dissipate accumulated heat. In dogs, it is characterized by core temperatures above 41 °C (105.8 °F) with central nervous system (CNS) dysfunction [3,4]. It results from exposure to a hot and humid environment (classic heat stroke), from voluntary strenuous physical exercise (exertional heat stroke) or severe, uncontrolled tremors or seizures [1,5].

In the initial stages of heat stress, cardiac output increases due to peripheral vasodilation and decreased vascular resistance. As hyperthermia progresses, cutaneous and splanchnic blood pooling combines with dehydration, which results in decreasing circulating blood volume – hypotension. Consequently, cardiac output declines due to decreased circulating blood volume, leading to failure of heat loss through the mechanisms of radiation and convection, causing an elevation in body temperature that may progress to heat stroke.

Accumulation of blood in these organs is a major contributor to the shock and consequent intestinal ischemia, hypoxia, and endothelial hyperpermeability that many heat stroke patients develop. Cytokine production, reactive oxygen and nitrogen species generation, endotoxemia, and endothelial injury are all contributors to increased vascular permeability and subsequent interstitial edema [6–8]. Activation of inflammatory and hemostatic pathways initiates a systemic inflammatory response syndrome (SIRS) which often progresses to multiorgan dysfunction syndrome (MODS) [7,9] (see Chapter 159).

Serious complications of heat stroke include rhabdomyolysis, acute kidney injury (AKI) (see Chapter 94), acute respiratory distress syndrome (ARDS), and disseminated intravascular coagulation (DIC) [10–12] (see Chapter 70). Consequently, despite appropriate cooling and supportive treatments, mortality rates above 50% have been reported in humans and canines suffering from heat stroke because no specific treatment is available to ameliorate the activated inflammatory and hemostatic pathways [13–16]. It seems that the main causes of death from heat stroke in canines are systemic hemodynamic deterioration and pulmonary lesions, as determined from postmortem studies of 11 dogs that suffered naturally occurring heat stroke [12].

Risk Factors for Developing Heat Stroke

Several factors are associated with the risk of developing heat stroke. These include prior occurrence of heat stroke or heat stress, obesity, breed (brachiocephalic, golden and Labrador Retrievers), body weight (>15 kg), high environmental temperature and humidity, and lack of acclimation and fitness [14,17,18]. Prior heat stroke may affect the thermoregulatory center in the preoptic zone

which is responsible for heat sensation and dissipation. Excess body fat increases the body's natural thermal isolation and impairs normal heat dissipation mechanisms in obese people and animals [3,19]. Large-breed dogs are significantly more at risk of developing heat stroke, particularly exertional heat stroke, suggesting that the ratio between body size and surface area is an important factor in heat dissipation during heat stress. The median body weight of 54 dogs with naturally occurring heat stroke was 31 kg, also supporting this theory [14].

Two endogenous adaptive mechanisms are directly invoked to combat heat stress: heat acclimation and the rapid heat shock response. Heat acclimation induces adaptive physiological and behavioral changes that improve the individual's ability to cope with extreme environmental heat. Acclimation is a time-dependent process leading to a dynamic expansion of the body temperature regulatory range due to left and right shifts in the temperature threshold for heat dissipation and thermal injury, respectively.

The heat shock response is a rapid molecular cytoprotective mechanism that involves production of heat shock proteins (HSP). When subjected to sublethal heat stress, the body enhances HSP transcription and synthesis to increase HSP72 cellular reserves, thus providing cytoprotection [20]. In a recent prospective study, the correlation between HSP 72, heat acclimation, and physical performance in military working dogs was evaluated. During the study, three consecutive physical performance tests were performed over a 2-year training period. Serum HSP72 concentrations and lymphocyte HSP72 and its corresponding mRNA levels were analyzed before and after the physical endurance test. Results showed that together with the profound enhancement of aerobic power and physical performance, HSP72 mRNA was induced and progressively increased, and there was also a significant rise in basal and peak serum HSP72 concentrations after physical exercise [17].

Clinical Signs and Diagnosis

The most common clinical signs of canine heat stroke include collapse, shock, tachypnea, spontaneous bleeding (e.g. petechiae, hematemesis, and hematochezia), disorientation/stupor, coma, and seizures. Although the definition of heat stroke is based on hyperthermia causing shock and hypotension, it is important to remember that patients can be hyper-, normo- or hypothermic on presentation, particularly if cooling measures were initiated by the owners prior to presentation. Furthermore, in a retrospective study of canine heat-related illness, hypothermia upon admission was a poor prognostic indicator [15]. Therefore, heat stroke should not be disregarded in

a patient with normal or low core temperature if the history reveals recent exercise or confinement in a hot and humid environment, recent cooling by the owner and clinical and/or clinicopathological findings compatible with heat-related illness.

Acute collapse, abnormal mentation, hypoglycemia, and hyperemic mucous membranes are common in dogs with heat-induced illness. Nonetheless, the median systolic and diastolic blood pressure upon admission to medical treatment in a prospective study of 30 dogs with naturally occurring heat stroke were in the normal range (>90 mmHg and >60 mmHg, respectively and HR of 160 bpm), except for one dog [21]. This is in contrast to the hypotension documented in both experimental models and human clinical reports [22]. The lack of hypotension suggests that the dogs were in a state of compensatory shock at the time of admission to the hospital (after cooling by their owners and/or by the referring veterinarian). The neurohormonal compensatory response of blood pressure is likely to be faster than the recovery/disruption of biochemical parameters.

Hematological Disorders and Biochemical Abnormalities

The most common hematological findings in canines with heat stroke are thrombocytopenia and increased packed cell volume (PCV) and hemoglobin concentrations. In a retrospective study of 54 dogs with heat stroke, 83% had thrombocytopenia upon admission and during hospitalization, although it was not found to be a significant risk factor for death (Table 147.1) [23]. In that study, only 50% of the dogs suffered from DIC, so thrombocytopenia is most likely caused by a combination of vasculitis, splenic sequestration with blood pooling, gastrointestinal bleeding, and hyperthermia-induced platelet aggregation [23].

Nucleated red blood cells (nRBCs) on peripheral blood smear are abundant in dogs with heat stroke (10–120%) and represent a significant risk factor for mortality. They most likely occur secondary to heat-induced damage to the bone marrow. Dogs presenting with >18 nRBC/100 WBC on peripheral blood smear were significantly more likely to die, have renal complications, and develop DIC. The maximum level of nRBC was detected upon admission with a gradual decline over the first 36 hours from the insult in all the dogs [10]. This phenomenon can be attributed to thermal lesions within the bone marrow, leading to blood–bone marrow barrier injury and subsequent release of nRBCs to the peripheral circulation. An alternative hypothesis might be that bone marrow release of nRBCs to the peripheral circulation in canine heat stroke is mediated via the actions of cytokines.

Table 147.1 Risk factors for mortality in 54 dogs with naturally occurring heat stroke.

Variable	RF present		RF not present		RR	Exact CI 95%	P
	n	Number of deaths (%)	n	Number of deaths (%)			
Timelag >90 min	34	21 (62)	15	4 (27)	2.32	1.08–5.90	0.032
Cooling by owners before admission	26	10 (39)	28	17 (61)	0.63	0.35–1.12	0.173
Obesity	11	9 (82)	36	15 (42)	1.96	1.11–3.21	0.040
Coma/semicoma upon admission	22	15 (68)	20	8 (41)	1.71	0.95–3.32	0.060
Seizures during illness	19	14 (74)	35	13 (37)	2.00	1.17–3.37	0.020
Prothrombin time >18 sec upon admission	8	7 (88)	39	18 (46)	1.90	1.05–2.94	0.050
aPTT >30 sec upon admission	14	13 (93)	33	12 (36)	2.55	1.57–4.28	<0.001
Thrombocytopenia* during illness	42	19 (45)	8	3 (37)	0.83	0.28–1.80	1.000
Creatinine >1.5 mg/dL at 24h from admission	20	15 (75)	17	4 (24)	3.19	1.41–8.39	0.003
Glucose <47 mg/dL upon admission	12	10 (83)	12	5 (42)	2.00	1.01–5.27	0.03
Presence of DIC	28	19 (68)	26	8 (31)	2.21	1.22–4.31	0.013
Presence of AKI	18	14 (78)	36	13 (36)	2.15	1.28–3.64	0.008
Presence of DIC + AKI	12	11 (92)	21	6 (29)	3.21	1.63–7.01	0.001
Presence of environmental heat stroke	20	10 (50)	34	17 (50)	1.00	0.55–1.72	1.000
Presence of exertional heat stroke	34	17 (50)	20	10 (50)	1.00	0.58–1.82	1.000

*Platelet count $150 \times 10^3/\text{mm}^3$.

AKI, acute kidney injury; aPTT, activated partial thromboplastin time; CI, confidence interval; DIC, disseminated intravascular coagulation; RF, risk factor; RR, relative risk.

Rhabdomyolysis is a prominent feature of heat stroke during and following the heat insult, and is exacerbated during the first 24 hours of hospitalization due to muscular hypoperfusion resulting from distributive shock and DIC. The degree of increase in serum muscle enzyme activities reflects the extent of cellular damage and direct thermal injury to myocardial and skeletal muscle myocytes [24]. Liver damage and acute liver failure have been described in humans and animals with heat stroke [25–28]. Therefore, the most commonly observed serum biochemistry abnormalities in canine heat stroke include increased serum activities of creatine kinase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and hypoglycemia [10,14]. In 46 dogs with heat stroke, CK was reported to be elevated in 97% at presentation, with a median of 11 000 U/L (range 107–345 000 U/L), AST and ALT in 80% (median 750, range 40–14 500 and median 225, range 44–3200 U/L), and ALP and GGT only in 25% of the dogs (median 135, range 24–586 U/L, median 5.5, range 1–38 U/L) (Bruchim et al. 2016, unpublished data). Interestingly, only ALP and GGT were significantly higher among non-survivors, perhaps indicating the role of sepsis-induced cholestasis and hepatic failure, as described in human heat stroke victims and animal models [26,27].

In a retrospective study of 54 dogs with heat stroke, hypoglycemia was evident in 62% of the dogs upon admission, and was found to be a significant risk factor of mortality. Hypoglycemia can result from increased utilization or decreased production of glucose, or be due to hepatic failure or sepsis, as seen in some dogs with persistent hypoglycemia despite initial stabilization of serum glucose levels (see Table 147.1) [14].

Coagulation Disorders and Disseminated Intravascular Coagulation

Thermal endothelial cell injury leads to diffuse vascular damage and initiation of coagulation and subsequent microvascular thrombosis. In addition, multiorgan cellular necrosis further stimulates the coagulation system and results in DIC, an important factor in the morbidity and mortality of heat stroke patients [29] (see Chapter 62). The injured endothelium releases thromboplastin and factor XII, which activate coagulation and the complement cascade, inducing SIRS and widespread DIC. Hepatic injury and failure due to hypoperfusion, microembolism, and direct hyperthermic damage may exacerbate the hemostatic disorders [29].

In vitro studies have shown that high temperatures ($>42^{\circ}\text{C}$) lead to platelet aggregation, activation of the coagulation cascade, and enhanced fibrinolysis [1,7,11,30,31]. Normalization of body temperatures inhibits fibrinolysis but not the coagulation cascade or platelet aggregation [30]. In a retrospective study of 54 dogs with naturally occurring heat stroke, 50% were diagnosed with DIC [14]. In 11 such dogs, severe bleeding and widespread microthrombosis, characteristic of hemorrhagic diathesis, were invariably noted at necropsy [12]. As DIC may appear hours to days after the initial hyperthermic insult, dogs with heat stroke should be monitored closely for coagulation abnormalities and clinical signs of DIC for at least 24 hours after the insult.

In a recent study in which serial monitoring of coagulation parameters was followed during the first 36 hours of hospitalization in 30 dogs with heat stroke, hemostatic analytes at presentation were not associated with mortality. However, prolonged PT and aPTT at 12–24 hours, lower total protein C activity at 12 hours, and hyperfibrinogenemia at 24 hours post presentation were significantly associated with mortality. Increased D-dimer concentration and low antithrombin activity were common at all time-points, but were not associated with mortality (Figure 147.1) [32]. Interestingly, in that study, which was performed 10 years following the first one at the same institution, DIC was not associated with mortality, the median number of fresh frozen plasma units administered increased from 2 to 4 units per dog, and mortality decreased from 50% to 40%.

Other Complications: Acute Kidney Injury, Central Nervous System Dysfunction, ARDS, Cardiac Arrhythmias, and Gastrointestinal Bacterial Translocation

Acute Kidney Injury

Azotemia is a common finding in patients with heat stroke (see Chapter 94). It results from prerenal and renal mechanisms, such as severe hypovolemia and direct renal tissue damage leading to tubular necrosis, a frequent finding at necropsy of dogs with heat stroke [12]. This probably occurs as a result of direct renal thermal injury, hypovolemia, hypoxia, and endotoxemia, release of cytokines and vasoactive mediators and microthrombosis associated with DIC [1,33]. The presence of AKI during hospitalization and serum creatinine levels $>1.5\text{ mg/dL}$ at 12 and 24 hours after presentation were found to be independent risk factors for death in dogs with heat stroke (see Table 147.1) [14,21,34]. Therefore, careful monitoring of renal function and early intervention are warranted.

Central Nervous System Dysfunction

Severe hyperthermia may lead to cerebral hypoperfusion, neuronal necrosis, direct vascular damage, cerebral edema, hemorrhage, and multifocal vascular thrombosis with tissue infarction that may lead to CNS dysfunction and death. The canine brain is considered more resistant to thermal injury than the human brain and other physiological factors, such as respiratory alkalosis, shock and hypoglycemia, may play a more significant role in the observed CNS clinical signs in canine heat stroke [35].

Acute Respiratory Distress Syndrome

Thermal and biochemical injury to the pulmonary endothelium may lead to non-cardiogenic pulmonary edema, also known as ARDS (see Chapters 39 and 159). Histopathological lung lesions in dogs suffering from heat stroke include pulmonary infarcts, marked alveolar hemorrhage, and edema [12].

Cardiac Arrhythmias

A few extracardiac mechanisms were proposed as contributing to the development of cardiac arrhythmias: myocardial hypoperfusion, lactic acidosis and electrolyte imbalance, and possibly direct thermal injury. Postmortem findings in 11 dogs with heat stroke showed mild to severe subendocardial, myocardial and epicardial hemorrhages and hyperemia in all dogs [12]. These findings suggest that DIC has a pivotal role in the pathogenesis of the reported cardiac arrhythmias. Antiarrhythmic therapy should be considered, however, only if the patient has related clinical signs (see Chapter 53).

Gastrointestinal Bacterial Translocation

In humans and experimental studies, marked increases in core temperatures are associated with blood flow redistribution, which is characterized by cutaneous vasodilation that occurs at the expense of decreased intestinal blood flow [4,6]. This splanchnic vasoconstriction may cause ischemia and limit local vascular heat exchange, thereby promoting bowel tissue hyperthermia. Both intestinal ischemia and hyperthermia may promote oxidative stress that stimulates cytoskeletal relaxation, thus contributing to the opening of tight junctions and/or injuries to the epithelium [6,36]. These morphological and functional changes enhance intestinal permeability, thus facilitating the translocation of bacteria and endotoxins that are normally contained within the intestinal lumen, and subsequently worsening a systemic inflammatory response syndrome that may culminate in multi-organ system failure and death [6,37].

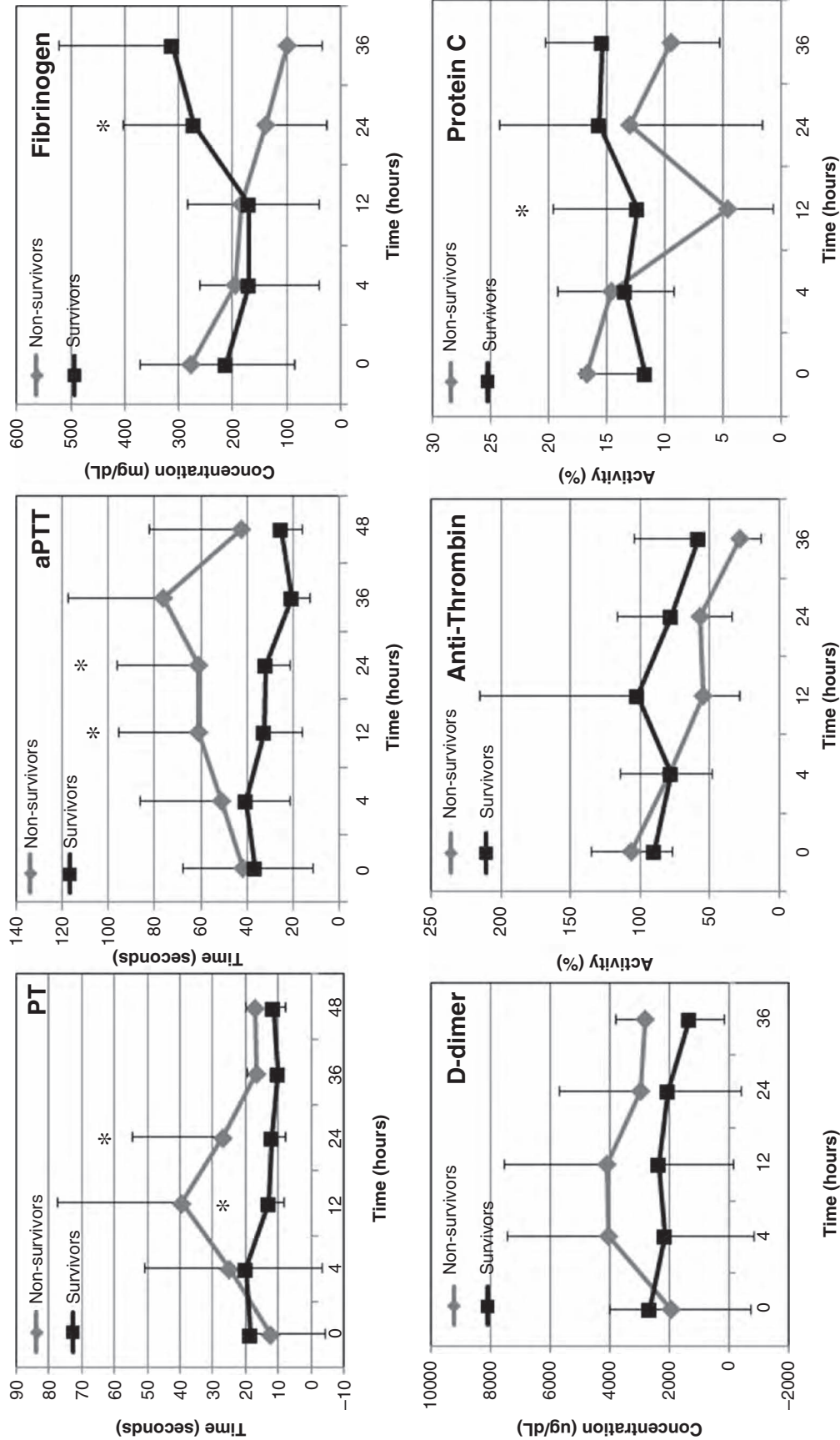


Figure 147.1 Trends in hemostatic parameters throughout hospitalization in 30 dogs with naturally occurring heat stroke. Mean values of survivors (n = 18, black squares) and non-survivors (n = 12, gray diamonds) are depicted. Whiskers represent the SD. * depicts significant difference between survivors and non-survivors. aPTT, activated partial thromboplastin time; PT, prothrombin time.

Gastrointestinal bacterial translocation has not been specifically documented in dogs with naturally occurring heat stroke but given the massive hemorrhagic diarrhea and hematemesis that rapidly ensue in dogs with severe heat stroke, it is reasonable to assume that it is a major contributing factor to SIRS, sepsis, and MODS that may occur in severe cases (see Chapter 159).

In summary, clinicopathological findings in canine heat stroke are mainly related to the primary thermal insult; however, secondary deterioration occurs due to dehydration, shock, and a poor perfusion to the tissues. Thus, early diagnosis and intervention are crucial to prevent further multiorgan dysfunction and exacerbation of coagulation abnormalities. Time lag from insult to admission (>1.5 h) was a crucial factor for survival in canines suffering from heat stroke [14].

Treatment Options

Whole-body cooling prior to admission is highly recommended. The literature suggests different cooling methods (e.g. cold enema, gastric lavage, ice baths); however, other successful and perhaps more practical methods use evaporative cooling via whole-body irrigation with tap water and placement of a fan facing the animal. Animals with thick undercoats may benefit from shaving prior to wetting. A cool environment with low humidity is also beneficial. Cooling with ice directly on body surfaces and/or peripheral blood vessels should be avoided as it may result in cutaneous vasoconstriction and decrease heat loss ability. During cooling, the patient's temperature should be monitored every 5–15 minutes to avoid hypothermia. Cooling should be terminated when body temperature has reached 39.5°C (103°F). Cooling does not result in suppression of the inflammatory response, but will prevent further cellular destruction.

Most canine heat stroke victims suffer from distributive shock, as described above. Although the absolute intravascular volume has not changed significantly, vasodilation and venous pooling of blood lead to a relative hypovolemia (see Chapters 153 and 155). As the animal is cooled, the vasomotor tone will return to normal. Therefore, judicious fluid therapy is warranted. An initial crystalloid dose of 10–20 mL/kg should be administered and perfusion parameters (HR, MM, CRT, pulse quality, blood pressure, mentation, urine output) continuously reassessed to help guide additional fluid therapy (see Chapter 167). When perfusion cannot be restored with crystalloids alone, synthetic colloids (hydroxyethyl starch solutions), vasopressor agents (dopamine, vasopressin, norepinephrine) and positive inotropes (dobutamine) should be considered (see Chapters 159 and 168).

Dextrose should be administered to hypoglycemic dogs as a single bolus (1 mL/kg of diluted 50% dextrose not to exceed a maximum of 10 mL) followed by a 2.5–5% dextrose CRI, with close monitoring of the glucose concentrations (see Chapter 111).

All dogs with heat stroke should be given oxygen therapy during triage (see Chapter 181). Animals with severe dyspnea or laryngeal edema should be intubated, although this can decrease self-cooling mechanisms inherent with panting. In the most severe cases, general anesthesia with 100% oxygen or positive pressure ventilation may be required.

Mannitol therapy may be beneficial in animals with cerebral edema causing intracranial hypertension, although it can also worsen cerebral hemorrhage, if present. Mannitol administration has beneficial effects on the kidney and will help restore urine output and flush tubular casts out in animals with AKI. A suggested treatment regime might be 0.5–1 g/kg of mannitol over 10–20 minutes after the initial fluid resuscitation, followed by 1–2 additional boluses over the ensuing 12 hours.

Benzodiazepines (diazepam, midazolam) are administered as a bolus followed by a CRI if the animal seizures (about 33% of the cases). Other causes for seizures such as hypoglycemia or metabolic and electrolyte imbalances should be ruled out (see Chapter 21).

Antimicrobial treatment is not warranted in mild to moderate cases. In severe cases, broad-spectrum antibiotics are indicated to treat sepsis due to presumed gastrointestinal bacterial translocation (see Chapter 200). A combination of antimicrobials effective against gram-positive, gram-negative, and anaerobic bacteria is recommended in severe cases, utilizing the “escalation–de-escalation” method. A combination of a potentiated penicillin and a fluoroquinolone or third-generation cephalosporin could be considered.

Gastric protectants such as H₂ blockers (e.g. famotidine) or proton pump inhibitors (pantoprazole) should be administered to prevent further gastric damage (see Chapter 77). Antiemetics and promotility agents are essential for prevention of vomiting and consequent aspiration pneumonia.

If urine output remains insufficient despite adequate fluid replacement and mean arterial blood pressure is >60 mmHg, medical therapy with furosemide and/or mannitol should be considered (see Chapter 95). Overhydration must be avoided in anuric/oliguric patients and fluid therapy adjusted based on urine output and intravascular volume status of the patient. Hemodialysis may be indicated in dogs with oligoanuria despite medical therapy, as well as those patients with severe overhydration, uremia or electrolyte derangements.

Treatment of the hemostatic abnormalities due to DIC is based on stabilization of the coagulation system

with fresh frozen plasma and concurrent prevention of thrombosis with anticoagulants (see Chapters 62 and 71).

Hemofiltration has been suggested as an effective treatment modality in an experimental model of severe canine heat stroke, causing early clearance of accumulated serum cytokines, creatinine, and BUN [38]. Clinical data are unavailable at this time.

Monitoring

Serial monitoring of the patient's clinical and clinicopathological parameters is essential for early identification of complications and appropriate intervention. Continuous monitoring of vital signs is warranted, including temperature, femoral pulse rate and quality and capillary refill time to assess perfusion, hydration and shock status. In addition, PCV/TS, serum glucose, coagulation profile (including TEG or ROTEM when available), CBC, lactate, blood gas (arterial or venous), arterial blood pressure, and urine output should be monitored. The mental status of the patient should be evaluated frequently and continuous ECG monitoring is recommended as arrhythmias may develop during the first 24 hours after the heat stroke occurs.

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Prognosis

Mortality rates in dogs suffering from severe heat stroke are reportedly 40–50% [14,21,34,39]. Animals with heat-induced illness have a reportedly lower mortality rate (35%) [15]. At the authors' institution, mortality rates decreased to 40% and 43% in two recent studies [21,34] compared to 50% 10 years earlier [14]. However, larger scale studies are needed to determine if this trend is real.

Conclusion

In conclusion, heat stroke in dogs is a life-threatening condition, resulting in serious secondary complications such as DIC, AKI, and ARDS, and a high mortality rate despite appropriate treatment. Early admission and treatment along with whole-body cooling by the owners and caregivers are important for survival. The diagnosis of canine heat stroke should not rely exclusively on hyperthermia or the presence of neurological abnormalities upon admission, but should be based on the combination of the history, clinical signs, and laboratory results. Treatment and monitoring should be intensive and prolonged since complications can have a delayed onset and present serious risk factors for mortality (see Table 147.1).

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Cold Exposure

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Introduction

Cold exposure may result in accidental hypothermia, defined as an unintentional decrease in core temperature without preoptic and anterior hypothalamic nuclei disease [1,2]. The normal range for core temperature in dogs and cats is 37.5–39.5°C (99.5–102.5°F). Hypothermia is defined as a core body temperature 2°C below normal in humans (35°C) (95°F) [3] which would correlate with a temperature below 36.0°C (97°F) in cats and dogs. Of importance is that, in the clinical setting, the rectal temperature is the initial mode of temperature assessment. Digital thermometers register to 32°C (89.8°F), making an accurate determination of degree of hypothermia difficult. In addition, the poor depth of measurement gives a lower reading compared to esophageal monitoring. This may continue through rewarming for up to an hour, during which time the rectal temperature may even drop by several degrees while the heart and esophageal temperatures are rising [4]. The electronic thermometers with probes approximately 10 Fr and 1 metre long (Sonatemp 400–700 Thermometer, Sheridan, Argyle, NY) record temperatures below 21°C (69.8°F) and can be placed intranasally into the esophagus or into the colon per rectum. It is recommended to cautiously place the rectal probe in at least 15 cm (10 htp); however, this is patient size dependent. Infrared otic thermometers have inherent inconsistencies.

In addition to exposure to low environmental temperatures, other factors exacerbating the effects of cold exposure resulting in hypothermia are immersion in water [5], trauma, and exhaustion. Freezing injuries (frostbite) of the extremities are common injuries associated with cold exposure. Underlying conditions such as hypothyroidism, very young or very old age, cardiac disease or malnutrition may predispose animals to accidental hypothermia at a temperature higher than would occur in a healthy animal. Recreational drugs, ethylene glycol, and phenothiazines, as examples, can disrupt

normal heat production and conservation by impairing perception of changes in ambient temperature, depressing mental status, and inhibiting the shivering response. These etiologies should be considered in any unexplained case of hypothermia.

Pathophysiology of Effects of Cold Exposure [1–3,6–10]

At temperatures 1–2°C below normal, thermogenesis, through shivering and hypermetabolism, attempts to compensate for heat loss. Intense vasoconstriction in peripheral tissues results in acrocyanosis and cool extremities due to shunting of blood away from the cold body surface to help sustain core body temperature. With prolonged exposure, thermoregulation fails as heat production is unable to offset the rate of heat loss from the body surface; further reduction in core temperature then occurs, leading to progressive multiorgan dysfunction. The increased circulating catecholamines result in increased respiratory rate, minute ventilation and oxygen consumption, increased heart rate, cardiac output and mean arterial pressure and elevated levels of serum cortisol, lactate, glycerol, ketones, and glucose.

Respiratory compromise occurs via various mechanisms. After the initial tachypnea, central respiratory depression occurs at 2–5°C below normal, leading to decreased respiratory rate and tidal volume. As core temperature approaches 25°C (85°F) or less, bronchiolar mucous plugs and atelectasis occur, increasing the risk of bronchitis and bronchopneumonia (see Chapter 37). Immersion injury/near drowning frequently results in pneumonia (see Chapter 40). Increased intracranial pressure may result in non-cardiogenic pulmonary edema. The compromised pulmonary gas exchange coupled with decreased perfusion to the tissues results in lactic acidosis, the significance of which increases with

decreasing temperature. Also, oxygen affinity for hemoglobin increases with low temperatures which further reduces oxygen delivery to the tissues.

Cardiovascular function decreases after the initial increase in arterial blood pressure and heart rate. Progressive hypothermia reduces cardiac output and mean arterial blood pressure as bradycardia, hypovolemia, and decreased ejection fraction occur.

Electrocardiogram changes related to body temperature can be seen. At approximately 32°C (90°F), the Osborn J wave may appear. The J waves are usually upright in aVL, aVF, in leads II and V6, at the junction of the QRS complex and ST segment. The size of these waves increases with temperature depression, but is unrelated to arterial pH. The waves are diagnostic but not prognostic or pathognomonic of hypothermia, as they are also associated with central nervous system lesions, focal cardiac ischemia, and sepsis. Atrial fibrillation may occur. Ventricular fibrillation (VF) and asystole may follow with core temperatures below 28°C (83°F) and 20°C (68°F) respectively. ECG changes accompanying mild hypothermia include prolongation of the P-R, Q-T and QRS intervals, atrial ectopy, and T-wave inversion. Ventricular fibrillation may be triggered by mechanical irritation, such as placing central lines, but mere handling of the patient can precipitate VF. In general, caution is warranted when handling these patients and extremely gentle care is required when drying the wet patient.

Neurological abnormalities, both central and peripheral, are frequently present. Cerebral blood flow is reduced at temperatures 2–5°C below normal, and patients may be uncoordinated, stuporous and eventually comatose as the temperature drops below 30°C (86°F). An increase in intracranial pressure may occur secondary to “cold edema,” an osmotic gradient associated with changing serum glucose levels, ischemic injury, or head injury. In humans, hyperreflexia predominates from 35°C (95°F) to 32.2°C (90°F), and is followed by hyporeflexia. The plantar response remains flexor until 26°C, when areflexia develops. The patellar reflex is usually the last reflex to disappear, and is the first to reappear during rewarming. From 30°C (86°F) to 26°C (78.8°F), both the contraction and relaxation phases of the reflexes are equally prolonged. Various traumatic injuries may also result in neurological abnormalities and true injury (spinal) cannot be assessed until the patient is rewarmed, unless obvious lesions are present.

Urinary output ranges from polyuria to anuria (see Chapter 95). Glomerular filtration rate (GFR) is enhanced as core temperature decreases below normal by 2–3°C, due to peripheral vasoconstriction, shunting of blood centrally, and increase in central blood volume. The resultant increase in GFR promotes withdrawal of antidiuretic hormone (ADH), leading to “cold diuresis.” Cold-related impairment of renal enzymatic activity inhibits tubular

reabsorption of glucose, sodium, and water with loss of extremely dilute urine contributing further to dehydration. As hypothermia progresses, cardiac output drops despite activation of the RAAS. The resultant afferent and efferent renal arteriolar vasoconstriction reduces glomerular plasma flow and peritubular capillary pressure. Renal blood flow is depressed by 50% at 27–30°C (80.6–86°F) which decreases glomerular filtration rate.

Acute kidney injury, secondary to depressed renal blood flow and defective tubular activity, often develops in patients who have prolonged and profound hypothermia (see Chapter 94). Acute tubular necrosis may be observed prior to azotemia. Blood urea nitrogen (BUN) and creatinine are often elevated because of decreased nitrogenous waste clearance by the cold diuresis. Prior renal disease is a possibility. The BUN is a poor indicator of volume status because of ongoing fluid shifts. The SDMA (IDEXX), an assessment of GFR, is more accurate.

Testicular torsion may occur due to cremasteric contractions (see Chapter 126).

Splanchnic blood flow and gastrointestinal motility diminish as the core temperature approaches 34°C (93°F). Ileus develops when the temperature drops below 30°C (86°F). Gastric dilation in pediatrics, abdominal distension or rigidity, obstipation, and poor rectal tone are frequently present in humans. As vasoactive amines histamine and serotonin are released in response to vascular compromise, punctate erosions of the stomach, duodenum, ileum and colon, and pancreatitis have been reported to occur in humans and animals (Mathews, personal observations) (see Chapter 86). Severe hypothermia often induces a hemorrhagic pancreatitis as a consequence of depressed pancreatic perfusion. The liver is relatively resistant to the effects of cold injury but depletion of glycogen stores occurs early in hypothermia and a general decrease in metabolic function leads to decreased detoxification and conjugation activity and diminished lactate metabolism. This is an important point to consider when administering various medications and lactate-containing fluids.

Hematological, biochemical, and coagulation parameters are altered as hypothermia progresses. Initially, hypokalemia may be present but K⁺ increases as temperature decreases. Hyperkalemia (>12 mmol/L) is a potential index of irreversibility (see Chapter 109). High lactic acid levels may predict a bad outcome. Alkalosis appears protective. In canine deep hypothermia studies, puppies and dogs with arterial pH reduced to, and maintained at, 7.4 had decreased cardiac performance and myocardial damage when compared to the control group, left uncorrected (alkalemic) pH > 7.4. The control group had increased cerebral blood flow, normal cardiac indices and improved electrical stability of the heart [11]. The fibrillation threshold of dogs markedly decreased when

arterial pH was held at 7.4 [11]. Isotonic dehydration increases the hematocrit and hemoglobin concentrations and total plasma solids. White blood cells and platelets may sequester within the spleen and perivascular tissue, causing leukopenia and thrombocytopenia. Disseminated intravascular coagulation may occur after prolonged hypothermia and hypoperfusion as a result of microvascular disruption, hemoconcentration, and activation of the clotting cascades (see Chapter 70).

Although coagulopathies occur in hypothermia, the clotting factor levels are normal. In a reported study of human trauma patients who developed lethal coagulopathies, the average temperature was 31.2°C. High CPK levels may indicate rhabdomyolysis.

Gluconeogenesis occurs with depression of insulin release and an increased peripheral receptor resistance to insulin due to the stress-induced catecholamine release. Hyperglycemia that persists during rewarming signals the potential for diabetic ketoacidosis or hemorrhagic pancreatitis (see Chapter 112). Insulin is ineffective until well above 30°C (86°F), and should be withheld to avoid iatrogenic hypoglycemia after rewarming.

Aspiration of gastric contents may occur after immersion/near drowning hypothermia or due to hypothermia itself [5]. Therefore, dyspnea may be present or develop upon rewarming.

Management [1–3,7–10]

Carefully place the patient on a warm surface. Noting all the above sequelae of hypothermia, management of hypothermic animals should include monitoring of all possible events.

Initially, establish the ABCs of resuscitation (see Chapter 2). Should cardiac arrest be suspected, ensure that the patient is arrested prior to commencing cardiopulmonary resuscitation as chest compression frequently causes VF. Due to severe vasoconstriction, it is often difficult to feel a pulse and weak myocardial contractions are barely, if at all, audible. Confirm myocardial wall motion with tFAST (see Chapter 182) [12]. A “flat ECG” may be due to asystole or just bad electrical conductance through cold skin or problems of adhesion of ECG electrodes. Sterile hypodermic needles should be placed through the gel portion of the electrodes which will improve adhesion and conduction, or place a 23–25 gauge hypodermic needle through the skin and attach the alligator clip to the needle. ECG monitoring may be difficult due to shivering (may look like VF). Oxygen administration may reduce the risk of VF during resuscitation (see Chapter 181). Should VF be diagnosed, note that the cold myocardium is relatively insensitive to DC shock defibrillation; however, administer three immediately and if no response,

administer a further three shocks after the patient has been rewarmed to 28–30°C (83–86°F) (see Chapter 150). The hypothermic heart is unresponsive to pacing and cardioactive drugs.

Medication to treat arrhythmias should not be given until body temperature is 30–32°C (86–90.3°F) as drugs are ineffective at temperatures below this. Atropine is ineffective for bradyarrhythmias at low temperatures. Rewarming alone will usually correct this rhythm and, frequently, atrial fibrillation [1,13]. Also, the heart generally cannot sustain rhythmic electrical function until this temperature is reached. Basic cardiopulmonary resuscitation should be performed, if cardiac arrest diagnosed, until the temperature is ≥32°C (90.3°F) when advanced cardiac life support (the use of medication) can be added if required. Administration of normal doses, and repeat doses of any medication, will lead to accumulation and be toxic to the patient when rewarmed. Patients may appear “dead” if the temperature is <28°C (83°F) but resuscitation should be attempted as occasional success has been recorded in individuals with temperatures <14°C (57.2°F). The American Heart Association recommendations are to rewarm patients to at least 35°C (95°F) before declaring futility and withdrawing support [14]. The saying “you’re not dead until you’re warm and dead” should be remembered.

Secondly, assess the cause and duration of hypothermia and institute appropriate therapy for the cause. Injuries associated with trauma, possible abusive elicit drug or alcohol administration, drowning or medical problems predisposing to exposure hypothermia should be identified. Following this, restoration of normothermia is the main objective.

Rewarming techniques depend on the degree of hypothermia, duration, and predisposing events. Blood should be collected for packed cell volume (PCV), total plasma solids (TS), blood urea nitrogen (BUN) or urea, creatinine, electrolytes, blood gases, glucose and ALT, prior to fluid administration. As even mild hypothermia causes a cold diuresis, all hypothermic animals should receive warmed intravascular fluid support; an alkalinizing solution, Plasma-lyte A, 148 or Normosol R, is recommended. Lactated Ringer’s should be avoided in severe hypothermia as the liver may be unable to metabolize the lactate.

Fluids should be warmed to 50°C (120°F) when hung with a standard intravenous delivery set or to 42°C (107.5°F) when using 60 mL syringes, short tubing, and a syringe pump. The temperature of the fluid drops rapidly due to ambient room temperature, even when warmed, therefore slow delivery will reach room temperature at the IV catheter [15]. Placing the intravenous delivery line under a warm water bottle or heating blanket will maintain warm fluid temperature. Ensure the directly administered temperature is not higher than 42°C (107.6°F).

Hydration status should be assessed and fluid requirements calculated. It is advisable to administer fluids cautiously initially due to possible depressed cardiac function and intense peripheral vasoconstriction. Blood pressure measurements should be attempted. Where indicated, after rewarming, a urinary catheter should be placed to measure urine output. Constant assessment is required as the core temperature increases; fluid therapy can be altered based on blood pressure, urine production, PCV, TS, mentation, and tolerance of fluids delivered.

External rewarming is usually adequate for temperatures $>32^{\circ}\text{C}$ (90.3°F). This can be in an active or passive form. If the patient is wet, dry them gently with a towel to remove as much water as possible.

Passive rewarming is usually adequate for the mildly hypothermic animal $\sim 34^{\circ}\text{C}$ (93.5°F). Shivering is usually present at temperatures $\geq 35^{\circ}\text{C}$ (95°F), but may be absent below this. Holding a small patient, covered with a blanket, close to your body is an efficient means of rewarming. For the larger patient, place them in a warm room wrapped in a blanket, where the animal can rewarm themselves via shivering and heat conservation. The head should also be covered. Ensure good coverage of the body and not just the limbs. With this method, the temperature can increase by $0.4\text{--}2^{\circ}\text{C/h}$. A degree of peripheral vasoconstriction is maintained which minimizes the risk of both hypotension and the temperature afterdrop. Afterdrop refers to a drop in the core temperature as a result of sudden peripheral rewarming and vasodilation where the cold acidic blood is returned to the core. Hypotension and potentially fatal dysrhythmias can result (especially notable in spinal cord transection where peripheral thermoregulation fails).

Active rewarming is required for patients with moderate to severe hypothermia and core temperatures below 34°C (93.5°F); this may include those which are hypoglycemic, hypothyroid, adrenal insufficient or have other disorders that limit endogenous thermogenesis, and patients with diabetic ketoacidosis or an unstable cardiovascular system. Active rewarming must be performed in any patient, whatever the degree of hypothermia, if initial passive rewarming methods fail to elevate body temperature. Warm water bottles (avoid contact to avoid thermal burns), heated blankets (Hot Dog warming blanket; Augustine Medical Incorporated, MN) or a warmed incubator for small animals can accomplish active external rewarming. Warming the ambient air and cage with hot water bottles will reduce heat loss. Fans should not be used as stationary air is less conducive to heat losses by radiation. However, forced air enclosed around the patient, has proved effective in core rewarming. Temperatures of $28.8 \pm 2.5^{\circ}\text{C}$ increased by $2.4 \pm 1.0^{\circ}\text{C/h}$ using the forced air system of disposable plastic and paper covers

and a heat source that directs warm air across the skin (Bair Hugger; Augustine Medical Incorporated, MN) in humans and dogs (Mathews, personal observation) who recovered rapidly and uneventfully. *Caution:* cutaneous burns may occur due to inability to move and the initial vasoconstriction blocks dissipation of heat from surface tissues. The temperature of external heat sources therefore should not exceed 45°C (113°F).

Afterdrop may develop with these heat sources, which may predispose to worsening of cardiac arrhythmias. Also, vasodilation associated with warming of the limbs may precipitate further hypotension. While it is recommended to limit the application of external heat to the trunk to minimize the afterdrop effect, where the limbs/feet are affected by frostbite, this and body rewarming is managed simultaneously [16]. Frostbite can result in severe injury/amputation which will frequently result in euthanasia, so frostbite must be treated immediately (see Frostbite below) (see Chapter 137). The warmed blood traversing the extensive AV network in the feet can be transferred into the body through the dilated AV shunt network, reducing afterdrop [17]. A soft padded bandage will reduce peripheral edema of the limbs.

The risk of circulatory collapse is determined primarily by the patient's degree of tolerance of intravenous fluids, the extent of hypothermia, and intensity of rewarming. If intolerance to fluids or colloids is demonstrated and ventricular function is impaired, a slow titration of dobutamine, starting at $1\text{ }\mu\text{g/kg/min}$ slowly increasing to effect and a maximum of $5\text{ }\mu\text{g/kg/min}$ until rewarmed, then a further increase, has been suggested.

Invasive internal rewarming is recommended for animals that have cardiac-arrested hypothermia, core temperatures $<30^{\circ}\text{C}$ ($<86^{\circ}\text{F}$) or higher if cardiovascular function is unstable and where other forms of rewarming are unsuccessful. Core rewarming minimizes afterdrop and potential deterioration, and hastens normalization of body temperature. In addition to using warm intravenous fluids, peritoneal dialysis with $10\text{--}20\text{ mL/kg}$ of 43°C (109.5°F) 0.9% saline or 1.5% dextrose dialysis fluid (similar to lactated Ringer's) is suggested [18]. Administer fluid with caution so as not to jeopardize ventilation. Do not use Plasma-lyte or Normosol as these appear painful when placed into the abdomen. An exchange every 30 minutes is recommended. The dialysate must be kept at $\sim 43^{\circ}\text{C}$ (109.4°F) or core rewarming may not occur or a temperature drop may be encountered. Avoid dialysis in patients with suspected abdominal trauma and/or where surgery was recently performed.

The author has used warm (43°C , 109.5°F) saline irrigation of the urinary bladder via a urinary catheter and found this to be very effective and less invasive than lavage of the peritoneal cavities. Gastric or colonic lavage

with 43°C (109.4°F) 0.9% saline has also been suggested but there is a potential for regurgitation/aspiration, alterations in electrolytes, and inability to obtain accurate rectal or esophageal temperature.

Heating inspiratory oxygen is also recommended in warming the patient. This may be accomplished by applying a heat and moisture exchange device (Intersurgical Inc., Liverpool, NY) between the oxygen tubing and the endotracheal tube or face mask.

There is no definitive recommendation on the rate of rewarming. Some recommend that the rate should not exceed 1.5–2°C/h to avoid development of pulmonary/cerebral edema. However, a more rapid technique may be desirable to facilitate treatment of associated medical problems. Quickly increasing the temperature to 30°C (86°F) may reduce the risk of VF and cardiovascular collapse, improve myocardial performance, and minimize acidosis and hypoxia associated with slower methods. Unless severe, do not correct the acidosis until after corrective fluid administration as this tends to normalize with fluid administration. Frequent measurement is required to monitor the trend. Acidosis causes a shift of the oxyhemoglobin dissociation curve to the right which will counter the shift to the left produced by hypothermia. However, if pH remains <7.3 after appropriate fluid administration, judicious correction is advised. Canine studies indicate that a pH >7.4 was cardioprotective during rewarming of extreme hypothermia [11]. It is recommended not to temperature correct for blood gas measurements [1,19].

Pain must be managed in patients whose temperature was <34°C (93°F). Human patients frequently complain of total body muscle aches, which can be quite severe for several days. This, in part, accounts for the depression observed post resuscitation. In both cats and dogs, slowly titrate fentanyl 3–5 µg/kg IV to effect, to avoid overdose, then continue the effective dose/hour, or titrate methadone or morphine 0.2–0.5 mg/kg to effect and continue the effective dose over 4 hours, or use hydromorphone 0.03–0.3 mg/kg administered in a similar way as methadone or morphine, once rewarmed.

Opioids may prevent the shivering reflex but where pain is evident, opioid analgesia is warranted during the active external rewarming process [6]. Avoid non-steroidal anti-inflammatory analgesics (NSAIDs) initially.

Continuous monitoring is essential as the rewarmed patient is at risk for developing multiple complications, including those associated with reduced splanchnic perfusion. Frostbite of peripheral tissues (ears, tail, distal limbs) may also be noted as rewarming progresses.

While the above are guidelines, not all hypothermic animals will present as described nor will they necessarily require the rewarming technique described. How-

ever, initial presentation and trending will dictate the appropriate therapeutic modality to pursue.

Frostbite

Pathophysiology [1,2,16,20]

Frostbite is the freezing, or effect of freezing, of a part of the body, the extent of which is dependent on time of exposure and degree of hypothermia. Intracellular water crystallization, temperature-induced protein changes, and membrane damage result in cellular injury.

Extracellular water crystallizes, decreasing the interstitial water in the liquid phase with subsequent increased osmolarity. In response, water moves out of cells, affecting intracellular electrolyte concentrations and modifying cellular protein structure. In addition, diversion of oxygen and nutrients away from the periphery due to vasoconstriction and hypoperfusion predisposes to cell death. The associated vasculitis, exacerbated by hemoconcentration, hyperviscosity, platelet sequestration/dysfunction and cold-induced inhibition of coagulation cascade enzymes, predisposes to thromboembolism [20]. This may also cause bleeding, which becomes evident on thawing of the tissues. As tissues thaw, marked edema occurs because of melting of water crystals, cellular damage, loss of endothelial integrity, and thrombosis.

Over a few days, the degree of necrosis +/- gangrene will be established. Local production of prostaglandins and thromboxanes enhances the degree of injury. In addition to limbs and feet, dogs and cats may also have frostbite of ears and nose. Dogs may also acquire freezing injury due to contact of parts of the body (penis, tongue) to ice or frozen metal which will accelerate the freezing process. Coccygeal muscle injury (limber tail) has been reported in working dogs when exposed to cold weather. The tail carriage is affected to a varying degree, and the tail appears flaccid (see Chapter 202) [21].

Superficial frostbite results when the epidermis and dermis are affected; deep frostbite occurs when the underlying structures freeze. After initial therapy, a further assessment is made. A first degree manifests as erythema after warming; second degree leads to blistering; third degree is skin necrosis and fourth degree devitalization of the whole part (gangrene). Third- and fourth-degree injuries are susceptible to infection and tissue loss. However, the severity of the injury cannot be fully assessed for several days. Superficial frostbite in people has been described as white, without blanching or evidence of capillary filling after mild pressure and feels somewhat soft or rubbery to palpation. Deep frostbite, which involves all tissues including bone, produces a hard or wooden-like extremity.

Management

Frostbitten tissues should be rapidly warmed. Immerse the affected part in water at 40–42°C (104–108°F) for at least 20 minutes or until thawing is complete. Dry heat should not be used. Never rub or massage the tissues. For mild injury, application of soft, dry bandages to the injured part is required to protect the area from self-inflicted, or other, trauma and reduce edema. Cage rest is required to reduce injury. Analgesics *must* be given as this injury is extremely painful. Where there are no contraindications in a fluid-resuscitated patient, a COX-2 selective/preferential NSAIA may be administered and could be therapeutic due to the anti-inflammatory and antithromboxane effect.

In third- and fourth-degree frostbite, it is recommended that blisters containing clear or milky fluid should be aspirated/debrided and covered in aloe vera q8h, which also has an antiprostaglandin, antithromboxane effect.

Padding should be put between the patient's digits, if affected; the limbs/feet should be wrapped in a loose, protective dressing, then splinted and elevated to reduce reperfusion edema. Hemorrhagic blisters should be left intact to prevent desiccation of the underlying tissue; however, aspiration, leaving the skin intact, is recommended if reduction is necessary due to location. Topical antiseptics may help prevent infection of necrotic tissue or ruptured blisters.

Prophylactic antibiotics are not recommended. Culture of an infected wound and antibiogram should be performed to select the appropriate antibiotic, when indicated. A superficial infection will respond to topical administration of raw honey with daily rinsing and bandaging until cleared (usually 3 days) [22]. Surgical management should be delayed until spontaneous amputation of necrotic tissue has occurred and is complete. Definitive surgical management is based on the individual injury. Heparin or low-molecular weight dextrans have not proven beneficial.

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Electrical and Lightning Injuries*F.A. (Tony) Mann, DVM, MS, DACVS, DACVECC**University of Missouri, Columbia, MO, USA***Introduction**

Electrocution may occur by contact with high-voltage or low-voltage electrical sources or by a lightning strike. It is generally accepted that chewing through household electrical cords is the most common cause of electrocution in dogs and cats. From 1968 through 2014, a database compiling patient encounter data from several veterinary institutions recorded that 318 dogs and 98 cats sustained electrical injuries. (The Veterinary Medical Databases (VMDB) are currently housed at the University of Missouri, Columbia, Missouri (<https://vmdb.org>). The VMDB does not make any implicit or implied opinion on the subject of this chapter.) Of these, 54 dogs and 26 cats had chewed electrical cords, and four dogs and no cats had been struck by lightning. It is likely that many of the unspecified electrocutions were low-voltage injuries from chewing household electrical cords.

Electrical Injury**Mechanisms of Electrical Injury**

The mechanisms of electrical injury are related to the direct effects of the electrical current and the transformation of electrical energy to heat. The electrical current may disrupt electrophysiological activity, leading to muscle spasms, cardiac arrhythmias, loss of consciousness, and respiratory arrest [1–3]. Direct cellular injury may occur through the process of electroporation, which is the development of momentary holes in cellular membranes induced by electrical shock. The holes allow passage of macromolecules across membranes, which causes osmotic damage to cells [4].

As electrical current is transformed into heat, intracellular and extracellular fluids may become superheated, which results in coagulation of tissue proteins,

thrombosis of small vessels, and degenerative changes in small arterial walls [1,2,4]. Ultimately, the result is necrosis of the superheated tissues, as well as tissues that become ischemic from the vascular consequences. Direct thermal injury may also occur from arcing of a current that leaves the electrical source, crosses an air gap, and strikes tissue [1].

The severity of electrical injury varies depending on the electrical resistance of the part of the body that is struck, the nature of the current (alternating versus direct), and the intensity of the current (amperage) [1,4]. Less energy will be transferred to areas of the body that have high resistance to electrical flow. Dry skin has high resistance so less energy will be transferred in dry skin than in wet skin. Wet skin and moist mucous membranes have low electrical resistance so one can expect high flow of electricity in these tissues and a propensity for maximal tissue damage.

Alternating current (AC) tends to cause more severe injury than direct current (DC) at the same amperage. Higher exposure may occur with AC than with DC because the former elicits muscular contractions that prevent the victim from releasing the power source. For this reason, the exposure time is typically longer with AC than with DC. Direct current electricity does not usually cause muscular tetany.

Given the same resistance, high-voltage electricity can be expected to cause more damage than low-voltage electricity. One might expect more injury from 240 volt outlets used for large household appliances than from standard 120 volt wall outlets. However, current (measured in amperes) is a function of voltage divided by resistance (Ohm's Law; $I = V/R$) so the magnitude of the current depends on the affected tissue as discussed previously [1,4].

Predisposition to Electrical Injury

Young dogs and cats are the most common victims of electrical injury because they are more likely to chew

on electrical cords than are older animals. The average age of dogs with electrical injury has been reported as 3.5 months (range, 5 weeks to 1.5 years; $n = 29$); the range of ages of seven cats with electrical injury was reported to be 2 months to 2 years [1]. A database compiled from several veterinary institutions revealed that, from 1968 through 2014, the most common age range for electrical injuries was 2–12 months; 213 (67%) of 318 dogs and 48 (49%) of 98 cats that had electrical injuries and 38 (70%) of 54 dogs and 12 (46%) of 26 cats that sustained electrical injury from chewing electrical cords were 2–12 months old. A seasonal predisposition is generally accepted, but there is some difference of opinion as to what time of year most injuries are seen. Holiday seasons characterized by use of decorative lights (Halloween, Christmas) certainly pose electrical risks [4], but one study reported that 79% of canine cases occurred during the 6 months from March through August [1].

Clinical Findings

Surface burns may be noted at the point of contact with the electrical source. The thermal injury may be superficial, characterized by mild hyperemia, or may manifest as a severe full-thickness burn. Burns from chewing electrical cords have been noted on the lips, gums, tongue (Figure 149.1) and palate [1–6]. Some oral cavity electrical shocks produce enough trauma to cause dental fractures and oronasal fistulae [6].



Figure 149.1 Puppy brought in dead on arrival after chewing an electrical cord. Note the burn evident on the left lateral tongue margin (arrow). Reproduced with permission of Elsevier.

Cardiac arrhythmias may be present, the severity of which depends on the intensity of the electrical current. Sudden death from electrical shock is likely due to ventricular fibrillation caused by low-voltage current, as with most household exposures [4–7]. High-voltage exposure may cause asystole [4]. Animals that survive the shock may experience ventricular arrhythmias, but ventricular tachycardia progressing to ventricular fibrillation is unlikely in survivors of the initial electrocution event [8] (see Chapter 53).

Respiratory distress is a common clinical feature noted in the form of tachypnea, cyanosis, orthopnea, coughing, or apnea (see Chapter 39). Respiratory arrest from tetanic contractions of respiratory muscles occurs during contact with the electrical source, but breathing typically resumes when the victim is separated from the source of electricity [9].

Causes of respiratory distress include facial or nasopharyngeal edema, diaphragmatic tetany, and neurogenic pulmonary edema. Non-cardiogenic pulmonary edema is typically considered to be a result of increased capillary permeability [10,11]. However, neurogenic pulmonary edema is a form of non-cardiogenic pulmonary edema with multiple possible etiologies, including both hydrostatic and permeability edema secondary to massive sympathetic outflow (see Chapter 39). The typical radiographic pattern is alveolar infiltration of the caudo-dorsal quadrants (Figure 149.2).

Respiratory distress is less severe with pulmonary edema induced by electrical cord shock than with other causes of non-cardiogenic pulmonary edema. Likewise, there is less radiographic involvement than with other causes of non-cardiogenic pulmonary edema [10], and there is often radiographic evidence of resolving pulmonary infiltrates within 18–24 hours (Figures 149.2 and 149.3) [1].

Neurological injury as a result of direct CNS stimulation may be noted immediately upon electrical contact. Stiffening of the animal has been noted by people who have witnessed a dog or cat biting an electrical cord [3]. The victim usually loses consciousness [3]. There may be focal muscle tremors or seizures, sometimes accompanied by defecation or vomiting [3,4]. Extensor rigidity and death may occur rather rapidly. Tetanic limb contraction has been noted after survival of high-voltage electrical shock [12]. Non-ambulatory tetraparesis due to focal cervical myelopathy has been reported in a dog immediately after chewing an electrical cord [13]. The acute neurological manifestations of electrocution are thought to be due to electrically induced neural activity rather than electroporation and resultant tissue hypoxia, although hypoxia from excess energy consumption could play a role [14]. Delayed neurological manifestations are thought to result from electroporation and free radical mechanisms [15].

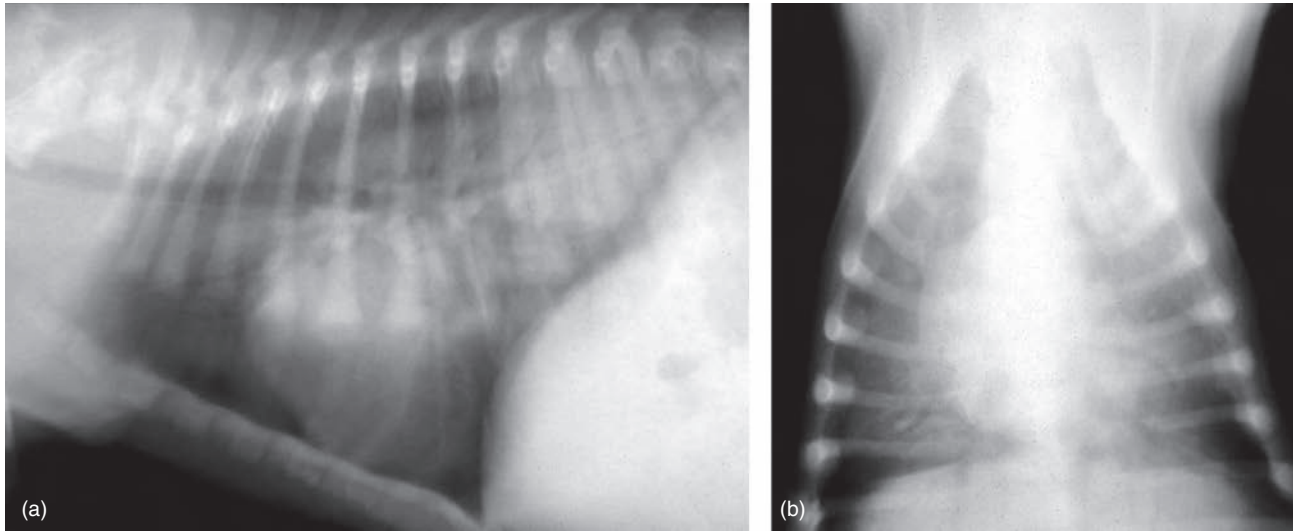


Figure 149.2 Lateral (a) and ventrodorsal (b) thoracic radiographs of a puppy that experienced severe electrical injury by chewing on an electrical cord. Note the prominent infiltration of the caudodorsal lung fields. Reproduced with permission of Elsevier.

Gastrointestinal (GI) abnormalities may result from electrical interference with motility. Abdominal radiographs or ultrasonography may show GI gas patterns characteristic of ileus [4].

Ocular manifestations of electrical injury (cataracts) are usually later findings, noted several months after the episode. Cataracts are commonly seen in human beings following near-fatal electrical injury and lightning strike and have been reported in a dog that was electrocuted by chewing an electrical cord [16].

Secondary Effects of Electrical Injury

Although complete blood count and serum chemistry results are usually within normal limits, tissue hypoxia from electrically induced ischemia and pulmonary edema may lead to necrosis of the affected tissues and subsequent hematological changes and additional organ damage. Tissue necrosis may lead to hyperkalemia, myoglobinemia, myoglobinuria, hemoglobinemia, and hemoglobinuria [4]. Hyperkalemia may also result from

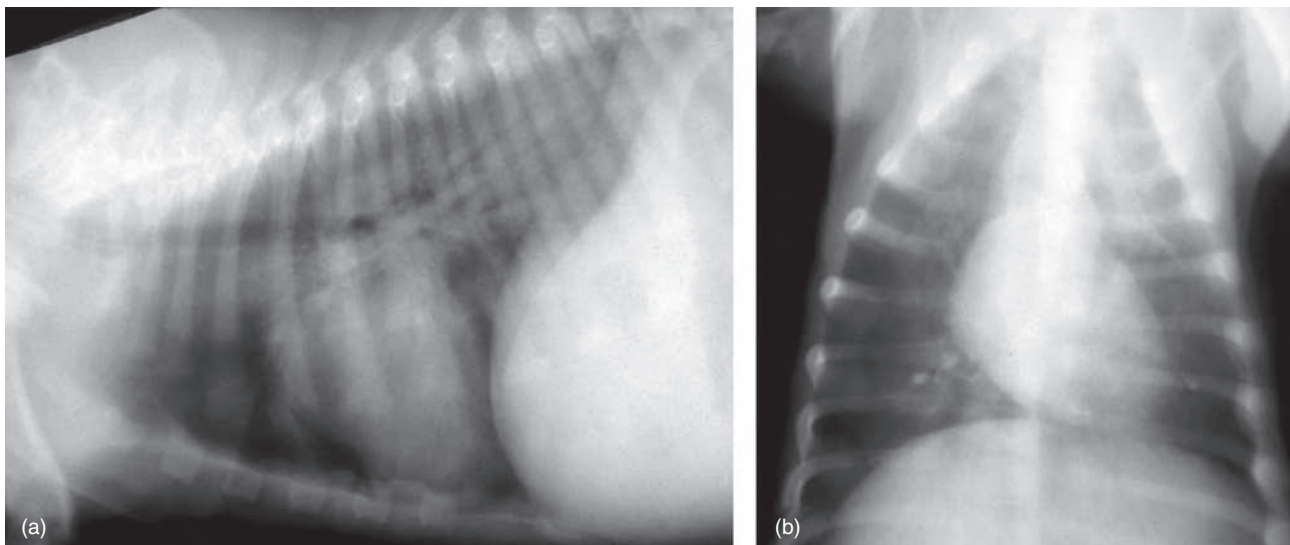


Figure 149.3 Lateral (a) and ventrodorsal (b) thoracic radiographs of the puppy in Figure 149.2 taken approximately 24 hours after the radiographs in Figure 149.2. Note the significant progress in resolution of the pulmonary infiltration. Reproduced with permission of Elsevier.

excessive muscular activity during electrical shock; this muscular activity also contributes to acidemia and hyperlactatemia [17]. Hypoproteinemia may ensue in patients with severe burns [4].

Treatment of Electrical Injury

Initial treatment at the scene of the exposure includes precautions to prevent inadvertent injury to rescuers. The source of electricity should be turned off before the victim is touched. Preferably, the electricity should be turned off at the electrical panel but alternatively, the offending electrical cord may be unplugged carefully from the outlet. Once the victim is removed from the electrical source, immediate medical attention should be sought regardless of the victim's apparent condition. Victims in cardiopulmonary arrest require cardiopulmonary resuscitation (see Chapter 150). Better results might be expected in a hospital environment, but life-saving techniques on the scene may be required if there is to be any hope of success.

Treatment of animals that survive the initial electrical insult is tailored to the clinical effects. Animals in shock are treated with intravenous fluids to expand intravascular volume because the mechanism of shock is likely a relative hypovolemia (see Chapters 39 and 152). However, because there may be a cardiogenic component to the shock from arrhythmias and subsequent decreased stroke volume, and because neurogenic pulmonary edema may develop quickly, judicious fluid therapy is indicated. Fluids that typically are given in low volumes (e.g. hypertonic saline, synthetic colloids) may be beneficial (see Chapters 167 and 168).

Respiratory distress requires prompt attention. Airway obstruction from edematous oropharyngeal tissues may require temporary tracheostomy tube placement. Partial obstructions may be managed conservatively with sedation and, if not contraindicated, anti-inflammatory drugs and diuretics. Supplemental oxygen is recommended (see Chapter 181), but if the respiratory distress is due entirely to obstruction, relief of the obstruction should return oxygenation to normal.

Oxygen supplementation should continue until it is ascertained that neurogenic pulmonary edema has not developed or has resolved (see Chapter 181). Positive pressure ventilation may be required if the patient is hypoxic and does not respond appropriately to supplemental oxygen (see Chapter 188).

Burned tissues are treated conservatively using standard wound treatment principles (see Chapter 166). Reconstructive surgery, if indicated, is performed after recovery from the electrical shock when it is determined that the patient is a stable anesthetic candidate and the tissues are healthy enough to expect good surgical results.

Ventricular arrhythmias are managed by administering antiarrhythmic agents and by reversing the underlying pathophysiological derangements (see Chapter 53). Seizures are controlled with anticonvulsant therapy (see Chapter 21). Gastrointestinal abnormalities are best managed with early nutritional support, via an appropriate feeding tube if necessary.

Pain management is necessary because burn wounds are painful and because there is likely muscle soreness from excessive activity during the electrical stimulation (see Chapter 190). Initially, opioids are preferred, but non-steroidal anti-inflammatory drugs may be used when GI integrity and renal and hepatic function are presumed to be normal.

Prognosis

The prognosis for victims that survive the initial shock episode is generally good, as long as the clinical effects are reversible. Respiratory abnormalities are the sequela most likely to alter prognosis. Most cases of electrically induced non-cardiogenic pulmonary edema resolve quickly, but one study reported a fatality rate of 38.5% [1]. Some animals will require follow-up surgery to treat residual effects of burns. Recovering victims should be monitored for potential long-term effects. Owners should be instructed to observe for cataract development, which could occur several months after recovery.

Delayed consequences of electrical injury in people (pain, peripheral neurological manifestations, neuropsychological disturbances, and cataract formation) have reportedly taken up to 5 years or longer to surface in some cases [18]. Incidence of late-onset consequences in veterinary species is unknown.

Lightning Injury

Lightning injury is more likely to occur in large animal species [19–22] than in dogs and cats because of their greater outdoor exposure. However, companion animals, especially dogs, share outdoor activities with human beings and, therefore, may occasionally be exposed. A carefully studied lightning strike at a scene where two adults and 26 girls were camping also affected seven dogs [23]. Fatal injuries occurred in four of the girls and four of the dogs.

Of the surviving dogs, the smallest one, a Maltese-poodle mix, escaped injury. One of the remaining surviving dogs sustained burns and the other suffered damage to an eye that subsequently became opaque. Because the deceased dogs were farther from the struck tent pole than surviving people, it was speculated that dogs might be more susceptible to the effects of lightning

injury than are human beings [23]. It is possible that small dogs, as in the camping site incident, are less susceptible to lightning injury than larger dogs [23]. Among cattle, adults are more likely to be struck by lightning than are calves [20]. Electrical injury from lightning strike has been reported to cause visual impairment in cattle as a result of cerebrocortical necrosis [24] and renal failure in people due to myoglobinuria from muscle damage [25]. These consequences have not been reported in dogs and cats, but are nonetheless possible.

The pathophysiology of lightning injury is similar to that of other electrical injuries, except for the mechanism by which the electricity reaches the victim and the potential for injury from mechanical energy. There are five possible mechanisms by which lightning can deliver electrical energy to a victim: direct lightning strike, direct strike of an object that the victim is touching (referred to as contact injury), side flash (splash) from a struck object, step voltages (ground potential) produced by current flowing through the soil beneath, and an upward streamer that does not connect or complete a full lightning strike [26–30]. With the latter mechanism,

injury is caused by the upward streamer of charge that is induced from an object on the ground as a lightning leader of flash approaches the ground from a thundercloud [23,26–30].

In addition to electrical and thermal injury, a sixth method of lightning-induced injury, barotrauma, may occur [30]. In this mechanism, internal injury is caused by the massive pressure differential created by the blast. The blast effect occurs when rapid air movement results from superheated air that is then cooled. The resultant mechanical energy imparted to the lightning victim can result in various forms of physical injury. People are often thrown to the ground and report muscle pain. Lumbosacral fracture with resultant spinal cord injury was the only lesion identified in three pigs in an outdoor pen that was struck by lightning [21]. Spinal fracture due to lightning strike has also been noted in pond fish [31], and the blast effect of lightning strike has been reported to cause vestibular injury in horses and human beings [32]. Although such injuries have not been reported in dogs and cats, the occurrence of mechanical energy effects similar to those reported in other species should not be surprising.

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Section 4

Trauma and Resuscitation

A. Cardiopulmonary Resuscitation

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Cardiopulmonary Resuscitation in the Emergency Room

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Recognition of Cardiopulmonary Arrest

Cardiopulmonary arrest (CPA) should be ruled out in any unresponsive patient presenting on emergency or being found collapsed while being treated in the emergency room. The Reassessment Campaign on Veterinary Resuscitation (RECOVER) guidelines recommend the use of the rapid airway-breathing (AB) assessment, which should be completed in no more than 10–15 seconds on triage examination [1–7].

Airway Assessment

The airway is visually inspected by opening the mouth and pulling out the tongue to examine the entire oral cavity for evidence of foreign objects or pathology causing airway obstruction. Suction or careful manual extraction is used to remove any fluid or foreign objects present in the upper airway. If the patient responds during the manipulation, the exam should be halted immediately, as CPA has been ruled out and the clinician should move on to a primary survey (see Chapter 2).

Breathing Assessment

The breathing assessment is focused on identifying apnea and hence a diagnosis of CPA. Breathing may be assessed by identification of a chest rise or feeling for air movement through the nares.

Diagnosis of CPA

Due to evidence of a high rate of false-positive assessments of the presence of a pulse, evaluation of the circulation is no longer recommended [8,9]. Unresponsive, apneic patients should be presumed to be in CPA and cardiopulmonary resuscitation (CPR) should be initiated immediately. Figure 150.1 shows the RECOVER

CPR algorithm, which summarizes the approach to the two aspects of CPR: Basic Life Support (BLS in blue) and Advanced Life Support (ALS in green).

Basic Life Support

Basic Life Support aims to restore oxygenation, ventilation, and blood flow to tissues using chest compressions and positive pressure ventilation. Numerous studies have documented that delays and prolonged pauses in BLS lead to lower rates of return of spontaneous circulation (ROSC) and decreased survival to discharge [10,11].

Chest Compressions

Once CPA is diagnosed, chest compressions must be started immediately. They can be done most effectively with the patient in right or left lateral recumbency in most cases [12]. Deep compressions, one-third to one-half the chest width, are delivered at a rate of 100–120 per minute, and full elastic recoil is allowed between compressions. Uninterrupted 2-minute compression cycles should be done because it takes 1 minute of continuous compressions to reach a stable arterial blood pressure [13]. After each cycle, a new compressor rotates in to reduce fatigue and maintain compression quality.

Larger breed dogs with chests that are approximately as wide as they are deep (round-chested conformations) likely benefit most from compressions over the highest point on the thorax with the patient in lateral recumbency, which will maximally employ the thoracic pump approach, dependent on increasing overall intrathoracic pressure (Figure 150.2a). In large dogs with chests that are deeper than wide (keel-chested dogs), the cardiac pump theory should be employed, with chest compressions delivered directly over the ventricles (the third–fifth

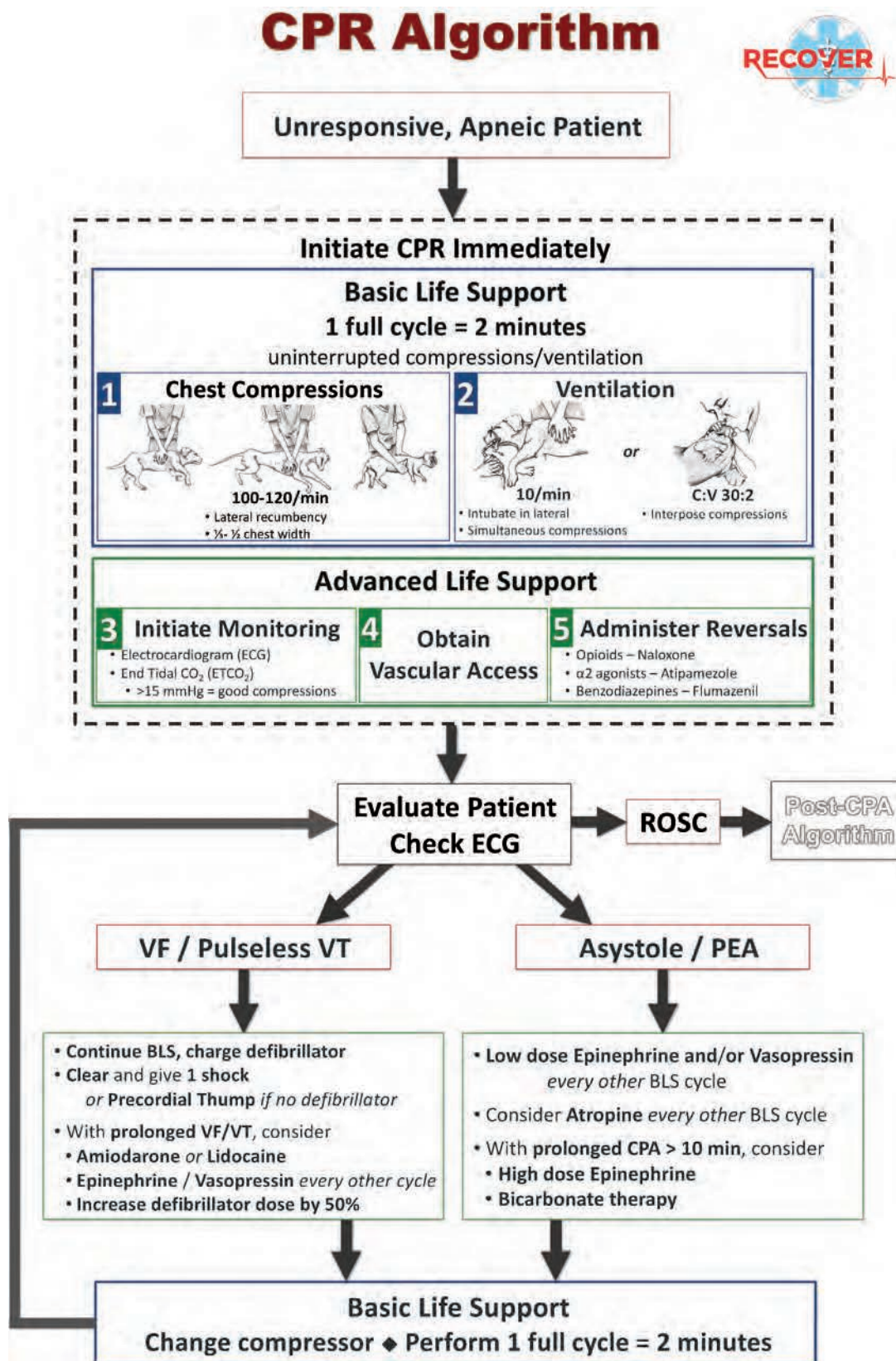


Figure 150.1 RECOVER CPR algorithm. Reprinted with permission from Fletcher et al. [7]. Reproduced with permission of John Wiley & Sons, Ltd.

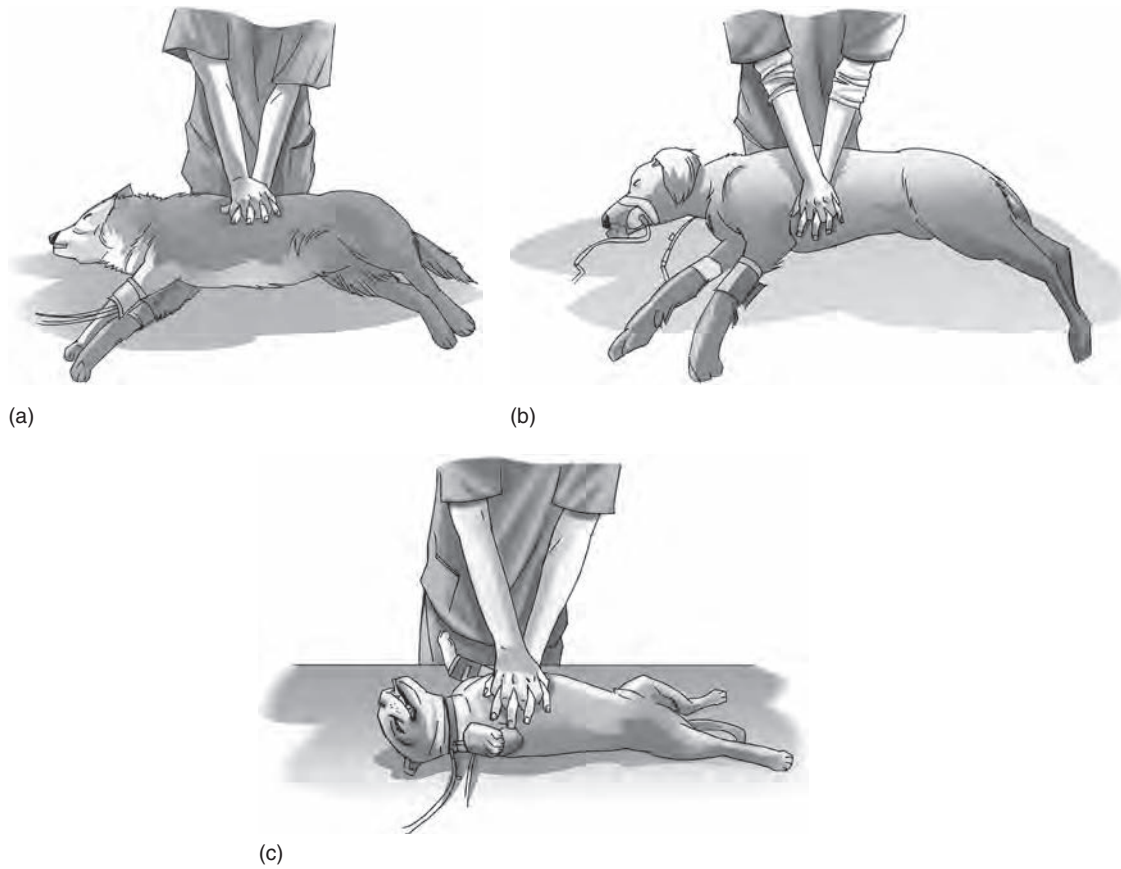


Figure 150.2 The approach to chest compressions in medium- to large-breed dogs. (a) The thoracic pump approach in round-chested dogs. (b) The cardiac pump approach in keel-chested dogs. (c) Sternal compressions in dorsal recumbency in flat-chested dogs.

intercostal space) (Figure 150.2b). In dogs with chests that are wider than they are deep (flat-chested dogs such as English bulldogs), compressions directly over the sternum with the dog in dorsal recumbency may be optimal (Figure 150.2c). Regardless of the chest shape of larger dogs, it is important to lock the elbows and interlace the fingers of both hands, with one hand on top of the other and the shoulders directly above the hands at all times. This compression posture maximally employs the core abdominal muscles rather than the arms, reducing rescuer fatigue (Figure 150.3).

For small patients with narrow chests, a one-handed technique with the thumb on one side of the chest directly over the heart and the other fingers on the opposite side may help reduce the potential to overcompress the heart to greater than one-half its width (Figure 150.4).



Figure 150.3 Rescuer posture for chest compressions in large and medium-sized dogs, with shoulders directly above hands, elbows locked, and compressions achieved by bending at the waist and engaging the core muscles.



Figure 150.4 Single-handed compressions using the cardiac pump approach in cats and small dogs.

Ventilation

Ventilation should be started as soon as possible in dogs and cats with CPA. Whenever possible, patients should be intubated immediately in lateral recumbency (or dorsal recumbency if sternal compressions are being delivered) with a cuffed endotracheal tube. The tube is secured to prevent dislodgment and the patient ventilated at a rate of 10 breaths per minute (one breath every 6 seconds). If intubation equipment is not immediately available, mouth-to-snout ventilation can be used until intubation supplies are available. For non-intubated ventilation, chest compressions must be paused while breaths are delivered, so BLS should consist of 30 chest compressions followed by a brief pause to deliver two quick breaths by making a seal over both nares with the mouth, extending the neck to ensure that the snout is aligned with the spine and observing the chest to ensure the lungs inflate. Another round of 30 chest compressions is initiated as soon as the two breaths are delivered.

Advanced Life Support

Once BLS is started, ALS therapies can begin, which consist of monitoring and drug and defibrillation therapy. The CPR algorithm in Figure 150.1 lists the first three steps of ALS: initiating monitoring, obtaining vascular access, and administering reversal agents if indicated. At the end of the first cycle of BLS, the ECG is evaluated, and additional therapies are administered based on whether the ECG rhythm is shockable or non-shockable.

Initiating ALS

Because ALS therapies are largely guided by the ECG rhythm, the top priority for ALS initiation is attaching an ECG monitor. During chest compressions, patient movement leads to electrical artifacts in the ECG that preclude rhythm identification, so it is imperative that the ECG leads be attached before the end of the first 2-minute cycle of BLS to ensure that the ECG can be analyzed during the brief pause in chest compressions while the compressors are rotating. Only non-flammable electrode gel is used when attaching ECG leads to minimize the risk of fire should electrical defibrillation be required.

Once the ECG leads are attached, the next priority is end-tidal carbon dioxide (ETCO₂) monitoring. Unlike the ECG, ETCO₂ monitors are highly resistant to motion artifact, and because the CO₂ exhaled with each breath is delivered to the lungs by blood from the tissues, when ventilation is consistent, the ETCO₂ is proportional to tissue blood flow. During CPR, an ETCO₂ of at least 15 mmHg suggests adequate tissue blood flow to limit tissue ischemia, and an ETCO₂ above this target during CPR has been associated with increased survival to discharge in small animal patients [14]. In addition, upon ROSC, tissue blood flow increases dramatically, leading to a marked increase in CO₂ delivery to the lung and hence a rapidly increasing ETCO₂. Therefore, a sudden dramatic increase in ETCO₂ during CPR (often to values in excess of 45–50 mmHg) is a sign of ROSC, and corroboration of this finding via pulse palpation or auscultation of the heart is indicated.

Once monitoring devices have been attached to the patient, the next ALS priority is securing vascular access. If an intravenous catheter is already in place, its patency is tested with a saline flush. If vascular access has not yet been secured, a peripheral catheter as close to the heart as possible (most commonly a cephalic catheter) should be placed as quickly as possible. Because of poor venous return during CPR, veins are often difficult to see even if occluded, and if a vein is not obvious on visual inspection, a cutdown procedure should be used to obtain vascular access. A large incision may be made parallel to or directly over the location of the vessel after tenting the skin above it to prevent laceration, and the vein isolated from the subcutaneous tissues using blunt dissection with a hemostat. After placing tension on the vessel using the hemostat, a catheter is introduced into the vein and secured with suture. In puppies and kittens, intraosseous (IO) catheterization with an 18 or 20 gauge needle can often be done quickly. If a spinal needle is available, it will be less likely to become plugged with bone than a regular needle. The authors prefer the use of the femur

for this procedure during CPR because it is most easily accessible without interfering with chest compressions. IO drill devices also facilitate very rapid vascular access in adult small animal patients.

Finally, in any patients that have received sedative drugs prior to CPA, reversal agents are administered as soon as possible. Because of slow drug metabolism in patients with poor perfusion, these drugs should be administered even if it has been several hours since the sedative was given. Figure 150.5 is the RECOVER drug and dosing chart, which lists the doses for the common reversal agents used in small animal medicine as well as dosing regimens for other ALS drugs. Naloxone may be used to reverse opioids, flumazenil for benzodiazepines, and atipamezole (or yohimbine) for alpha-2 agonists.

Interpreting the ECG

At the end of each 2-minute cycle of BLS, chest compressions are paused briefly as a new compressor rotates in. During this pause, every member of the team should look at the ECG monitor and assess the rhythm. The team leader should call out the rhythm diagnosis and ask all team members to weigh in on the diagnosis. If there is disagreement about the rhythm diagnosis, chest compressions are resumed and the team members in disagreement should discuss their perspectives on the diagnosis. Ultimately, based on input from the team, the team leader will make a final decision on the rhythm diagnosis. ECG interpretation is important during CPR because it determines the best ALS therapies.

CPR Emergency Drugs and Doses

			Weight (kg)	2.5	5	10	15	20	25	30	35	40	45	50
			Weight (lb)	5	10	20	30	40	50	60	70	80	90	100
DRUG			DOSE	ml	ml	ml	ml	ml	ml	ml	ml	ml	ml	ml
Arrest	Epi Low (1:1000; 1mg/ml) every other BLS cycle x3	0.01 mg/kg		0.03	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5
	Epi High (1:1000; 1 mg/ml) for prolonged CPR	0.1 mg/kg		0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
	Vasopressin (20 U/ml)	0.8 U/kg		0.1	0.2	0.4	0.6	0.8	1	1.2	1.4	1.6	1.8	2
	Atropine (0.54 mg/ml)	0.04 mg/kg		0.2	0.4	0.8	1.1	1.5	1.9	2.2	2.6	3	3.3	3.7
Anti-Arrhythm	Amiodarone (50 mg/ml)	5 mg/kg		0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
	Lidocaine (20 mg/ml)	2 mg/kg		0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
Reversal	Naloxone (0.4 mg/ml)	0.04 mg/kg		0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
	Flumazenil (0.1 mg/ml)	0.01 mg/kg		0.25	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5
	Atipamezole (5 mg/ml)	100 µg/kg		0.06	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
Defib Monophasic	External Defib (J)	4-6 J/kg		10	20	40	60	80	100	120	140	160	180	200
	Internal Defib (J)	0.5-1 J/kg		2	3	5	8	10	15	15	20	20	20	25
Defib Biphasic	External Defib (J)	2-4 J/kg		5	10	20	30	40	50	60	70	80	90	100
	Internal Defib (J)	0.2-0.4 J/kg		1	2	2	3	4	5	6	7	8	9	10

Figure 150.5 CPR drug and dosing chart.

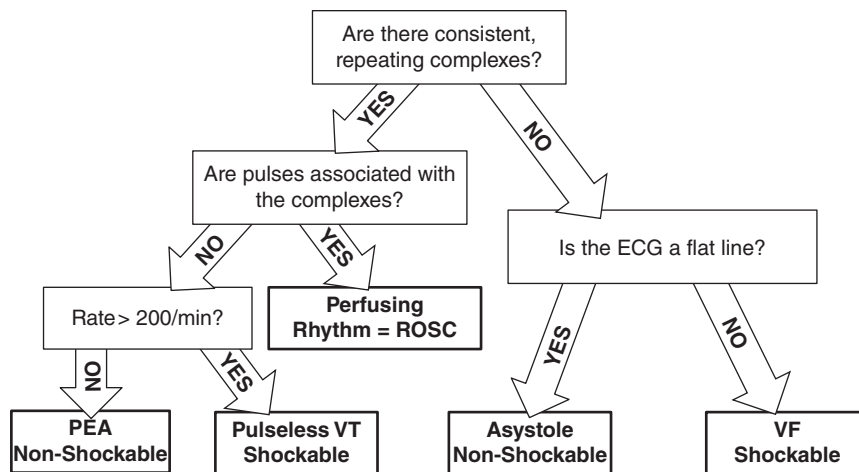


Figure 150.6 ECG algorithm for differentiating shockable, non-shockable, and perfusing rhythms during CPR.

After each cycle of BLS, the ECG rhythm is characterized as one of the following: ROSC, a non-shockable rhythm (the most common arrest rhythms in small animals), or a shockable rhythm. Figure 150.6 demonstrates a simple algorithm for characterizing the ECG rhythm during CPR. First, determine if the ECG contains consistent, repeating complexes. If it does not, determine if the ECG is a flat line, which would indicate asystole, a non-shockable rhythm. If it instead consists of apparently random activity on the baseline, this is most likely ventricular fibrillation (VF), a shockable rhythm. If the ECG does contain consistent, repeating complexes, feel for pulses. If some complexes are associated with pulses, the patient has achieved ROSC. If there are no pulses, the rate is evaluated. If it is less than 200 per minute, the most likely diagnosis is pulseless electrical activity (PEA), a non-shockable rhythm. If the rate is greater than 200 per minute, this is most likely pulseless ventricular tachycardia (pulseless VT), a shockable arrest rhythm.

Non-Shockable Arrest Rhythms

Figure 150.1 summarizes ALS therapies recommended for non-shockable arrest rhythms (asystole and PEA). Because cardiac output during external CPR is approximately 30% of normal, maintenance of adequate perfusion to the core organs is critical. Therefore, therapy targeted at peripheral vasoconstriction and redirection of blood flow to the core organs is recommended. Options include low-dose epinephrine (0.01 mg/kg) and vasopressin (0.8 U/kg). These drugs may be administered IV, IO, or intratracheally (IT) if vascular access has not yet been secured. Vagolytic therapy (atropine 0.04 mg/kg IV, IO or IT) may also be considered for routine use, and may confer additional benefit in patients arresting due to high vagal tone (e.g. bradyarrhythmias due to gastrointestinal, respiratory, and ocular disease). Both

vasopressor and vagolytic drugs are repeated every other cycle of BLS (i.e. every 4 minutes) during CPR.

High-dose epinephrine (0.1 mg/kg) should only be used in cases of prolonged CPA (greater than 10 minutes) where the rescuers are considering stopping CPR because of a lack of response. Although it has been associated with a higher rate of ROSC than low-dose epinephrine, it leads to a decreased rate of survival to discharge [15]. For patients with acute, reversible causes of CPA, further delay beyond 10 minutes before considering high-dose epinephrine is likely warranted. Sodium bicarbonate therapy (1 mEq/kg IV or IO, but not IT) may also be considered for patients with prolonged CPA, but ideally should only be administered after confirming the presence of severe metabolic acidosis on blood gas analysis.

Shockable Arrest Rhythms

The only effective therapy for shockable rhythms is electrical defibrillation. Dosing depends on the type of defibrillator (summarized in Figure 150.5). All personnel should be trained in the safe use of the electrical defibrillator.

The defibrillator paddles are placed on opposite sides of the chest directly over the heart with the patient in dorsal recumbency. The person delivering the shock should shout a warning to all other personnel and ensure that no one is touching the patient or the table before discharging the defibrillator. The goal is to stop the uncoordinated electrical activity of the ventricular myocardial cells, allowing the normal pacemakers in the sinus node to take over. Non-shockable arrest rhythms should never be shocked, as this will only lead to myocardial injury and reduced likelihood of achieving ROSC.

If an electrical defibrillator is not available, a precordial thump (a firm blow with the heel of the hand delivered

directly over the heart) may be attempted. Unfortunately, this has extremely low efficacy, and should never be used if electrical defibrillation is available [16].

Defibrillation is repeated after each 2-minute cycle of BLS until a non-shockable rhythm or ROSC is achieved. Defibrillator doses may be increased by approximately 50% after each shock up to a maximum dose of 10 J/kg.

For patients with prolonged CPA (greater than 10 minutes) due to a shockable rhythm, antiarrhythmic medications (amiodarone 5 mg/kg or lidocaine 2 mg/kg slow IV or IO) may be considered as adjunctive therapy to defibrillation. Studies using monophasic defibrillators demonstrated potential deleterious effects of lidocaine on electrical defibrillation efficacy, but this phenomenon has not been observed with biphasic defibrillators [17]. In addition, vasopressors as described for non-shockable

rhythms may be considered for patients with prolonged CPA due to shockable rhythms.

Prognosis

Dogs and cats with perianesthetic CPA had greater survival to discharge (approaching 50%) than the overall CPA patient population (6–7%) [14]. When considering initiating CPR, it is important to differentiate patients with CPA due to acute reversible conditions, who likely have a fair prognosis, from those with progressive, irreversible diseases leading to death. By applying the evidence-based guidelines summarized in this chapter, it is likely that many patients with acute, reversible conditions can survive to discharge if the CPA is identified rapidly and CPR is initiated immediately.

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Small Animal Cardiopulmonary Resuscitation Initiatives

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Strategically Advancing the Field of Veterinary CPR

Cardiopulmonary arrest (CPA) in dogs and cats is a highly lethal process and constitutes a significant problem in small animal practice across all clinical settings. Proficiency in conducting CPR is considered an important skill for veterinarians and especially emergency and critical care clinicians, but CPR is a source of stress and anxiety for resuscitation team members [1,2]. A perception of futility may prevail when considering the more recently published survival-discharge rates of 6% percent in dogs and 3–6% percent in cats [3,4]. However, evidence suggests that survival rates are not just dependent on patient factors, but can be improved through systems changes such as improving CPA treatment recommendations and CPR training programs. A recent Japanese study indicates that a marked increase in rates of return of spontaneous circulation (ROSC) and survival to discharge can occur after implementing staff training according to RECOVER CPR guidelines [5]. In human medicine, training initiatives and improved CPR guidelines were associated with increased survival rates of sudden cardiac arrest victims [6,7]. The survival rates of sudden cardiac arrest patients with ventricular fibrillation also varied substantially with the geographic region of arrest, and ranged from 7.7% (Alabama) to 39.9% (Seattle) [8].

Taken together, these data indicate that the survival rate can be significantly improved by preparedness initiatives. The Reassessment Campaign on Veterinary Resuscitation (RECOVER) set out to implement a systematic review of knowledge to generate treatment recommendations for dogs and cats with CPA in 2011, and published the first evidence-based small animal CPR guidelines in 2012 [9].

RECOVER, founded by the American College of Veterinary Emergency and Critical Care (ACVECC) and the Veterinary Emergency and Critical Care Society (VECCS), is evolving into an international organization with the intent to encourage and facilitate veterinary resuscitation research around the globe. An important milestone to that end is recently published consensus guidelines on standardized reporting of small animal CPR, as they present fundamental instruments to conduct collaborative CPR research and establish CPR registries [10]. A strategy that consists of:

- continuing reassessment of knowledge relevant to veterinary CPR
- development and dissemination of evidence-based guidelines
- identification of knowledge gaps
- conducting studies to address these gaps, and
- measuring shifts in the epidemiology of CPR in response to treatment recommendations and training programs

may lead to sustained progress in survival rates in veterinary patients (Figure 151.1).

Evidence-Based Consensus Small Animal CPR Guidelines

RECOVER brought together almost 100 collaborators, predominantly specialists in veterinary ECC and anesthesia, who volunteered to systematically review the literature relevant to small animal CPR and to devise treatment guidelines [9,11]. RECOVER partnered with the International Liaison Committee on Resuscitation (ILCOR), which conducts evidence analysis and provides CPR treatment recommendations in people [12]. Consequently, RECOVER utilized a process similar to ILCOR

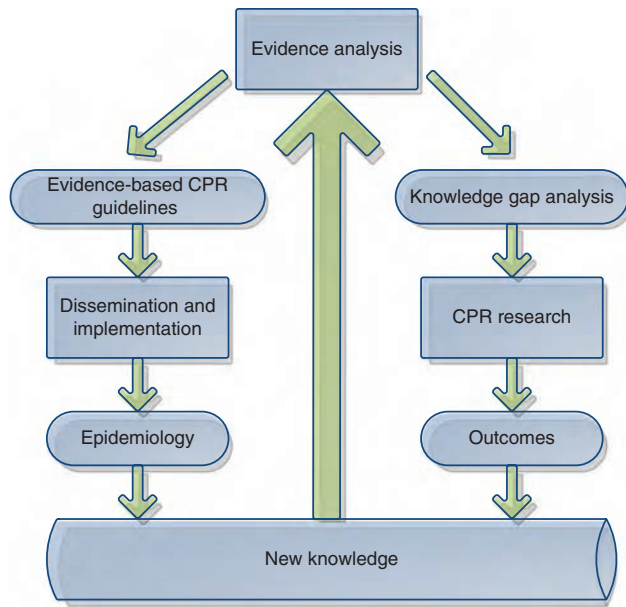


Figure 151.1 Veterinary resuscitation science strategy. Evidence analysis leads to CPR practice guidelines and a knowledge gap analysis. Through passive (publications) and active (training initiatives) dissemination steps, a change in the CPR practice in veterinary hospitals is evoked with an effect on the epidemiology of CPA (i.e. ROSC, survival). This will provide important new knowledge on the effect of the applied guidelines and of different implementation strategies and training initiatives. Knowledge gaps will be addressed by conducting specific observational studies, interventional trials, and/or by analysis of registry data. The outcomes that result from these studies will provide new understanding on how to better treat CPA in dogs and cats. This new evidence will in turn influence revised guidelines and change the list of knowledge gaps.

to systematically review the literature and to summarize findings in a process aimed at minimizing reviewer bias [11].

This process was initiated by identifying key clinical questions in five domains of CPR: preparedness/prevention, Basic Life Support (BLS), Advanced Life Support (ALS), monitoring, and post-cardiac arrest (PCA) care. Each question was posed in PICO format (Patient – Intervention – Comparator – Outcome). The results of all studies relevant to a specific question were categorized in an evidence grid according to level of evidence, study quality, and direction of the effect (e.g. benefit or harm). Based on the number and quality of studies and the risk:benefit ratio of the examined interventions, each treatment recommendation was assigned a level (Level A: High-quality evidence; Level C: Consensus/expert opinion) and class (Class I: Benefit >>> risk; Class III: Risk > benefit) designation. This approach allowed clear recommendations to be made while explicitly stating the strength of the evidence.

RECOVER led to 101 treatment recommendations (see Chapter 150) that were published open-access and have been widely disseminated with translations into several languages [9,13]. Revised versions of the RECOVER guidelines will be published as new relevant knowledge emerges. In addition, future guidelines will target additional issues that could not be addressed during the RECOVER 2012 process due to a lack of reviewers.

Knowledge Gaps

The RECOVER evidence analysis process exposed a large list of knowledge gaps, which lowered the level of recommendation for many of the guidelines (Table 151.1). The identified knowledge gaps serve as a list of prioritized research objectives that should be addressed by the veterinary resuscitation science community. More clinical veterinary CPR studies are needed to improve the quality of evidence available. While RECOVER guidelines are based on the best available evidence, the vast majority of this evidence consisted of research conducted in species other than dogs and cats. To the authors' knowledge, there was only one clinical veterinary randomized controlled trial published in the English literature by March 2018 [14].

Clinical veterinary CPR research is challenging. The unforeseen nature of CPA makes enrollment of cases difficult and the immediacy of CPR renders acquisition of informed consent impossible. The high mortality rate makes investigation of the most relevant outcomes, such as survival to hospital discharge and functional recovery, exceedingly challenging. The general lack of funding available for veterinary research leads to underpowered studies. Lack of technology to measure quality of CPR in dogs and cats further limits high-quality studies. Finally, a common nomenclature and consistent definitions of key data elements of veterinary CPR are necessary for multicenter studies and meta-analyses across studies.

Some of the above roadblocks are not readily overcome in the short term. Others, such as the development of a uniform set of terms surrounding veterinary CPR, are easier to address.

Glossary and Guidelines For Standardized Reporting

A common CPR terminology is of central importance for clear communication and collaborative studies. Unambiguous operational definitions for terminology used in CPR research studies and registries are a prerequisite for valid data collection.

Table 151.1 Select knowledge gaps across all five domains of CPR.

Preparedness and prevention	Basic Life Support	Advanced Life Support	Monitoring	Post-cardiac arrest care
Influence of cause of CPA on outcome in dogs and cats	CPR-related injuries in dogs and cats	Dose of epinephrine in dogs and cats	Utility of pulse palpation and apex beat for diagnosis of CPA in dogs and cats	Evidence on the utility of a hemodynamic optimization strategy on outcome in dogs and cats
CPA risk factors in anesthetized patients in dogs and cats	Efficacy of non-invasive ventilation in dogs and cats	Epinephrine versus vasopressin in dogs and cats	The utility of bedside echocardiography during CPR in dogs and cats	Evidence on the utility of a respiratory optimization strategy on outcome in dogs and cats
Effectiveness of CPR training programs and simulation in dogs and cats	Optimal ventilation parameters in dogs and cats	Efficacy of atropine in small animal CPR or subset of CPA populations	The utility of ETCO ₂ values at initiation and over the course of CPR in dogs and cats	PCA hemodynamic performance and influence on outcome in dogs and cats
Influence of leadership training on CPR team performance	Optimal compression depth in dogs and cats	The effect of amiodarone for refractory VF in dogs and cats	The utility of ETCO ₂ to confirm endotracheal intubation during CPR in dogs and cats	PCA blood gas, electrolyte, and acid–base abnormalities and influence on outcome in dogs and cats
Influence of team size on CPR team performance	Optimal compression location in dogs with various chest conformations	The effect of buffer administration during CPR in dogs and cats	Prognostic value of ETCO ₂ during CPR in dogs and cats	Feasibility of TTM in dogs and cats
Influence on debriefing on CPR team performance/patient outcomes	Optimal compression rate in dogs and cats	Timing and effect of open-chest CPR on outcome in dogs and cats	Blood gas, electrolyte and acid–base abnormalities during CPR in dogs and cats	Temperature goals of TTM in dogs and cats
Influence of posttraining assessment on knowledge/skill retention	Timing of rescuer fatigue during veterinary CPR, and in relation to animal size/species	Effect of impedance threshold device in dogs	Frequencies of heart rhythms and association with outcome in dogs and cats	PCA rewarming rates of hypothermic dogs and cats
	Extent of no-compression fraction in dogs and cats	Evidence toward development of stopping recommendations in dogs and cats	Development and utility of feedback technology to guide CPR performance	Effects of PCA neuroprotective and metabolic drugs on outcome in dogs and cats
			Development and utility of physiological feedback technology to guide CPR effectiveness	Impact of referral to critical care department for PCA care on outcome of dogs and cats

CPA, cardiopulmonary arrest; CPR, cardiopulmonary resuscitation; ETCO₂, end-tidal carbon dioxide; PCA, post-cardiac arrest; TTM, targeted temperature management.

Standardized reporting of data in the field of resuscitation science is commonly referred to as the “Utstein style.” Utstein Abbey was the location of a meeting on the Norwegian island of Mosteroy where a group of resuscitation experts convened in 1990 to develop consensus guidelines for standardized reporting of CPR in people [15]. In 2013, the RECOVER initiative formed an international group of veterinary emergency and

critical care experts, representatives of veterinary critical care organizations and ILCOR, to develop Utstein-style guidelines for uniform reporting of small animal CPR events. The finalized consensus guidelines were published in 2016 and provide an important tool to veterinary researchers to conduct clinical studies [10]. The document contains a veterinary CPR glossary and also suggests key data elements to be reported in

clinical veterinary CPR studies and included in research reports.

It is the hope of the RECOVER initiative that the veterinary Utstein-style reporting guidelines will increase the quality of small CPR research, facilitate data comparison across studies, and encourage multicenter studies.

CPR Registry

A registry is a health-related database that contains clinical and demographic information about individuals and serves a specific health-related purpose [16]. While observational research projects focus on short-term data collection, medical registries are used for long-term data gathering.

The RECOVER initiative developed a CPR registry with the principal objective of collecting epidemiological information of CPR in dogs and cats. Such epidemiological data are currently only reported in observational studies conducted in single academic centers [3,4,17,18]. Because the veterinary CPA population is heterogeneous, large sample sizes are needed to examine the effects of specific variables (e.g. co-morbidities) on outcome. A more accurate description of the CPA population may allow a more appropriate focus of future CPR guidelines.

Although study designs such as randomized controlled trials are required to prove cause and effect of a specific therapeutic intervention, this registry will be able to address many significant knowledge gaps. As an example, the characteristics of CPA cases that are associated with a favorable outcome can be more fully elucidated. In addition, determining ROSC and survival rates after CPR

of various durations would be of great value. What is the association between the duration of CPR and the length of recovery? How are survival rates of animals changing over the years and with the advent of new guidelines? A registry is an indispensable tool to create new knowledge on small animal CPR. The RECOVER initiative CPR registry utilizes the Utstein-style reporting guidelines as a data collection framework. These provide clear operational definitions for all data elements included and identify data elements that absolutely require reporting (i.e. core variables), and those that cannot always be reliably collected or are of hypothesis-generating value (i.e. supplemental variables). The registry is implemented in an electronic, secure data capture system that can be accessed internationally via the internet.

Conclusion

The RECOVER evidence-based clinical guidelines serve as an important foundation in our attempts to improve CPR outcomes, but future progress in veterinary resuscitation science will depend upon addressing the identified knowledge gaps and actively observing the effects of new training programs and broader acceptance of these clinical approaches. While still lagging behind the dramatic progress in human resuscitation over the last 20 years, these strategies for advancing veterinary resuscitation science through systematic evidence evaluation, training programs to improve guideline adoption, uniform reporting of small animal CPR in an international registry, and research focused on identified knowledge gaps have the potential to improve outcomes in dogs and cats with CPA.

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B. Circulatory Shock

152

Pathophysiology of Shock

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Introduction

Shock can be defined in a number of ways. Classically, shock has been considered to be any situation which results in insufficient perfusion (blood flow) to tissues, resulting in cellular oxygen debt. Categorical examples of perfusion-related shock include hypovolemic, obstructive, maldistributive, and cardiogenic. However, situations may arise in which perfusion is adequate but oxygen delivery is still compromised (such as with severe anemia and hypoxemia). These potential causes of shock and their underlying mechanisms can be elucidated by consideration of the major “players” in cardiovascular hemostasis and oxygen delivery – as represented by the so-called “tree of life” (Figure 152.1). And while

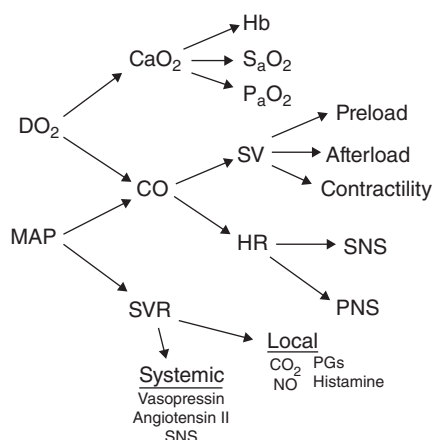


Figure 152.1 Schematic representation of the “tree of life” – factors that determine perfusion pressure and oxygen delivery. CaO₂, blood oxygen content; CO, cardiac output; CO₂, carbon dioxide; DO₂, oxygen delivery; Hb, hemoglobin; HR, heart rate; MAP, mean arterial pressure; NO, nitric oxide; PaO₂, arterial partial pressure of oxygen; SaO₂, arterial oxygen saturation; SNS, sympathetic nervous system; SV, stroke volume; SVR, systemic vascular resistance.

disruption of these factors encompasses many types of shock, it does not take into account the possibility of impaired cellular oxygen utilization and/or energy production, despite adequate delivery (such as severe hypoglycemia or mitochondrial dysfunction). And so in the broadest sense, shock is the result of any condition in which the metabolic demand for oxygen exceeds uptake and utilization, resulting in a cellular energy debt and a measurable change in organ function.

Specific causes, clinical manifestations, and potential management of shock will be covered in greater detail in subsequent chapters (see Chapters 153, 154, and 155). What follows is a description of the pathophysiological impact of a shock state, the ensuing compensatory efforts, and (if left untreated) progression to cardiovascular collapse. In addition, there will be consideration of the subsequent systemic impact of tissue ischemia, necrosis, and reperfusion injury which can occur even if shock reversal is successful.

Cellular Impact

Regardless of underlying cause, shock is characterized by an imbalance between oxygen and nutrient delivery to tissues, cellular consumption, and the removal of cellular metabolic end-products. Delivery of oxygen to tissues (DO₂) is a function of cardiac output (CO) and the oxygen-carrying capacity of the blood (CaO₂) (see Figure 152.1). The major determinants of CO are heart rate and stroke volume. CaO₂ is dictated predominantly by hemoglobin content (Hb) and percent saturation (SO₂), with dissolved oxygen (PaO₂) contributing only a small amount ($\text{CaO}_2 = 1.34 \times \text{Hb} \times \text{SO}_2 + 0.003 \text{ PaO}_2$). Normally the delivery of oxygen is well in excess of what is needed for cellular metabolism. This redundancy provides a buffer so that a significant decrease in delivery will not have a major impact on cellular oxygen consumption

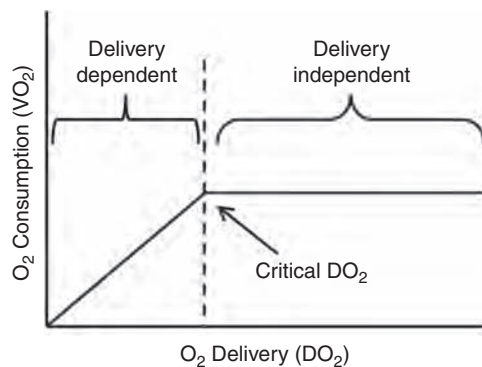


Figure 152.2 Schematic representation of the relationship between oxygen delivery (DO_2) and cellular oxygen consumption (VO_2).

(VO_2), also known as “delivery independent” (Figure 152.2).

Tissues can further offset a decrease in oxygen delivery by increasing oxygen extraction. Under normal circumstances, approximately 25% of oxygen is removed as arterial blood moves across the capillary and in times of need this can potentially increase to 70–80% or more [1]. However, eventually the reduction in DO_2 will reach a threshold (or critical DO_2) and O_2 consumption will necessarily diminish (“delivery dependent”). At this stage demand outweighs supply, resulting tissue ischemia and cellular hypoxia [2].

As such, the initial impacts of shock occur at the cellular level. Mitochondria function at the lowest oxygen tension in the body but consume almost all of the available oxygen in order to provide more than 95% of aerobic chemical energy for cellular metabolism [3]. Decreased oxygen delivery and cellular uptake (especially in muscle and splanchnic organs) impairs the ability of mitochondria to perform oxidative phosphorylation and produce adequate amounts of adenosine triphosphate (ATP). In response, cells will try to decrease metabolic activity of “non-essential” functions to reduce energy (and oxygen) consumption [4]. Eventually, even this capacity is exceeded, resulting in a switch to anaerobic metabolism and lactic acid production.

Intracellular acidosis can lead to denaturing of proteins, diminished enzyme function, and disruption of transport mechanisms. In addition, without the oxygen-dependent ability to produce adequate cellular energy, multiple intracellular systems, including membrane-associated ion transport pumps, begin to fail [5]. Cells are no longer able to maintain membrane integrity and an intracellular shift of fluid results in cellular edema and further dysfunction.

If injury is severe enough, cellular necrosis or apoptosis will be triggered. Sufficient loss of cells will result

in loss of tissue function and ultimately organ failure. Insufficient availability of ATP, largely related to mitochondrial dysfunction, results in cellular acidosis, oxygen free radical formation, and loss of adenine nucleotides from the cell, all further contributing to tissue injury [2].

Systemic Impact

On a global scale, the systemic impact of shock can be characterized in three phases. The initial phase involves the body’s attempt to maintain/restore core tissue perfusion and oxygenation. This primarily involves activation of the sympathetic nervous system mediated through baroreceptors (sensing decreased vessel wall distension) and chemoreceptors (sensing hypoxia, hypercapnia, and/or acidemia) [6]. The ensuing release of catecholamines promotes peripheral vasoconstriction, tachycardia, and increased cardiac contractility (and also creates most of the outward clinical signs of shock). The associated increase in cardiac output and systemic vascular resistance helps to restore mean arterial (perfusing) pressure [7]. In addition, activation of the renin-angiotensin-aldosterone system and increased release of vasopressin (antidiuretic hormone) serve to promote further vasoconstriction and diminished urinary water losses [7]. In patients with hypovolemia (whether absolute or relative), the associated decrease in hydrostatic pressure will naturally cause a shift of fluid from the interstitial compartment to the vascular space, partially helping to restore circulating volume.

It is important to note that these compensatory changes may occur at the expense of peripheral and splanchnic perfusion. Therefore, even though blood flow to vital organs is maintained, peripheral tissues may be experiencing ischemia and hypoxia. Further, if the inciting cause of shock persists and there is no intervention, eventually these compensatory efforts will be overwhelmed and progression to decompensated shock will occur. This stage is characterized by evidence of impaired core perfusion (systemic hypotension, hyperlactatemia). The resulting prolonged tissue hypoperfusion and development of metabolic (lactic) acidosis serve to worsen cardiovascular compromise. This is predominantly mediated by progressive catecholamine insensitivity and eventual exhaustion of compensatory mediators, leading to vasodilation and bradycardia [7]. Loss of vasomotor tone is especially prominent in skeletal muscle, leading to a reduction of blood flow to “non-essential” organs, with further impairment of venous return and cardiac output [8]. This terminal stage of shock is irreversible, ultimately progressing to complete cardiovascular collapse and death.

Secondary Systemic Sequelae

Given the potentially progressive and fatal impact of shock itself, early recognition and intervention are key. Clinical signs should reflect the presence of a shock state, whereas history and diagnostic evaluation serve to reveal the specific (or at least categorical) cause to help guide resuscitation. Therapy is then aimed at rapidly restoring tissue perfusion/oxygen delivery as well as addressing the underlying cause (see Chapters 153–155 for specific aspects of shock diagnosis and treatment). However, it is important to remember that significant tissue injury may have occurred even if initial resuscitation is successful. Depending on the cause, extent, and duration of shock, multiple systemic implications can arise in the postresuscitation period. As such, awareness, recognition, and management of these sequelae can be just as important as management of shock itself.

Systemic Inflammatory Response

Systemic inflammatory response syndrome (SIRS) occurs secondary to the widespread tissue ischemia and/or reperfusion injury that can be associated with shock. It is covered in greater detail elsewhere (see Chapter 159), so a brief overview is provided here in the context of shock sequelae.

Cellular damage or death triggers a complex cascade of events that ultimately results in further tissue destruction and potentially organ failure [9]. One of the initial steps in this process involves upregulation and release of inflammatory cytokines such as interleukin-6 (IL-6) and granulocyte colony stimulating factor (G-CSF) that serve as chemotactic factors for enhanced infiltration of neutrophils into affected tissues [10]. Increased rolling and sticking of neutrophils to the endothelium can lead to capillary plugging and obstruction of microcirculatory blood flow and transcapillary exchange [11]. Once diapedesis occurs, neutrophils release reactive oxygen and nitrogen species as well as proteolytic enzymes (elastases, metalloproteinases, etc.), leading to vasodilation, increased capillary permeability, and destruction of the extracellular matrix [9]. This results in leakage of protein and fluid into the interstitium and associated tissue edema. Ultimately, this can lead to disturbance of oxygen and metabolite exchange and cellular swelling and dysfunction [9].

Activation of the complement system also plays a major role in the pathogenesis of systemic inflammation secondary to shock [12]. Tissue injury leads to the release of split-products, including C3a and C5a, the anaphylatoxins. These mediators can increase vascular permeability, stimulate histamine and arachidonic acid product release, induce cytokine production and release, and

promote adherence and aggregation of granulocytes to the vascular endothelium [13–15].

Hypoxic cellular injury also leads to an increased activity of phospholipases A₂ and C, which stimulate production of prostaglandins and leukotrienes [9]. These mediators exert a variety of effects, including further recruitment of inflammatory cells, alterations in vascular permeability and vasomotor tone, and enhanced platelet activity and aggregation [9]. The intestinal tract serves as another portal for systemic inflammation when reduced intestinal perfusion associated with shock results in increased permeability and intestinal barrier dysfunction (so-called “shock gut”) [16]. These changes allow for translocation of bacteria and other mediators from the intestinal lumen, leading to infectious complications (sepsis) and thereby further upregulation of the inflammatory cascade.

Yet another major contributing factor is the liberation of toxic metabolites and reactive oxygen species after reperfusion occurs. Accumulation of hypoxanthine (a breakdown product of ATP) during ischemia leads to the formation of potent free radicals once oxygen is reintroduced [9]. These reactive oxygen species are then responsible for lipid peroxidation, disruption of cell membranes, and DNA damage, resulting in cellular apoptosis or necrosis (see Chapter 158 for additional information) [9].

Coagulopathy

Inflammation-induced activation of the coagulation pathway can lead to microvascular thrombosis, exacerbation of ischemic injury and eventually disseminated intravascular coagulopathy (DIC). Most of the proinflammatory cytokines (such as IL-1, IL-6, TNF- α , and arachidonic acid metabolites) are also procoagulant, leading to platelet and clotting factor activation [17]. One of the major contributing steps is an increased expression of tissue factor on endothelium and monocytes which, in conjunction with factor VII, initiates the coagulation cascade [9]. The resulting increased generation of thrombin is then a multifactorial catalyst for driving platelet aggregation and fibrin formation. Further contributing to excessive clot formation is the consumption and downregulation of natural anticoagulants, such as antithrombin and protein C [18]. Finally, increased activity of plasminogen activator inhibitor (PAI-1), as well as thrombin-activatable fibrinolysis inhibitor (TAFI), impairs clot degradation and worsens thrombosis [18].

The excessive clot formation associated with this hypercoagulable state promotes the formation of microthrombi throughout the vasculature. On the arterial side, these thrombi will cause occlusion of flow and result in downstream ischemic injury (and further tissue damage,

inflammatory response, etc.). Venous thrombosis can cause obstruction in venous return, resulting in tissue edema, decreased right ventricular preload, and/or hypoxemia (with pulmonary thromboembolism). Eventually consumption of platelets and clotting factors will cause a switch to a hypocoagulable state and bleeding tendency. The associated potential hypovolemia and anemia can then worsen global perfusion and oxygen delivery.

Mitochondrial Dysfunction

As previously indicated, diminished mitochondrial energy production plays a major role in the pathogenesis of shock and cellular hypoxia. However, even when oxygen delivery is restored, there is evidence to suggest that mitochondrial function can still be impaired. This is related to the effects of various inflammatory mediators, such as tumor necrosis factor alpha (TNF- α), leading to uncoupling of oxidative phosphorylation and increased mitochondrial permeability and apoptosis [19].

Increased production of reactive oxygen and nitrogen species is another major contributor to mitochondrial injury. Reactive species are produced through normal cellular metabolism and removed by natural antioxidant systems. However, in the face of cellular injury and inflammation, the ability to scavenge free radicals is significantly reduced [20]. The formation of various reactive species is further increased in the face of ischemia and reperfusion (as previously mentioned). The membrane-bound nature of mitochondria is particularly susceptible to lipid peroxidation and free radical injury, as are the various proteins associated with electron transport [20]. As such, the resulting structural and functional damage to the mitochondria can lead to persistent dysfunction even after resuscitation.

Microcirculatory Dysfunction

In a shock state, decreased microvascular perfusion can certainly be expected (secondary to hypovolemia, hypotension, vasoconstriction, etc.). However, microvascular derangements can persist or develop even after resuscitation. One potential contributor to impaired flow through the microcirculation is endothelial edema secondary to ischemic injury, increased permeability, and influence of inflammatory mediators [21]. Given their normal diameter ($<10\mu\text{m}$), even small increases in capillary wall thickness can have a significant impact on flow. In addition, inflammation-induced endothelial activation and increased leukocyte adhesion can result in capillary plugging, as can less deformable red blood cells [21]. The development of arterial microthrombi (associated with SIRS and DIC) can also severely impair blood flow to downstream microcirculatory units.

Finally, tissue ischemia, necrosis, reperfusion, and inflammation can all result in disruption of metabolic flow coupling that normally plays a major role in local regulation of microvascular flow [21].

Multiple Organ Dysfunction Syndrome

The widespread tissue damage that occurs with severe shock, in conjunction with the ensuing systemic inflammatory response (and other mechanisms described above), can ultimately lead to multiple organ dysfunction syndrome (MODS). The gastrointestinal tract is believed to be one of the earliest organ systems to be affected in this process as both victim and perpetrator. As previously mentioned, prolonged hypotension with shock can lead to epithelial injury and loss of mucosal barrier function with subsequent translocation [16]. In addition, recovery from shock is associated with decreased gut motility, resulting in gastrointestinal atony and functional ileus [17]. The lungs are also highly susceptible to systemic inflammatory injury, leading to acute respiratory distress syndrome (ARDS). The pathogenesis of ARDS involves inflammation-induced diffuse alveolar-capillary injury and subsequent severe accumulation of proteinaceous edema in the pulmonary interstitium and alveoli [17].

The kidneys can be very sensitive to microcirculatory disorders (thrombosis, hypoperfusion) with renal ischemia leading to tubular necrosis [17]. The resulting acute kidney injury is typically characterized by an increase in serum creatinine and blood urea nitrogen along with an onset of oliguria (urine production $<0.5\text{ mL/kg/h}$) or anuria (see Chapters 94 and 95). During a shock state, there can be primary ischemic injury to the highly metabolically active hepatocytes. In addition, inflammatory mediators can cause hepatocytes to undergo significant alterations in synthetic activity, biliary transport, bile flow, and glucose metabolism [22]. Kupffer cells, macrophages found within the hepatic parenchyma, release chemokines that attract neutrophils into the liver and activate them [22]. After migrating into the parenchyma, activated neutrophils produce oxygen-derived radicals and proteases that cause further injury to hepatocytes and ultimately lead to organ failure (see Chapter 90) [22].

Conclusion

The conditions that occur during shock can be fatal if not sufficiently addressed. In addition, a shock state can initiate a self-perpetuating cycle of tissue injury, inflammation, coagulation, microvascular dysfunction, and organ failure, even after successful resuscitation. Therefore, early recognition and intervention are essential to limit the extent of tissue damage and minimize the ensuing systemic impacts.

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Hypovolemic Shock

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Pathophysiology of Hypovolemic Shock

Hypovolemia may be caused by loss of crystalloid-like fluid, plasma-like fluid or whole blood. Physiological compensation for loss of volume is fairly similar across the different types of volume loss, although fluid shifts across the endothelium may be different depending on oncotic pressure balance.

Loss of blood volume, whether it is due to plasma fluid loss or hemorrhage, causes a cascade of physiological responses [1–3], starting with a decrease in venous return and cardiac output (Box 153.1). Decreased cardiac output leads to a decrease in wall stretch of the aortic arch and carotid arteries, which is detected by baroreceptors in these areas. Subsequently, several neural pathways are stimulated that cause an overall increase in sympathetic tone, including increased inotropy, chronotropy, and lusitropy due to direct cardiac innervation, and peripheral arteriole constriction due to circulating catecholamines and increased transmural pressure. Epinephrine and norepinephrine are released from the adrenal medulla in proportion to the degree of shock and explain the typical physical examination signs of arterial vasoconstriction, including tachycardia, pale mucous membranes, prolongation of capillary refill time (CRT), small pulse wave amplitude, and cool limbs. Venos constriction, as well as splenic contraction in some species, also provides an increase to central circulating blood volume, although these changes are not as visible on physical examination. This compensation for hypovolemic shock can normalize and maintain arterial blood pressure. In contrast to the periphery, the cerebral and coronary arterioles dilate during the sympathetic response in response to beta-2 adrenergic receptor stimulation.

When oxygen delivery decreases below the level needed for oxygen consumption of the cell, cellular oxygen demand is no longer being met and oxygen consumption becomes dependent on delivery. Below this

point, termed the critical oxygen delivery point, anaerobic metabolism predominates and cellular lactate and hydrogen ion production increases. Due to intracellular buffering of hydrogen ions, carbon dioxide (CO_2) also increases. These changes cause hyperlactatemia, metabolic acidosis, and increased venous partial pressure of CO_2 (PCO_2). Increased venous and tissue PCO_2 can be utilized by various monitoring techniques to detect decreased tissue perfusion (see Diagnosis of Hypovolemic Shock). Peripheral chemoreceptors detect decreased pH and enhance local vasoconstriction, as well as stimulating ventilatory drive in order to excrete more CO_2 . This may be detected clinically by tachypnea and hyperventilation.

As renal perfusion decreases, the renin-angiotensin-aldosterone system is stimulated due to decreased stretch in the afferent arteriole and decreased chloride delivery to the macula densa. Angiotensin II also causes peripheral vasoconstriction and maintains glomerular filtration rate by constriction of the efferent arteriole. Aldosterone release from the adrenal gland causes sodium reabsorption in the cortical collecting tubule. Antidiuretic hormone (ADH) is released from the pituitary due to decreased stretch in the cardiac atria and the stimulation of angiotensin II. In addition to stimulating peripheral vasoconstriction, ADH also increases water reabsorption in the collecting tubule. In this way, sodium and water reabsorption together help to increase circulating blood volume.

Starling's forces also help to restore blood volume by favoring fluid movement from the interstitium to the intravascular space, which is one reason why packed cell volume (PCV) starts to fall during mild prolonged hemorrhage. This decrease in interstitial volume is not usually detectable by assessing dehydration parameters in the acute phase but may become more obvious if the animal has a slow blood loss over a number of hours to days. There is also some degree of interstitial osmotic drive

Box 153.1 Physiological responses to hypovolemic shock.**Compensated**

- Decreased venous return
 - Decreased stroke volume
 - Decreased aortic and carotid arterial wall stretch
- Increased sympathetic nervous system tone
 - Increased cardiac inotropy, chronotropy, lusitropy
 - Release of catecholamines from adrenal medulla
 - Peripheral arteriolar vasoconstriction
 - Cerebral and coronary arteriolar vasodilation
 - Venoconstriction
 - Splenic contraction
- Supply-dependent oxygen consumption
 - Hyperlactatemia
 - Increased cellular hydrogen ion production
 - Peripheral chemoreceptor stimulation
 - Local arteriolar vasoconstriction
 - Increased ventilatory drive
- Stimulation of renin-angiotensin-aldosterone system
 - Increased angiotensin II
 - Peripheral vasoconstriction
 - Maintenance of glomerular filtration rate
 - Increased aldosterone
 - Increased renal sodium reabsorption
- Increased antidiuretic hormone
 - Peripheral vasoconstriction
 - Increased renal water reabsorption
 - Increased thirst
- Decreased intravascular hydrostatic pressure
 - Fluid movement from interstitial space

Decompensated

- Decreased sensitivity of adrenergic receptors
- Exhaustion of antidiuretic hormone stores
- Local release of vasodilatory mediators
- Progressive intracellular acidosis
- Progressive bradycardia and hypotension

Post-resuscitation after severe shock

- Ischemia and reperfusion injury
- Intestinal villous sloughing
- Systemic inflammation
- Microthrombosis
- Coagulopathy
 - Initial hypercoagulability
 - Subsequent hypocoagulability

that favors some water movement from the intracellular space. It is theorized that ischemic tissues release products from proteolysis and lipolysis, therefore increasing osmolality in the extracellular fluid space. Lastly, hypovolemia also stimulates thirst, via ADH, and increased sodium “appetite,” which helps to restore blood volume.

Decompensation

The vasoconstrictive response eventually wanes due to decreased sensitivity of adrenergic receptors to catecholamines and exhaustion of ADH stores. Ischemic tissues also release chemicals that cause local vasodilation. Progressive intracellular acidosis in the myocardium reduces calcium concentration and decreases contractility, and progressive myocardial necrosis leads to ultimate failure. Acidosis also interferes with pump mechanisms in the cell membrane, disturbing the cardiac conduction system. The result of these effects on the patient is progressive hypotension, bradycardia, and death. This degree of shock may be irreversible; the patient may die despite subsequent blood volume expansion.

If the patient responds to blood volume expansion during severe shock, consequences of ischemia and reperfusion injury can still cause complications (see Chapter 158). Cellular necrosis, interstitial edema, and microthrombi in vital organ systems can lead to organ failure, similar to the pathophysiology of septic shock. Sloughing of intestinal villi and increased intestinal permeability, especially in dogs, lead to further losses due to intestinal hemorrhage, endotoxin release, and bacterial translocation. Hypercoagulability due to the initial response of the hypoxic endothelium soon turns to hypocoagulability and bleeding complications can further impair organ function. Intensive support and monitoring are often required for patients that have suffered from severe shock and develop multiple organ dysfunction (see Chapter 159).

Diagnosis of Hypovolemic Shock**Physical Examination**

Physical examination is central to the diagnosis of hypovolemic shock and can be rapidly performed during the initial evaluation. Hypovolemic shock alters six key physical examination parameters, termed the *perfusion parameters*: mentation, heart rate, pulse quality, mucous membrane color, CRT, and extremity temperature (Table 153.1). Changes in these parameters reflect both the effects of decreased perfusion and the sympathetic compensatory response. Tachycardia is a consistent feature of compensated shock in dogs whereas cats often present with bradycardia, even with mild to moderate shock. It is often the first parameter to change. Thorough evaluation of perfusion parameters should include palpation of both the femoral and distal limb pulse, as changes in pulse amplitude typically occur distally first. With progression of shock, the number of abnormal variables increases, as well as the severity of these changes.

Table 153.1 Changes in the six perfusion parameters that are expected with hypovolemic shock of increasing severity.

Perfusion parameters	Severity of shock		
	Mild	Moderate	Severe
Mentation	Mildly obtunded	Obtunded	Stuporous to comatose
Heart rate	Increased	Increased (may be decreased in cats)	Increased or decreased
Pulse quality	Fair to good	Poor	Non-palpable
Mucous membranes	Pink to mildly pale	Pale pink	White/gray
Capillary refill time	2 seconds	2–3 seconds	> 3 seconds
Extremity temperature	Normal	Cool	Cold

Tachypnea and increased respiratory effort also typically accompany shock, although they are not consistent indicators of decreased perfusion.

Similar alterations in perfusion parameters will also occur with cardiogenic or obstructive forms of shock (see Chapters 154 and 155). Differentiation of these types of shock can be challenging at times, but the presence of jugular vein distension should increase the suspicion for cardiogenic or a form of obstructive shock, rather than hypovolemic shock.

Blood Pressure

Blood pressure is often maintained in mild to moderate hypovolemic shock as a result of the compensatory response, but it will be reduced as shock progresses. In the circumstance of severe shock, physical examination parameters should be obviously abnormal and measurement of blood pressure should not delay diagnosis or treatment of shock. Direct arterial blood pressure measurement is usually not available in the emergency setting and non-invasive techniques may be inaccurate [4], so the measurement of blood pressure is not prioritized until treatment of hypovolemic shock has been implemented.

The shock index is a triage tool employed by some emergency clinicians to simplify detection of shock. It is calculated from the heart rate divided by the systolic blood pressure and may assist in the detection of mild shock states where neither parameter alone is abnormal. Although this parameter has not been validated against a criterion standard diagnosis of shock, its clinical use has been reported in dogs [5,6], with a shock index of greater than 0.9–1.0 being generally consistent with a clinical diagnosis of shock. However, further research is required before it can be recommended in the routine evaluation for hypovolemic shock in an individual patient.

Pulse pressure, or pulse amplitude, variation with the respiratory cycle may also assist with diagnosis of

hypovolemia, especially in a patient receiving positive pressure ventilation (PPV). There is a normal variation in pulse pressure during the respiratory cycle generated by PPV due to several factors, primarily increased right atrial pressure and subsequent decreased venous return during inspiration [7]. This difference is increased in hypovolemia, due to the greater collapsibility of the vena cava, greater right atrial compliance, and greater sensitivity of the ventricles to preload changes when operating on the steep portion of the Frank–Starling curve [7]. A pulse pressure variation greater than 10–15% is consistent with hypovolemia [7–9]. In patients without an arterial catheter, it may be possible to estimate pulse pressure variation from the pulse oximeter plethysmograph [10]. Frequency domain analysis of the plethysmograph can improve the utility of this technique [11]. Pulse pressure variation has not yet been clinically evaluated in small animals presenting as emergencies and may be of limited value in spontaneously breathing patients.

Electrocardiogram

Electrocardiogram R-wave amplitude may decrease during hypovolemia, with one dog model showing amplitude reduction in all leads during hemorrhagic shock [12]. In humans, ECG changes are less sensitive than pulse pressure variation in detecting hypovolemia [13]. Lack of R-R interval variation is also an indicator of increased sympathetic tone and may be an early sign of hypovolemia [14]. Calculation is complicated and not standardized, and there is currently limited evidence of clinical utility [15,16].

Laboratory Tests

Several point-of-care laboratory tests can serve as an adjunct to the assessment of hypovolemic shock, including blood lactate concentration and arteriovenous blood gas differences. These tests should be used in conjunction

with clinical assessment of the patient, as the cause of changes in these parameters may be multifactorial.

Blood lactate concentration increases in moderate to severe shock due to inadequate oxygen delivery, but this is not a specific finding as lactate will increase with severe tissue hypoxia of any cause [17]. Lactate will also increase in some non-hypoxic scenarios such as diseases that affect tissue oxygen utilization or lactate metabolism [17]. Infusion of lactate-containing fluids such as lactated Ringer's solution may transiently increase blood lactate concentration [18]. Elevated lactate has been associated with worse outcomes in traumatized dogs [19] and humans [20], and has been associated with more severely abnormal perfusion parameters in cats [21]. Base excess has been used as a surrogate marker for lactate [22] but it is important to remember that this will be confounded by other metabolic acid–base disturbances (see Chapter 107). Lactate can be serially monitored during resuscitation (see Chapter 156). While it is not specific for shock, a persistently elevated lactate should prompt careful evaluation for ongoing shock.

Several blood gas parameters may also be altered in hypovolemic shock. These parameters should only be interpreted from mixed venous blood samples, which may not be possible to attain in the emergency room, or from central venous blood as a surrogate [23]. Peripheral venous samples may not reflect systemic oxygen utilization, as the peripheral tissues are affected by the compensatory response, including arteriovenous shunting of blood. In all types of shock, the mixed or central venous oxygen saturation of hemoglobin (S_{mvO_2} or S_{cvO_2}) will decrease due to increased tissue oxygen extraction. An S_{cvO_2} of <70% is considered consistent with shock [23]. This parameter is unlikely to be a sensitive measure of shock when an animal is heavily sedated or under general anesthesia due to decreased oxygen utilization.

The arteriovenous partial pressure of carbon dioxide difference ($P_{v-a}CO_2$) is an indicator of the adequacy of cardiac output, with increased levels seen due to increased tissue CO_2 production [24]. Once again, this is not specific for hypovolemia. Dividing the $P_{v-a}CO_2$ by the arteriovenous oxygen content difference ($C_{a-v}O_2$) provides an assessment of the degree of anaerobic metabolism occurring in the tissues, which will also be elevated in shock [24].

Diagnostic Imaging

Bedside ultrasound is a rapid and relatively easy modality to use for detecting hypovolemic shock, without delaying other assessment or treatments. A short-axis view of the ventricles can be assessed subjectively for diastolic filling and contractility using the standard thoracic focused assessment with sonography for triage

(TFAST) pericardial chest site view (see Chapter 182) [25–27]. Caudal vena cava size can be estimated using the diaphragmaticohepatic view of the TFAST, where the vena cava crosses the diaphragm. Decreased vena cava diameter and dynamic collapse of the vena cava during inspiration are supportive of hypovolemia [27]. Other echocardiographic parameters supporting hypovolemia in dogs include decreased left ventricular end-diastolic volume, cardiac index, and mitral valve E-wave velocity [28]. In cats, hypovolemia causes a decrease in the left atrial to aortic root diameter ratio and an increased wall thickness in diastole [29].

Changes detected on thoracic radiography that occur during hypovolemia include reduction in the size of the heart, caudal vena cava, and pulmonary vasculature. Due to the time and restraint required, thoracic radiographs should not be used as a primary means of diagnosing hypovolemic shock, but may be supportive in conjunction with other clinical data.

Response to Treatment

Response to treatment is a useful tool in supporting a diagnosis of hypovolemic shock. This takes the form of a *fluid challenge* [30,31]. An intravenous fluid bolus, for example 10–20 mL/kg of an isotonic crystalloid for a dog (see below), is rapidly administered (see Chapter 167). Perfusion parameters, especially heart rate, should be constantly monitored during the fluid bolus. Improvement, even if transient, in perfusion parameters or adjunctive tests is supportive of a diagnosis of hypovolemic shock. If central venous pressure measurement is available, large increases (increase >3–5 mmHg or final reading >15 mmHg) should prompt ceasing the fluid challenge [31]. For most animals, there is low risk in administering a fluid challenge. A lack of response to the fluid challenge should prompt investigation of other causes, such as septic shock. Fluid challenges should be performed with caution in animals with pulmonary disease, cardiac disease, and anuria. Also, the approach should be more conservative in cats due to the risk of adverse effects of fluid overload; therefore, 5–10 mL/kg of an isotonic crystalloid fluid is recommended for a fluid challenge in cats.

Emerging Diagnostic Techniques

Near infra-red spectroscopy (NIRS) measures oxygenated and deoxygenated hemoglobin and myoglobin in tissues, reflecting the balance of tissue oxygen delivery and consumption [11]. It can predict the need for blood transfusion in traumatized humans that otherwise appear hemodynamically stable [32]. This technology has not been clinically evaluated in small animals.

Transthoracic bioimpedance is a non-invasive technology that can be used to estimate cardiac output [11]. It can discriminate between normovolemia and hypovolemia in humans [33] but has not been clinically evaluated in small animals.

Treatment of Hypovolemic Shock

Treatment of hypovolemic shock requires rapid replacement of circulating blood volume with intravenous (or intraosseous) fluid boluses. Several different fluid types are available for this purpose, including isotonic crystalloids, hypertonic crystalloids, synthetic or natural colloids, and blood products (see Chapters 167–170 and 176). The fluid chosen will depend on the type of hypovolemia: loss of crystalloid-like fluid, loss of plasma-like fluid, or loss of whole blood.

Loss of crystalloid-like fluid is treated with isotonic crystalloids. Doses are often expressed as a percentage of blood volume (approximately 80–90 mL/kg in a dog and 50–60 mL/kg in a cat). As a rough guide, mild hypovolemia will require approximately 25% of blood volume, and moderate to severe hypovolemia approximately 50–100% of blood volume. Only approximately 25% of the administered dose remains in the intravascular space within 1 hour [34], with the remainder redistributing to the interstitial space. These patients are usually also interstitially dehydrated, and the fluid redistribution will assist in rehydration. This should be taken into account in the subsequent formulation of a rehydration plan (see Chapter 171). If available, serum electrolyte concentrations can also guide the choice of an appropriate isotonic crystalloid. The isotonic crystalloid of choice is usually lactated Ringer's solution (LRS). Plasmalyte-148 and Normosol-R contain acetate, which may cause vasodilation when rapidly administered [35]. Large-volume administration of 0.9% sodium chloride can cause a hyperchloremic metabolic acidosis [36].

Loss of plasma-like fluid is also often treated with isotonic crystalloids, which are certainly the initial fluid of choice. This may lead to hypoproteinemia and, consequently, decreased colloid osmotic pressure, favoring fluid movement into the interstitial space. In a normally hydrated patient, this can rapidly lead to interstitial edema. Synthetic colloids may be considered as an alternative in order to maintain colloid osmotic pressure and avoid excessive tissue edema, but adverse effects of synthetic colloids, including coagulopathy and acute kidney injury (see Chapters 168 and 169), need to be weighed against the possible benefit of maintaining colloid osmotic pressure (COP).

The ideal treatment of blood loss is transfusion of fresh whole blood, but availability is often limited. Blood

component therapy with packed red blood cells and fresh frozen plasma is often used instead (see Chapter 176). These should generally be administered after the initial resuscitative period with isotonic crystalloids, to avoid the need for rapid administration. However, speed of administration will be guided by the current state of active bleeding. Management of hemorrhagic shock is further covered in Chapter 170.

Resuscitation Endpoints

Whilst fluid doses can be estimated based on the severity of shock, treatment of an individual patient should continue until appropriate resuscitation endpoints are reached. These endpoints are parameters that indicate that shock has resolved and tissue oxygen delivery is adequate. They may include normalization of perfusion parameters, blood pressure, blood lactate concentration, and subjective assessment of volume on bedside echocardiogram.

In situations where there is ongoing hemorrhage, resuscitation may be performed to subnormal endpoints until there is definitive control of hemorrhage. *Hypotensive resuscitation* refers to fluid resuscitation to a blood pressure that is subnormal but still supports major organ function, such as systolic blood pressure of 90 mmHg or mean arterial pressure of 60 mmHg. *Delayed resuscitation* involves not administering any fluid therapy until after definitive control of hemorrhage. See Chapter 170 for further detail.

Complications of Hypovolemic Shock

Several detrimental complications may occur following the treatment of hypovolemic shock. These complications are more likely to occur if treatment is delayed, inadequate or excessive. This emphasizes the need for prompt recognition of hypovolemic shock and close monitoring during treatment towards appropriate endpoints.

Reperfusion injury may occur when tissue oxygen delivery is restored following a period of tissue hypoxia. This may result in a systemic inflammatory response and multiple organ dysfunction (see Chapter 158).

Large volumes of crystalloid, colloid or packed red blood cells can result in a dilutional coagulopathy and thrombocytopenia (see Chapter 70). In turn, this may result in further hemorrhage and perpetuation of hypovolemia. When large volumes of fluid resuscitation are needed, it is prudent to monitor coagulation tests and treat appropriately if these tests are abnormal and there is ongoing hemorrhage (see Chapter 176).

Administration of high volumes of intravenous fluids can result in interstitial edema, especially in the lung, with

subsequent impairment of organ function. The endothelial glycocalyx can also be damaged by hypervolemia, leading to multiple adverse effects including increased vascular permeability, hypercoagulability, and a proinflammatory

response [37,38]. Patients should be closely monitored during treatment of hypovolemic shock. Fluid therapy should be stopped if resuscitation endpoints are reached before the entire empiric dose has been given.

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Cardiogenic Shock

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Introduction

The definition of cardiogenic shock is decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume. The clinical definition, originating from studies of a cardiogenic shock model in dogs, is persistent hypotension (systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg) with severe reduction in cardiac index (<1.8 L/min/m² without support or <2.0 to 2.2 L/min/m² with support) and left ventricular end-diastolic pressure (LVEDP) >18 mmHg [1]. These parameters are obtained with pulmonary artery (PA) catheterization, which is not routinely performed in veterinary medicine. However, Doppler echocardiography may be used to estimate elevations of the ventricular filling pressure [2]. Cardiogenic shock may develop secondary to an acute and rapidly progressive cardiac disorder or may be the end stage of a previously diagnosed cardiac disease. In either situation, the fatality rate may be high.

Essentially, cardiogenic shock may occur with any disease that causes myocardial damage or otherwise inhibits the cardiac contractile mechanism [3].

Pathophysiology (see Chapter 152)

Shock is identified in most patients based on findings of hypotension and inadequate organ perfusion and cellular energy production. This condition may be caused by either low cardiac output or low systemic vascular resistance (SVR). Circulatory shock can be subdivided into four distinct classes: hypovolemic, cardiogenic, obstructive, and distributive.

Cardiogenic shock is characterized by primary myocardial dysfunction resulting in inability of the heart to maintain cardiac output despite adequate intravascular

volume (forward flow failure). Cardiac output (CO) is a product of stroke volume (SV) and heart rate (HR).

$$\text{CO (L min}^{-1}\text{)} = (\text{SV}) \times (\text{HR})$$

A state of shock develops when the decrease in cardiac output is severe enough to cause inadequate tissue perfusion. A vicious cycle is initiated when the deficient cardiac output decreases coronary perfusion, causing global metabolic derangements to the myocardium (Figure 154.1). These patients demonstrate clinical signs of hypotension, cool extremities, poor capillary refill time, tachycardia, low urine output, and altered mentation.

Tachycardia is a normal physiological response triggered by baroreceptor-mediated sympathetic stimulation to preserve blood pressure and tissue perfusion. In most cases, sinus tachycardia is an appropriate reflex and best addressed by treating the underlying cause such as hypotension, hypoxia, and/or acid-base disorders. As contractility worsens, although hypotension results in decreased afterload and augments cardiac output to an extent, cardiac output worsens. The degree to which the left ventricular end-systolic volume increases is a powerful hemodynamic predictor of mortality in people with systolic dysfunction and an echocardiographic parameter for the diagnosis of systolic dysfunction in both human and veterinary medicine [4–7].

In the face of systolic dysfunction (decreased contractility) and systemic hypotension (decreased afterload), neurohormonal mechanisms to increase preload (i.e. renin-angiotensin-aldosterone system) are activated to increase diastolic filling and augment cardiac output. However, ultimately, the elevated left ventricular diastolic filling pressures increase myocardial oxygen demand and can lead to pulmonary edema and congestive heart failure. Arterial oxygen desaturation ensues from the increased tissue oxygen extraction, which is due

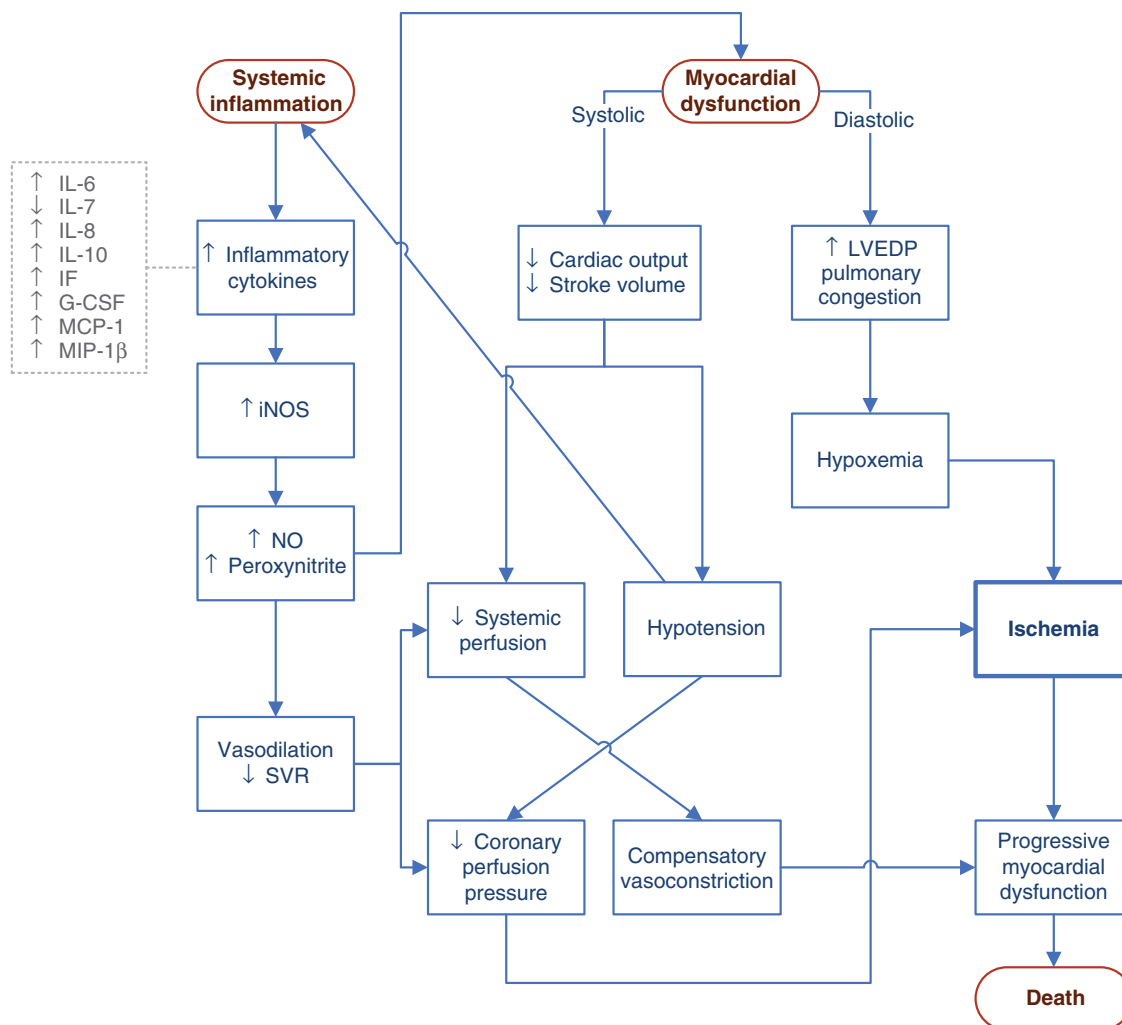


Figure 154.1 Systolic and/or diastolic myocardial dysfunction lead to a decrease in cardiac output with derangements to the systemic perfusion and arterial blood pressure resulting in a cascade of events that further exacerbates myocardium function, leading to myocardial ischemia and ultimately death.

to the low cardiac output, combined with intrapulmonary shunting [8].

The reduction in cardiac output triggers the release of catecholamines that result in peripheral vasoconstriction and help maintain perfusion to vital organs. Vaso-pressin and angiotensin II levels increase, which leads to improvement in coronary and peripheral perfusion at the cost of increased afterload. The increased afterload further impairs myocardial function, and decreased perfusion to the myocardium, coupled with systemic hypotension, can lead to systemic inflammatory response syndrome (SIRS) (see Chapter 159). SIRS can result in impaired perfusion of the intestinal tract, enabling transmigration of bacteria and sepsis [9]. Cytokine levels rise over the 24–72 hours after the development of cardiogenic shock. Tumor necrosis factor- α and interleukin-6 have myocardial depressant action and in

combination with other factors (e.g. complement, pro-calcitonin, neopterin, C-reactive protein) have been reported to contribute to SIRS and vasodilation during cardiogenic shock (see Figure 154.1) [10,11]. Microcirculatory abnormalities are present in addition to the global hemodynamic derangement [12,13].

Incidence and Etiology

There are no data available regarding the true incidence of cardiogenic shock in the veterinary patient. In humans, the American Heart Association (AHA) estimates that cardiogenic shock occurs in approximately 10% of patients with acute myocardial infarction [14]. Regardless of the underlying condition, cardiogenic shock is typically the result of severe left ventricular

contractile failure (systolic dysfunction). Other types of cardiac dysfunction leading to cardiogenic shock have been reported in animals, including diastolic dysfunction (e.g. cardiac tamponade, hypertrophic cardiomyopathy (HCM), valvular dysfunction (e.g. degenerative mitral valve disease (DMVD)), and cardiac arrhythmias (tachyarrhythmias or bradyarrhythmias) [15] (Box 154.1). When an underlying cardiac disease is present, cardiogenic shock usually is the result of an acute exacerbation of the disease. Patients with decompensated heart failure and concomitant diseases (e.g. hypertension, diabetes mellitus, neoplasia, pneumonia, kidney disease) may be at higher risk of developing cardiogenic shock.

Studies in human patients with myocardial ischemia complicated by cardiogenic shock demonstrated that approximately three-fourths develop shock after hospital presentation and initiation of therapy [16]. The use of beta-blockers, angiotensin converting enzyme inhibitors, morphine, and diuretics translated into a substantial number of cardiogenic shock events [17,18]. There are no studies evaluating the effects of common cardiac drugs and the development of iatrogenic cardiogenic shock in animals.

Sepsis-induced cardiomyopathy (SICM) is characterized by left ventricular dilation and a depressed ejection fraction [19]. Several studies exist in dogs reporting that left ventricular dysfunction followed sepsis and neoplasia [20–22]. Theoretically, sepsis, or severe illness, induces chemical mediators (e.g. endotoxins, cytokines, and nitric oxide), resulting in depressed cardiac contractility and subsequent cardiogenic shock.

Diagnosis

Cardiogenic shock affects various organs and may be present with a large array of symptoms. When suspecting cardiogenic shock in people, the diagnosis is often made with a combination of invasive techniques (e.g. PA catheterization) to obtain hemodynamic parameters as well as non-invasive techniques such as echocardiography. A patient with cardiogenic shock is expected to have low cardiac output and an increase in the preload parameters of central venous pressure and pulmonary arterial pressure. In veterinary critical patients, the diagnosis is usually suspected by findings noted during history, physical exam, thoracic radiographs, electrocardiography, indirect blood pressure, and echocardiography.

Physical Examination

The physical examination findings vary according to the underlying disease as well as the degree of hypoperfusion/hypotension. The presence of altered mentation,

Box 154.1 Examples of cardiac dysfunction that can result in cardiogenic shock.

Left ventricular failure

Systolic dysfunction

- Ischemia/myocardial infarction
- Global hypoxemia
- Valvular disease
- Myocardial depressant drugs (e.g. beta-blockers, calcium channel blockers)
- Myocardial contusion
- Respiratory acidosis
- Metabolic derangements (e.g. acidosis, hypophosphatemia, hypocalcemia)
- Myocarditis
- Cardiomyopathy
- Cardiotoxic drugs (e.g. doxorubicin)

Diastolic dysfunction

- Ischemia
- Ventricular hypertrophy
- Restrictive cardiomyopathy
- Prolonged hypovolemic or septic shock
- External compression by pericardial tamponade

Increased afterload

- Aortic stenosis
- Hypertrophic cardiomyopathy
- Dynamic aortic outflow tract obstruction
- Coarctation of the aorta
- Systemic hypertension

Valvular and structural abnormalities

- Mitral stenosis and/or regurgitation
- Endocarditis
- Obstruction due to cardiac neoplasia or thrombus
- Chordae tendineae rupture
- Tamponade

Right ventricular failure

Increased afterload

- Pulmonary thromboembolism
- Pulmonary vascular disease
- Hypoxic pulmonary vasoconstriction
- High alveolar pressure
- Acute respiratory distress syndrome
- Pulmonary fibrosis
- Chronic obstructive pulmonary disease

Valvular and structural abnormalities

- Tricuspid valve dysplasia
- Tricuspid regurgitation
- Pulmonic stenosis

disorientation, poor responsiveness, or unconsciousness is indicative of poor central nervous system perfusion. Poor perfusion is usually apparent from cool extremities and pale mucous membranes; the pulse strength may be weak or absent as a result of poor cardiac output. Pulses

may also be irregular if arrhythmias are present. Animals with right-sided congestive heart failure often exhibit peripheral venous distension and jugular pulses. The respiratory system may be affected by the development of lactic acidosis and secondary tachypnea or pulmonary edema if left heart failure is present. Cardiac auscultation may reveal muffled sound in patients with pericardial effusion. Tachycardia is the most common heart rate observed unless severe bradyarrhythmia (e.g. third-degree AV block) is the cause of the cardiogenic shock. Pulse deficits may be noted with some arrhythmias (premature ectopic beats and atrial fibrillation). A heart murmur should be present in dogs with DMVD and may or may not be present in dogs with dilated cardiomyopathy (DCM). Cats with HCM may develop a gallop sound associated with increased left ventricular filling pressure.

Electrocardiogram (ECG)

Multiple types of arrhythmias might be present in a patient in a state of shock. ECG monitoring should always be performed when cardiogenic shock is suspected. The most common arrhythmias are sinus tachycardia/bradycardia, atrial fibrillation, and ventricular tachycardia, but the presence of an arrhythmia does not imply that the patient has cardiogenic shock. Patients with other types of shock may also develop arrhythmias (see Chapter 53).

Thoracic Radiography

The decision to obtain thoracic radiographs should be exercised with caution in a very fragile patient. It is highly recommended to postpone radiographs in favor of emergency treatment and patient stabilization. Common changes noted on thoracic radiographs of patients with underlying cardiac disease include an enlarged cardiac silhouette, pulmonary venous and caudal vena cava engorgement. Patients with congestive heart failure will have changes consistent with a pulmonary infiltrate or pleural effusion. Pericardial effusion results in a globoid cardiac silhouette and loss of the normal contour of the cardiac silhouette (see Chapter 54).

Laboratory Exam findings, Lactate, Biomarkers, and Arterial Blood Pressure

The hemogram is often normal in these patients unless there is evidence of generalized inflammation or infection. A chemistry profile may reveal azotemia and elevated liver enzymes reflective of poor perfusion to the kidney and liver. Venous or arterial blood is helpful to evaluate the patient's acid-base status as well as oxygenation capacity. Patients with cardiogenic shock are often acidotic due to the combination of inadequate

cellular oxygenation leading to anaerobic metabolism and metabolic acidosis. Hyperlactatemia, a prominent feature of cardiogenic shock, can be attributed to increased tissue production or impaired utilization of lactate caused by dysoxia or tissue underperfusion, respectively.

In humans, biomarkers may be helpful to diagnose and monitor patients with cardiogenic shock. In veterinary patients, BNP and cardiac troponin-I can be used to help distinguish between heart and lung disease as well as to identify patients with myocardial injury [23]. Increased levels of NT-pro-BNP and cTnI were associated with worse prognosis in dogs with DCM and cardiogenic shock [24].

Arterial blood pressure (ABP) monitoring is recommended with Doppler ultrasound and sphygmomanometry in a continuous manner to help titrate therapeutic efforts. Placement of an arterial catheter, commonly in the dorsal pedal artery, allows direct measurement and continuous monitoring of arterial blood pressure. This method provides the most accurate measurement of blood pressure but is more invasive, and placement of arterial catheters can be challenging, especially in small patients or those with severe hypoperfusion.

Echocardiography

Echocardiography is important for definitively diagnosing the form of underlying heart disease (if present) and monitoring therapy in patients with cardiogenic shock. Based on echocardiography, a diagnosis of cardiogenic shock can be made if there is evidence of systolic dysfunction in the presence of adequate end-diastolic volume.

Sublingual Microcirculation

Because cardiogenic shock affects the microcirculation and may exacerbate hypotension and increase the risk of developing sepsis, a more direct assessment of the microcirculation can be performed using handheld video microscopy for observation of the sublingual microcirculation [25].

Treatment and Monitoring

Cardiogenic shock results in temporary or permanent derangement of the entire circulatory system, much of which is partially or completely reversible with appropriate treatment. Since cardiogenic shock has multiple etiologies, treatment should be directed to correct the underlying disease when possible (e.g. relief of cardiac tamponade with pericardiocentesis, addressing sepsis,

etc.). Unfortunately, these conditions make up only a small proportion of cases of cardiogenic shock. In the absence of an intervention that can reverse the underlying pathology, treatment of cardiogenic shock in animals aims to acutely improve hemodynamics with the goal that chronic medical management may result in clinical compensation [15].

The hallmark of cardiogenic shock in the veterinary patient is the combination of hypotension and heart failure, which offers a therapeutic challenge because the treatment of either abnormality can worsen the other (Figure 154.2). If systolic dysfunction is present, the use of inotropes such as dobutamine is warranted. If the animal is stable enough for oral medications, pimobendan may be considered. Although pimobendan is considered an inodilator, it rarely causes a reduction in systemic blood pressure. Glucagon may have a role as an adjunctive

therapy in patients with cardiogenic shock unresponsive to initial therapy. Exogenously administered glucagon has a positive inotropic effect on the heart that results in increased cardiac output and blood pressure [26]. Pulmonary edema is treated with diuretics (furosemide) and oxygen support. The use of vasodilators for managing pulmonary edema is contraindicated in the presence of hypotension.

Vasopressors are used with caution in patients with cardiac dysfunction because the increased afterload negatively affects cardiac output. While the use of inotropic agents and vasopressors may temporarily improve cardiac output and peripheral perfusion, these agents increase myocardial oxygen demand and ATP consumption, predisposing to the development of arrhythmias. There are no studies in veterinary patients to draw any recommendations for the use of one inotropic/vasopressor agent

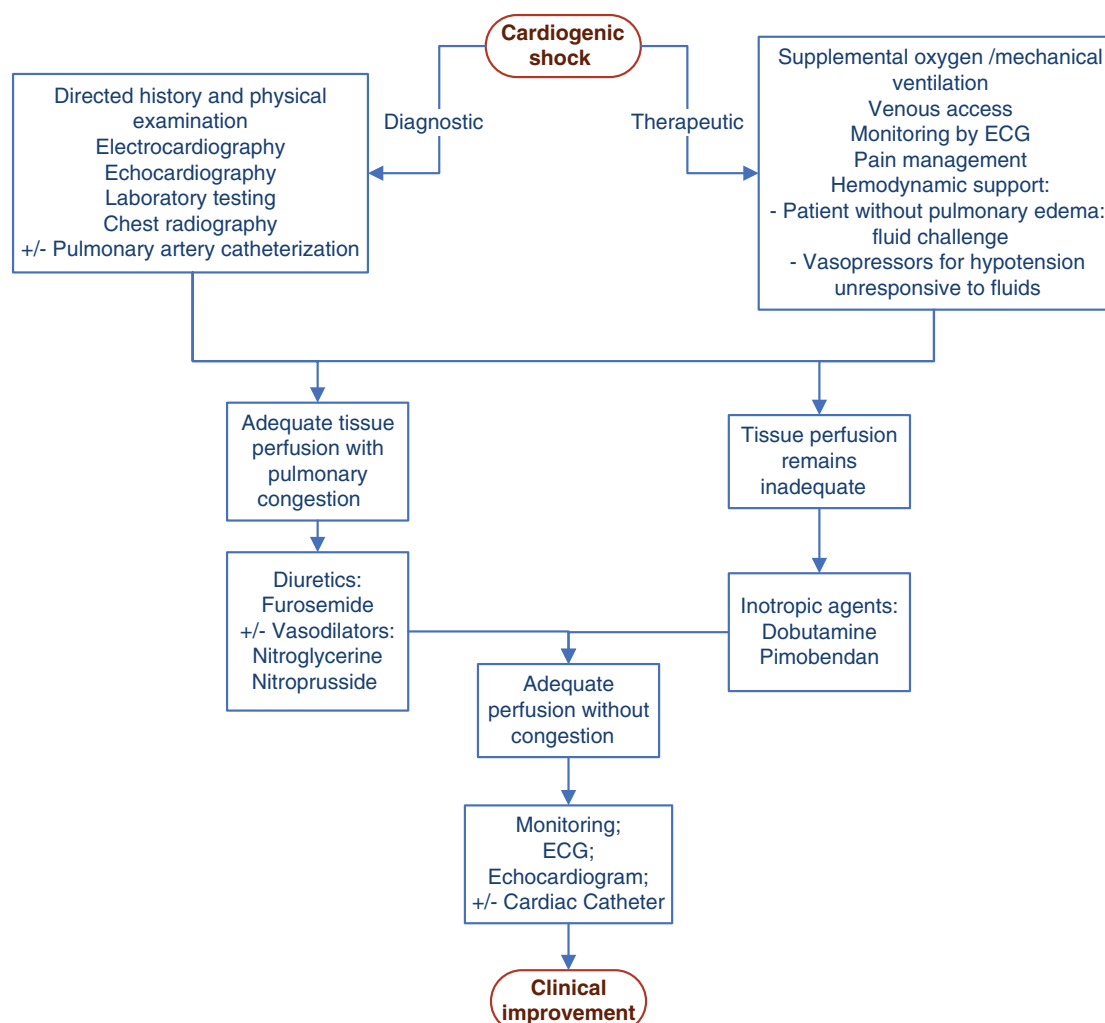


Figure 154.2 Treatment of patients with poor tissue perfusion and congestion is always challenging. If systolic dysfunction is present, the use of inotropes such as dobutamine is warranted. Pulmonary edema is treated with diuretics (normally furosemide). The goal is to eliminate congestion while re-establishing good tissue perfusion.

versus another, but higher doses of vasopressors were associated with poorer prognosis and survival in people with cardiogenic shock [27]. Dopamine has been shown to increase arrhythmias and likely mortality and for that reason, it is no longer recommended in the management of cardiogenic shock [28]. In patients with cardiogenic shock without an underlying cardiac disease (e.g. sepsis-induced cardiomyopathy), there is widespread agreement that standard treatment should focus on optimization of hemodynamic parameters by fluid resuscitation and vasopressor therapy as well as infection control in the case of sepsis [29].

Some arrhythmias may predispose the heart to inadequate ventricular filling and decreased venous return (see Chapter 53). Therapy of tachyarrhythmias includes vagal maneuvers, calcium channel blockers, and beta-blockers. However, if systolic dysfunction is suspected, beta-blockers should be avoided. High-grade second-degree and third-degree AV block both lead to decrease in cardiac output. An atropine response test should be performed for initial treatment and therapeutic planning. Dobutamine or isoproterenol may help increase the heart rate, although isoproterenol can exacerbate hypotension and should be used cautiously. If the bradycardia continues to be unresponsive and the cardiogenic shock state persists, cardiac pacing may be indicated.

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Conclusion

Cardiogenic shock patients are gravely ill and their condition is extremely unstable, requiring close and continuous monitoring so changes can be made appropriately to treatment plans. In addition to the monitoring described above, regular assessment of rectal temperature, coagulation testing and platelet counts, urine output monitoring, and excellent nursing care are critical to successful outcome.

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Additional Mechanisms of Shock

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Introduction

Shock as proposed by Cox and Hinshaw in 1972 was classified as hypovolemic, cardiogenic, distributive, or obstructive [1]. Despite the popularity and persistence of this classification system, its utility is limited in that it only addresses causes of circulatory compromise leading to tissue ischemia. Other mechanisms beyond ischemia can be responsible for the shock state. Regardless of the classification, shock results in cellular dysfunction through a lack of energy (ATP) production by the mitochondria (see Chapter 152).

A recent veterinary reference has approached shock utilizing an expanded functional system beyond the classic model to include hypovolemic, cardiogenic, distributive, metabolic, and hypoxemic shock. Hypoxemic refers to not only decreased oxygen tension (partial pressure), but also hemoglobin and oxygen content in the arterial blood. Metabolic refers to hypoglycemia and aberrations in cellular respiration. This paradigm deviates from the classic model by including cardiac tamponade under cardiogenic shock and obstructive causes under distributive [2].

Conditions such as sepsis can have multiple contributors to the decrease in cellular energy production and do not fit neatly into one classification. Despite any inconsistencies in such classifications and artificial delineation as applied to clinical patients, the clinician should adopt a paradigm that will provide a comprehensive approach to the etiology of shock in the emergent patient. Hypovolemic and cardiogenic shock have been addressed in Chapters 153 and 154 but other causes should also be considered upon presentation, especially if initial efforts to resuscitate the patient are unsuccessful. See Box 155.1 for additional rule-outs for shock.

Box 155.1 Shock beyond hypovolemic and cardiogenic causes.

Distributive

SIRS/sepsis
Anaphylaxis/anaphylactoid
Hypoadrenocorticism
Neurogenic

Obstructive

Cardiac tamponade
Pleural space disease
Pleural effusion
Pneumothorax
Diaphragmatic hernia
Pulmonary thromboemboli
GDV

Decreased arterial blood oxygen content

Decreased arterial oxygen tension in blood
Decreased PiO_2
Hypoventilation
V/Q mismatching
Diffusion barrier
Anatomical shunting
Decreased oxygen-carrying capability
Anemia
Dyshemoglobinemias

Metabolic

Hypoglycemia
Mitochondrial dysfunction
Intoxications
Disease related

GDV, gastric dilation-volvulus; PiO_2 , partial pressure of inspired oxygen = $FiO_2 \times (\text{barometric pressure} - \text{saturated vapor pressure of } H_2O)$; SIRS, systemic inflammatory response syndrome; V/Q, ventilation/perfusion.

Distributive Shock

When there is a maldistribution of blood flow due to a marked decrease in systemic vascular resistance, shock results from inadequate perfusion. Vascular volume and cardiac function may be normal but clinically, there are conditions in which an aspect of hypovolemia and cardiac compromise also contributes to the shock state. While increasing the vascular volume or cardiac output may provide a degree of compensation, distributive shock often requires pharmacological intervention to reverse the decrease in systemic vascular resistance along with therapies aimed at the inciting cause [3]. Distributive shock may also result from a marked increase in systemic vascular resistance from an overdose of, for example, epinephrine, cocaine, amphetamines, phenylpropanolamine, pseudoephedrine, etc. (see Chapter 135) or in animals with a functional pheochromocytoma. Treatment typically involves addressing the underlying cause and the use of alpha-adrenergic antagonists.

SIRS and Sepsis

Distributive shock is the predominant mechanism of shock in the patient with systemic inflammatory response syndrome (SIRS) and sepsis (SIRS secondary to an infection; see Chapter 159). Distributive shock is commonly associated with SIRS or sepsis due to inappropriate vasodilation induced by release of inflammatory cytokines, resulting in a relative hypovolemia, so that the blood volume remains constant but the total vascular capacity increases, resulting in a drop in blood pressure [4].

This also causes leakage of fluid from the vascular compartment. The release of inflammatory cytokines into the peripheral circulation will cause a breakdown in the normally non-porous endothelial glycocalyx and fluid extravasation into the interstitial space, resulting in a degree of hypovolemic shock. The component of hypovolemic shock may be exacerbated by continued loss of fluid into the peritoneal or pleural space, as seen with septic peritonitis and pyothorax, respectively. To complicate the management of the patient with SIRS/sepsis further, the presence of cytokines in the systemic circulation can also directly cause cellular metabolic dysfunction through reduced energy production (ATP) by the mitochondria; this can occur in the presence of increased or decreased blood flow to the tissue.

The patient with distributive shock caused by SIRS/sepsis can have one of two distinct clinical characteristics, “warm shock” or “cold shock,” depending upon cardiac function. In a patient with warm shock, there is a compensatory increase in cardiac output caused by an increase in cardiac contractility, in response to the vasodilation (see Chapter 159). Examination of this

patient will reveal hyperdynamic pulses, hyperemic mucous membranes with a rapid capillary refill time, warm extremities, and increased rectal temperature. The increased cardiac output results in normal or even increased blood flow to organs and tissue beds. However, despite this increased blood flow, these patients remain at risk for the development of organ dysfunction.

The patient with cold shock will have the same vasodilation but there is an associated reduction in cardiac output caused by decreased cardiac contractility. The cause of this decrease in cardiac contractility is multifactorial but includes cytokine-induced mitochondrial dysfunction, altered cellular substrate provision, and desensitization of beta-adrenergic receptors of the myocardium; these changes are reversed once the patient recovers (see Chapter 154). Upon examination, the patient in cold shock will have reduced pulse quality, pale mucous membranes with a prolonged capillary refill time, cold extremities, and hypothermia. The decrease in cardiac output (cardiogenic shock) will result in reduced perfusion of organs and tissue beds, putting these patients at risk of developing organ dysfunction induced by ischemic and sepsis [5] (see Chapter 154).

Anaphylaxis

Anaphylaxis is an acquired immune reaction mediated by immunoglobulin E (IgE) from a previous sensitization while anaphylactoid reactions do not require previous exposure and are not IgE mediated (see Chapter 146). Coronary artery vasoconstriction plays a role in the pathogenesis. History may yield exposure to antigens commonly associated with allergic reactions (e.g. vitamin K1, envenomation, etc.). Acute cardiovascular collapse often ensues with or without signs attributable to upper airway swelling, bronchial constriction, and gastric acid production. Epinephrine is the mainstay of treatment in addition to IV fluid support, corticosteroids and histamine antagonists (see Chapter 146) [6].

Hypoadrenocorticism

Hypoadrenocorticism is a lack of or decrease in the hormones produced by the adrenal medulla resulting in corticosteroid and mineralocorticoid deficiencies. Hypovolemia and electrolyte abnormalities ensue, in addition to a decrease in vascular tone, possibly due to an overproduction of nitric oxide (NO). History and physical exam can range from classic presentations of weakness, vomiting, diarrhea and electrolyte abnormalities to those that are more subtle. If hypoadrenocorticism is suspected, in addition to supportive care with replacement IV fluids, for example, corticosteroid therapy is instituted. Dexamethasone should be used if the patient

is undergoing cortisol testing as it does not cross-react with cortisol measurements (see Chapter 115) [7–9]. Critical illness-related corticosteroid insufficiency has also been described in patients with sepsis and results in hypotension resistant to fluid support and vasopressor therapy [10].

Neurogenic Shock

A neurogenic component of shock was proposed and demonstrated in dogs in 1942 [11]. Clinically, disruption of sympathetic pathways (e.g. a spinal cord injury, SCI) can lead to both cardiogenic shock in the form of bradyarrhythmias and distributive shock with loss of sympathetic input to the distal vasculature. A central nervous system (CNS) lesion, such as a SCI, would be supported by history, physical examination, and advanced imaging. Maintaining appropriate blood pressure with IV fluids and vasopressors, along with anticholinergics to address bradyarrhythmias, is appropriate to maintain perfusion, especially to the CNS which may have lost autoregulation since further ischemia may worsen the insult [12].

Obstructive Shock

Physical impedance to blood flow resulting in decreased perfusion is referred to as obstructive shock [3].

Cardiac Tamponade

If pericardial effusion accumulates within the pericardium, it will eventually distend the sack and transmit the increase in pericardial pressure to the external heart wall, decreasing ventricular filling and therefore cardiac output [13]. Although air is compressible, when confined within the pericardium, it may result in enough pressure to cause cardiac tamponade [14]. History may include progressive exercise intolerance or lethargy, vomiting, or acute collapse. In addition to signs of circulatory shock, physical exam findings may include distended jugular veins, pulsus paradoxus, and muffled heart sounds. Electrical alternans may be seen on ECG. Pericardiocentesis should offer immediate relief [15] (see Chapter 54, Pericardial Effusion).

Pleural Space Disease

Fluid, air, or tissue within the pleural space often leads to hypoxemia due to compression of lung lobes. Additionally, pressure on the heart or great vessels limits venous return and therefore cardiac output, exacerbating the shock state. History usually includes some symptom attributable to respiratory embarrassment. Trauma

raises a high index of suspicion for pneumothorax, hemothorax or diaphragmatic hernia, but many other conditions, ranging from spontaneous pneumothorax to neoplasia, can lead to pleural space disease. Physical examination can include abnormal respiratory rates and effort to include paradoxical breathing along with dull breath sounds, distended jugular veins, and pulsus paradoxus [16]. Imaging such as radiographs, ultrasound, and laboratory analysis of the fluid will help delineate the cause. Thoracocentesis should be viewed as an emergent *diagnostic* tool as well as a therapeutic procedure in the case of air or fluid [17] (see Chapters 44–49 and 183).

Pulmonary Thromboembolism (see Chapters 42 and 62)

The presence of a pulmonary embolism (PE) causes obstruction on the pulmonary vascular bed, with the severity of obstructive shock dependent upon the size of the obstruction (see Chapter 42). Causes of pulmonary embolism include fat, metastatic neoplasia, parasites, and blood clots. Pulmonary thromboembolism is the result of blood clots forming at a distant site, dislodging and traveling to the pulmonary vasculature, clots forming in the right side of the heart and migrating to the pulmonary vasculature, or they can form *in situ* associated with other pulmonary artery pathology, such as pulmonary hypertension or heartworm disease.

The initial approach to a patient with suspected PE is focused on stabilizing the patient while clinical evaluation and diagnostic testing are carried out. The majority of patients with a PE will be hemodynamically stable and therefore the clinician should instigate general supportive measures including intravenous fluids, oxygen supplementation, and empiric anticoagulation (see Chapter 71). In the subset of patients that are hemodynamically unstable, significant hypotension will be present and the initial treatment focus is on restoring perfusion with intravenous fluid resuscitation and vasopressor support, in addition to oxygen support which may require intubation and mechanical ventilation (see Chapter 188) [18].

Gastric Dilation-Volvulus

In gastric dilation-volvulus (GDV) syndrome, the stomach is distended with gas (see Chapter 82). The distended stomach places pressure on the low pressure vena cava, decreasing or occluding venous return, leading to a decrease in cardiac output. The stomach may undergo ischemia directly from increased transmural pressure within the gastric wall or due to a torsion of the stomach (and associated vasculature). Beyond obstructive mechanisms, SIRS, cardiogenic compromise, and hypoventilation add to the shock state [19]. The classic

presentation is a large- to giant-breed dog that is retching unproductively with a distended abdomen and clinical signs of shock; however, any dog presenting in shock, especially with signalments associated with the disease, should have GDV ruled out with radiographs. In addition to intravascular volume expansion, decompression of the stomach and surgical derotation and exploration are warranted.

Non-Circulatory Shock

The arterial circulation delivers oxygen and fuel to the cells. While cardiogenic, hypovolemic, distributive, and obstructive mechanisms lead to circulatory shock, the lack of oxygen, its utilization at the cellular (mitochondrial) level or lack of energy substrate also lead to or contribute to the shock state.

Decreased Oxygen Content

Oxygen is carried in the blood, with over 98% normally bound to hemoglobin in the red blood cell and <2% dissolved in the plasma. Hypoxemia usually refers to low arterial oxygen tension or partial pressure of oxygen dissolved in the blood and is caused by decreased inspired oxygen, hypoventilation, ventilation-perfusion mismatching, alveolar diffusion impairment, and anatomical shunting of venous blood into the arterial system. However, due to the oxygen hemoglobin dissociation curve, low oxygen tensions result in low saturation of hemoglobin and therefore decreased *content* of oxygen [20]. However, even with normal or high oxygen tensions, that is, partial pressure of oxygen, the content may be low if there is a lack of hemoglobin, for example due to anemia (see Chapter 10) or the hemoglobin's ability to carry oxygen is compromised, as with carboxyhemoglobin (HbCO) [21] or methemoglobin (HbMet) [22].

Respiratory embarrassment would be indicated by history and physical examination. Pale mucous membranes may indicate anemia and decreased hemoglobin concentration; packed cell volume and hematocrit can also help in assessing adequate red cells numbers. History of intoxications, such as acetaminophen in cats that can lead to HbMet (see Chapter 132), or smoke or other combustion inhalation (see Chapter 139) that can lead to HbCO should raise the index of suspicion for dyshemoglobinemia. Pulse oximetry can screen for hypoxemia, although blue mucous membranes make this an academic exercise; however, the converse is not true – the presence of pink mucous membranes does not indicate the absence of hypoxemia. Brown and bright red mucous membranes upon physical examination support HbMet and HbCO, respectively, and co-oximetry can confirm their presence. Pulse oximetry, unless equipped to assess HbMet or HbCO, is misleading in patients with dyshemoglobinemias [23,24]. Oxygen therapy (see Chapter 181) is initially administered and transfusions (see Chapters 176 and 177) are given as needed.

Metabolic Aspects

In the face of adequate circulation and arterial oxygen content, shock can occur if there is not an energy substrate, as in hypoglycemia, or the energy-generating capability of the cell, such as in the mitochondria, is compromised.

Hypoglycemia can be ruled out in patients with obtundation, seizures or hypothermia with simple point-of-care testing and treated with intravenous administration of dextrose (see Chapter 111).

Mitochondrial dysfunction is seen in certain intoxications, such as bromethalin [25,26] (see Chapter 130), and is known to occur in a number of metabolic derangements, including sepsis [27]. In the emergent patient with altered mentation, and in the absence of supporting history, such dysfunction becomes a diagnosis of exclusion after ruling out the other causes of shock.

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Lactate Monitoring

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Introduction

Lactate was first measured in patients in the early 1900s, and it was found that the accumulation of lactic acid accounted for the metabolic acidosis observed in patients with decreased blood flow and shock [1]. Later, Huckabee described populations of hospitalized patients with marked accumulation of lactate and acid–base disturbances [2]. Based on categorization of these patients on the presence or absence of an acidosis and clinical hypoperfusion or hypoxia, marked differences in mortality were noted, suggesting the use of lactate as a monitoring and prognostic tool. Following this seminal work, decades of research have been dedicated to the utilization of lactate monitoring in both human and veterinary patients.

Lactate Physiology

Lactate is a negatively charged molecule that is almost completely dissociated at physiological pH. It exists in two isoforms, D-lactate and L-lactate, but most clinical analyzers will only measure the L-lactate isoform. D-lactate is produced by some forms of bacteria, whereas L-lactate is produced by mammalian cells. Under normal aerobic conditions, glucose enters glycolysis, resulting in the production of pyruvate and a net of 2 moles of adenosine triphosphate (ATP) per mole of glucose. Pyruvate then enters the mitochondria and undergoes further metabolism to produce 36 moles of ATP per mole of glucose. Using this pathway, only a small amount of pyruvate is converted to lactate via the cytosolic enzyme lactate dehydrogenase [3].

Causes of Hyperlactatemia

Hyperlactatemia has traditionally been thought to arise due to inadequate oxygen delivery, and as such has been

considered a marker of anaerobic metabolism. However, hyperlactatemia can also occur in the presence of aerobic metabolism. In his seminal papers discussing elevations in plasma lactate, Huckabee described three categories of patients with increased plasma lactate: patients with hyperlactatemia with no change in serum pH (type 1 hyperlactatemia) versus patients with hyperlactatemia and concurrent acidemia (type 2 hyperlactatemia). He further divided type 2 hyperlactatemia into type A lactic acidosis (2A) and type B lactic acidosis (2B). Type 2A describes lactic acidosis due to inadequate oxygen delivery to meet cellular demand, while type 2B includes all causes of lactic acidosis that occur despite adequate oxygen delivery [4]. Causes of hyperlactatemia are shown in Box 156.1 [2,4].

Type 1 Hyperlactatemia without Acidosis

Although commonly associated with an acidosis, hyperlactatemia can occur without a decrease in plasma pH (acidemia). This may be due to the presence of a concurrent metabolic alkalosis or as a result of the underlying mechanism for lactate production. Detecting the presence of a concurrent alkalotic process may require advanced acid–base analytical techniques such as the semi-quantitative approach [5]. There are also causes of increased lactate production that are not associated with a concomitant accumulation of hydrogen ions.

When lactic acidosis develops, the production of lactate occurs through a different cellular pathway from that of hydrogen ion accumulation (discussed further below). If accelerated glycolysis occurs in the face of normal mitochondrial function, increases in pyruvate production lead to increased lactate due to a mass effect. Hydrogen ions do not accumulate in the extracellular space in these circumstances, as they can enter the functional mitochondria for use in oxidative phosphorylation [6].

Box 156.1 Classification and etiology of lactic acidosis [3,6,7].**Type A – inadequate oxygen delivery for cellular demands**

Shock (cardiogenic, septic, hypovolemic, hypoxic)
 Regional hypoperfusion (splanchnic)
 Severe hypoxemia ($\text{PaO}_2 < 40 \text{ mmHg}$)
 Severe, acute anemia (hematocrit $< 15\%$)
 Carbon monoxide toxicity
 Muscle activity: seizures, trembling, shivering, exercise, excessive restraint

Type B – no clinical evidence of inadequate oxygen delivery**1B– associated with underlying disease**

Diabetes mellitus
 Liver disease
 Neoplasia
 Sepsis
 Pheochromocytoma
 Thiamine deficiency

2B – caused by drugs or toxins

Ethanol
 Methanol
 Ethylene glycol
 Sorbitol
 Xylitol
 Salicylates
 Acetaminophen
 Epinephrine
 Terbutaline
 Cyanide
 Propylene glycol

3B – due to inborn errors of metabolism

Glycogen storage diseases
 Pyruvate dehydrogenase phosphatase-1 deficiency
 Mitochondrial oxidative phosphorylation disorders

Type 2A Lactic Acidosis

In states of inadequate oxygen supply, the rate of glycolysis outstrips that of mitochondrial metabolism. This results in the accumulation of both pyruvate and nicotinamide adenine dinucleotide (NADH), altering the cellular NADH to NAD ratio (cellular redox state). In this state, ongoing glycolysis may become the main source of cellular energy production. In order to provide adequate substrate for glycolysis to continue, pyruvate is converted to lactate, producing oxidized nicotinamide adenine dinucleotide (NAD) (Figure 156.1). Lactate dehydrogenase activity significantly increases due to the redox state present in anaerobic conditions, increasing

the lactate to pyruvate ratio [7]. The process of lactate generation from pyruvate consumes hydrogen ions, providing protection from intracellular acidosis. Lactic acidosis occurs as a result of concomitant accumulation of lactate and hydrogen ions through two separate cellular pathways. The hydrogen ions responsible for the acidosis are the product of hydrolysis of ATP. In the healthy state, these hydrogen ions diffuse into the mitochondria. In anaerobic conditions, hydrogen ions accumulate and are transported out of the cell via various mechanisms. This adaptive strategy prevents worsening of a cellular acidosis. This results in the commonly observed acidosis associated with hyperlactatemia.

Once oxygen delivery or supply is restored, lactate is converted back to pyruvate, with conversion rates in humans of up to 320 mmol/L/h , far exceeding normal rates of production [7].

Type 2B Lactic Acidosis

Type 2B lactic acidosis occurs in patients without clinical evidence of decreased oxygen delivery such as hypoperfusion, anemia or hypoxemia. When lactic acidosis is recognized in the emergency room patient, every effort should be made to ensure that oxygen delivery to tissues is adequate. Evaluation of perfusion parameters, blood pressure, packed cell volume, and blood oxygenation status are all recommended. If lactic acidosis persists without any evidence of inadequate oxygen delivery, a type B lactic acidosis should be suspected. Causes of type B lactic acidosis are shown in Box 156.1. Treatment is based on resolution of the primary disease [6,7].

Lactate Measurement

Various devices are available for lactate monitoring, including handheld point-of-care (POC) analyzers and large benchtop blood gas and acid–base analyzers. Lactate can be measured in plasma or whole blood.

The most common technique for lactate analysis is amperometry, where a lactate-sensitive electrode is coated with lactate oxidase, converting lactate to pyruvate and hydrogen peroxide. Hydrogen peroxide is then measured amperometrically [8]. Although there is some difference between arterial, venous, and capillary blood lactate values, several studies have concluded that this variation is unlikely to be clinically significant [8,9]. It is important to note that the majority of lactate analyzers only measure the L-lactate isoform. Analysis for the D-lactate isoform is available from specialty laboratories.

A few studies have evaluated the agreement of point-of-care analyzers with benchtop machines. Based on these studies, POC analyzers may result in slight

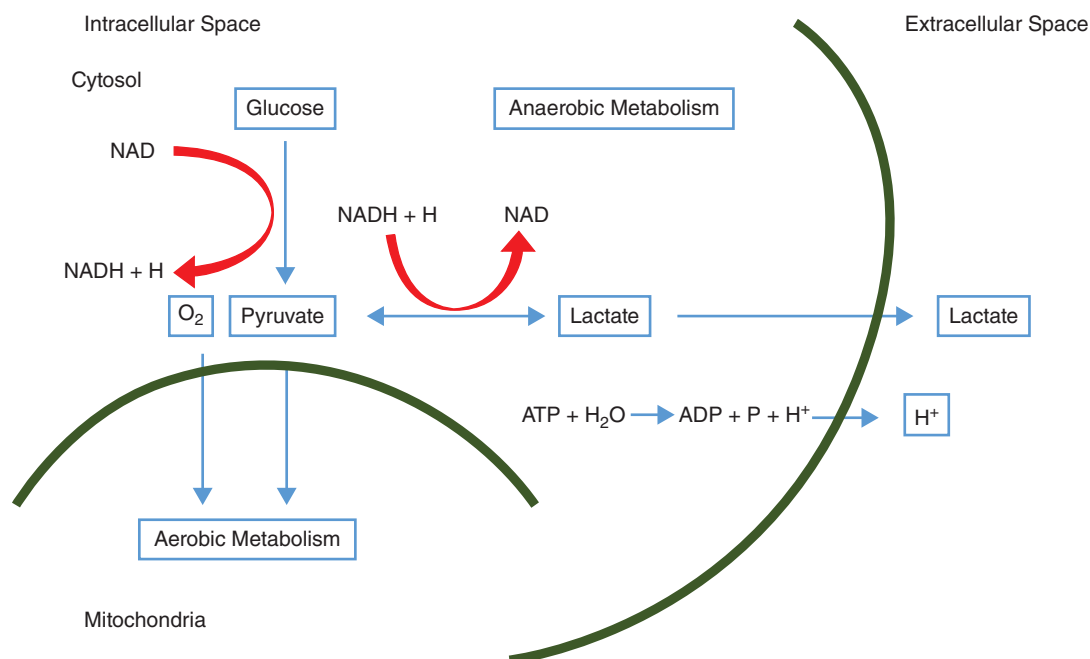


Figure 156.1 Overview of cellular lactate production. Glucose is converted to pyruvate through glycolysis. This is an anaerobic pathway occurring in the cytosol. Pyruvate can be converted back to glucose through the Cori cycle or can move into the mitochondria for further metabolism. Mitochondrial metabolism of pyruvate requires the presence of oxygen. When pyruvate cannot be metabolized by the mitochondria, such as in anaerobic states, pyruvate will be reduced to lactate and transported out of the cell. The hydrogen ions responsible for a lactic acidosis are not produced through the same pathway as lactate. Instead they are the result of hydrolysis of adenosine triphosphate (ATP) in the cytosol. NAD⁺, oxidized nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide.

underestimation and larger disagreement noted at higher lactate levels [10,11]. In general, disagreements between POC and benchtop analyzers were less than what would be clinically significant, but the reader is encouraged to review the various studies assessing specific analyzers for more information.

Since hyperlactatemia can exist with or without concurrent acid–base derangements, accompanying acid–base parameters will likely provide valuable information regarding the significance and etiology of hyperlactatemia. For this reason, lactate is ideally analyzed in conjunction with a complete acid–base and electrolyte panel. Finally, some analyzers using lactate oxidase methodology will report erroneously elevated lactate levels in patients with ethylene glycol toxicity [12]. Markedly elevated lactate values measured in patients without an obvious cause should be interpreted with caution if exposure to ethylene glycol is possible.

Sample Handling

In many circumstances, blood lactate is measured in ill or injured animals with POC or rapid turnaround diagnostic analyzers. Therefore, prolonged storage time prior to

analysis is unlikely to occur. A delay in measuring whole-blood lactate may cause as much as a 70% increase in lactate due to ongoing glycolysis, especially in the presence of leukocytosis or polycythemia [8]. Samples that cannot be analyzed immediately should be placed on ice, in the appropriate sample tube for the analyzer, and analyzed preferably no more than 60 minutes post sampling [13]. As some, if not all of the sodium lactate within lactate-containing fluids such as lactated Ringer's or Hartmann's is L-lactate, it will be measured by lactate analyzers causing falsely elevated levels. Special attention to appropriate scavenging technique is important if blood samples are collected from catheters through which lactate-containing fluids are running [14].

Patient Selection

Lactate monitoring is indicated in many animals presenting to the emergency room. It should be considered in any patient with perfusion abnormalities or evidence of significant systemic disease. Lactic acidosis is a common cause of an elevated anion gap metabolic acidosis and should be measured whenever this acid–base abnormality is identified. It is important to note that the presence

of a normal anion gap does not exclude hyperlactatemia, as many emergency and critically ill patients have concurrent hypoalbuminemia, leading to a decreased anion gap [15,16].

Normal Lactate Concentration

Normal resting plasma lactate levels have been reported to be less than 2.5 mmol/L in people and dogs [17]. There has been variability in the reported lactate concentration of healthy cats; this likely reflects the impact of struggling and muscle activity on lactate levels [18,19].

Assessment of Hyperlactatemia

When hyperlactatemia is identified in an emergency room patient, it should prompt an immediate evaluation for potential life-threatening abnormalities. This should include assessment of perfusion parameters, blood pressure, and hematocrit. Any significant abnormalities should be addressed as indicated. Muscle activity can rapidly increase blood lactate concentration so hyperlactatemia identified in the post-seizure patient or the patient with tremors or difficulties with restraint should be interpreted with caution. The patient with hyperlactatemia that has no evidence of decreased oxygen delivery or other obvious cause identified should have a further diagnostic work-up. This may or may not be necessary on an emergency basis, depending on the overall severity of illness of the animal. Concurrent acid–base analysis can be of diagnostic benefit. Consideration of diseases that can cause type B lactic acidosis or hyperlactatemia without acidosis (see Box 156.1) will aid in guiding the diagnostic approach.

In addition to its diagnostic role, blood lactate measurement can be an excellent tool for monitoring response to therapy. Following identification of hyperlactatemia due to inadequate oxygen delivery, serial monitoring of blood lactate is recommended. Ideally, monitoring should be continued until the blood lactate concentration has returned to normal. Changes in blood lactate over time not only help guide therapy but have been shown to have prognostic significance in many patient populations and are generally considered superior over a single admission value of lactate for prognosis [20–23].

Administration of a large quantity (180 mL/kg in an hour) of lactate-containing fluids to healthy dogs has been shown to cause a small but significant increase in blood lactate concentration [24]. Studies in experimental animals suggest that resuscitation of animals in hemorrhagic shock with lactate-containing fluids can be associated with persistence of hyperlactatemia despite

improvement in cardiovascular performance [25]. Caution is advised when interpreting blood lactate concentration in patients following volume resuscitation with lactate-containing fluids.

Prognostic Implications

Elevations in serum lactate have been evaluated in several small animal veterinary populations. In general, an increase in lactate has been associated with an increased mortality or other negative outcomes in the following diseases or conditions in dogs: IMHA [21], gastric dilation-volvulus (GDV) [22], hypotension in ICU [26], SIRS [27], severe soft tissue infections [28], *Babesia* [29], and heartworm-associated caval syndrome [30]; and in cats with hypertrophic cardiomyopathy [31] or septic peritonitis [32,33]. Additionally, lactate has been incorporated into a veterinary illness severity scoring system for both dogs and cats, and is one of the most significant variables included [34,35].

In addition to its possible prognostic utility in certain veterinary patient populations, lactate was also found to be an independent predictor of mortality in a large population of dogs and cats presenting to an emergency room [36]. Interestingly, in this study, mortality in dogs with hyperlactatemia and normal acid–base parameters was not different than in dogs with a normal lactate. This underscores the importance of concurrent acid–base analysis along with lactate. In a separate study in cats presenting to the emergency room, increased lactate concentration was associated with decreased systolic blood pressure and worsening physically assessed perfusion variables. Interestingly, in this study, there was no statistically significant difference in lactate between survivors and non-survivors [37].

The prognostic value of blood lactate concentration has been extensively studied in dogs with GDV. The initial blood lactate value has been evaluated for its association with both gastric necrosis and mortality. In these studies, the median lactate in dogs with gastric necrosis was between 6.35 and 6.95 mmol/L whereas lactate in dogs without gastric necrosis was between 3.3 and 4.5 mmol/L. Dogs that survived had median lactates between 3.4 and 6.2 mmol/L and those that died had a median lactate between 6.8 and 10.3 mmol/L [22,38,39]. It is important to note that no single lactate value resulted in 100% sensitivity and specificity for gastric necrosis or mortality, and as a result, lactate values obtained from patients with GDV should be interpreted similarly to any other patient with injury or illness.

Although hyperlactatemia and lactic acidosis have prognostic implications, they should not be used solely to determine whether or not treatment for the primary

disease process should be attempted. Rather, they should be used to document patients that may have severe, unexplained or occult perfusion or oxygen delivery deficits, where attentive monitoring and appropriate therapy are paramount to a successful outcome. Lactate monitoring is not a substitute for a thorough physical examination and must be interpreted in concert with the entire clinical picture.

Lactate Measurement in Other Body Fluids

Due to the difficulty in consistently documenting bacterial peritonitis, and the significant difference in management strategies, there has been interest in utilizing abdominal effusion lactate concentration to increase sensitivity and specificity in diagnosing septic peritonitis (see Chapter 87). It was shown that in dogs, an abdominal fluid lactate value of 2 mmol/L higher than

a peripheral lactate had 100% sensitivity and specificity in detecting bacterial peritonitis [40]. It should be noted that this study only had peritoneal lactate concentrations for seven dogs, therefore peritoneal lactate concentration should not overshadow other clinically important findings.

A separate study reported that all dogs with septic peritonitis had peritoneal effusion lactates greater than 2.5 mmol/L, and a peritoneal effusion lactate concentration higher than blood lactate [41]. It is also important to note that these studies evaluated dogs on presentation prior to any other surgical procedure. It has been reported that the presence of a closed suction drain may alter lactate concentrations in abdominal fluid, therefore the utility of abdominal fluid lactate concentration is questionable in the postoperative patient [42].

Based on previous studies, it does not appear that peritoneal lactate concentration is useful in detecting septic peritoneal effusion in cats [40,41].

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Emerging Monitoring Techniques

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Introduction

Animals with hemodynamic compromise often require intensive and continuous monitoring to assess the response to treatment as well as to rapidly identify deterioration in clinical status. There are numerous potential tools for hemodynamic monitoring and this chapter will review some of the newer monitoring techniques available.

Venous Oxygen Monitoring

Venous hemoglobin oxygen saturation (SvO_2) has been utilized as an effective resuscitation endpoint. SvO_2 is an indirect measure of tissue oxygenation. There are three main determinants of SvO_2 : cardiac output, hemoglobin concentration, and arterial oxygen content (CaO_2). An uncompensated rise in VO_2 (such as fever or seizure activity) or a decrease in DO_2 will reduce SvO_2 . On the other hand, an improvement of oxygen supply, as well as reductions in VO_2 , can increase the SvO_2 [1,2].

Venous hemoglobin oxygen saturation can be measured continuously by an indwelling oximetry catheter, or intermittently evaluated via blood gas analysis or co-oximetry. Most blood gas machines measure PvO_2 and use a human algorithm for the oxygen-hemoglobin dissociation curve to calculate the corresponding SvO_2 . Some blood gas machines contain a co-oximeter and assess hemoglobin saturation directly. It is important to note that all commercial blood gas machines designed for human blood and can impair their accuracy for assessment of SvO_2 in animals.

Venous hemoglobin oxygen saturation measured via a pulmonary artery catheter has been considered ideal for hemodynamic assessment but as mixed venous blood samples are unlikely to be available in the emergency room patient, central venous SvO_2 (ScvO_2) is most

commonly used for monitoring purposes. Central venous SvO_2 values of $\geq 70\%$ are recommended as a resuscitation endpoint [3,4]. The SvO_2 of peripheral venous blood may not reflect central venous values in the hemodynamically unstable patient and are not recommended for use as a resuscitation endpoint. Central venous blood samples can be obtained by intermittent jugular venepuncture or more ideally an indwelling jugular catheter.

A reduction in SvO_2 may be an early indicator that the patient's clinical condition is deteriorating, even when blood pressure or heart rate are normal after resuscitation in dogs [5,6]. When SvO_2 is less than 65%, it indicates increased oxygen extraction due to decreased oxygen supply. This oxygen supply may drop with inadequate cardiac output, anemia, hypoxemia or even with a rise in oxygen demand. On the other hand, an SvO_2 higher than 75% may suggest an underlying defect in oxygen extraction, as can occur with mitochondrial dysfunction with sepsis or cytotoxic tissue hypoxia (cyanide poisoning for example) (see Chapter 159) [2].

The ScvO_2 was used as a gold standard parameter for resuscitation of human septic patients and as a guide by the Global Sepsis Alliance and the Surviving Sepsis Campaign until 2015. Although some studies on early goal-directed therapy in patients with severe sepsis and septic shock showed that maintenance of a continuously measured ScvO_2 above 70% resulted in a reduction in mortality compared with the same treatment without ScvO_2 monitoring, new evidence has shown that its interpretation should be carefully assessed in conjunction with a complete clinical examination and lactate clearance, preferably with the circulatory system sonographic assessment [4,7–10].

One study in dogs with severe sepsis and/or septic shock evaluated changes in tissue perfusion parameters in response to goal-directed hemodynamic resuscitation. In this study, resuscitation was aimed at restoring parameters related to tissue perfusion, including capillary refill

time, central venous pressure, blood pressure, lactate, base deficit, and ScvO₂. A higher ScvO₂ was associated with a lower risk of death [5].

Given the current evidence, ScvO₂ appears to be an effective endpoint to guide resuscitation but integration with other parameters such as lactate concentration and physical examination is important (see Chapter 156).

Peripheral Hemodynamic Parameters

Being very well defined as “acute circulatory failure” by Weil in 1979, when the cardiovascular system fails to provide cells with adequate oxygen flow to maintain physiology, shock is a very complex syndrome that continues to challenge many emergency doctors [11,12].

Clinically, arterial hypotension represents as a cardinal sign of classic shock, but it is not always present with occult or cryptic shock [11,13]. Therefore, the diagnosis of peripheral vasoconstriction (peripheral hypothermia, pale mucous membrane, delayed capillary refill time, oliguria, decrease of bowel sounds or loss of sensitivity to detect a pulse curve by pulse oximeter) is an essential part of emergency patient evaluation. When vasoconstriction is caused by activation of the sympathetic nervous system, it can prevent the fall in blood pressure [14–19]. Parameters such as peripheral temperature, sublingual capnometry, and tissue oximetry may allow identification of patients with hemodynamic instability despite the absence of hypotension.

Temperature Gradient Monitoring

In most species (dogs, cats, and humans, for example), the physiological response in the face of low tissue perfusion consists of raising the sympathetic tone while reducing the vagal efferent activity (parasympathetic). This reflex will induce tachycardia and vasoconstriction reflex, mainly in the skin, skeletal muscle, kidneys, gastrointestinal tract, and splanchnic vascular bed, thereby enabling it to divert blood to the central circulation. This will maintain the activity of essential components for immediate survival, including the heart, central nervous system (CNS), and lungs [18,20–22].

Temperature gradient monitoring is based on the concept that skin vasoconstriction is an early sign of hypoperfusion [15,19]. The technique is performed by checking the temperature of the interdigital space or the plantar pad of the posterior limb of dogs and cats. A double laser infra-red thermometer with emissivity adjusted to 0.98E is directed to the interdigital membrane (metatarsal if possible) or the plantar pad (if smooth and absent of hyperkeratosis), as shown in Figure 157.1. The peripheral temperature is compared

to the core temperature measured simultaneously. It is critical to measure the peripheral temperature at other points (tip of the nose, axillary and inguinal areas) to evaluate whether there is heterogeneity of peripheral flow, common in severe sepsis and septic shock, indicative of poor prognosis [22–27].

In a worldwide multicenter study performed by the author and colleagues, with 523 patients treated in emergency services in Spain, Portugal, and Brazil, the vast majority of emergency patients had a normal level of consciousness and heart rate, systemic blood pressure, and rectal temperature, all within physiological limits. These parameters, when analyzed separately, generate a false sense of safety, since they are considered the gold standard in assessing systemic perfusion, when in fact they reflect the status of the central circulatory bed, with low sensitivity in the evaluation of the peripheral hemodynamic segment [28,29]. Many of these same patients demonstrated peripheral hypothermia and hyperlactatemia (occult or cryptic shock), often with concurrent low urinary output and no bowel sounds. This supports the concept that the central circulation is maintained thanks to this flow deviation from the peripheral bed [28,30–33].

The temperature gradient between the core and the periphery (delta Tcp) should be $<6.5^{\circ}\text{C}$ in dogs and $\leq 7.5^{\circ}\text{C}$ in cats. If delta Tcp is increased but core temperature is still within the normal range, this suggests that peripheral vasoconstriction is compensating effectively. If delta Tcp is reduced and core temperature is low, the animal is more seriously hemodynamically compromised [31,32,34]. Figure 157.2 describes the Line of Life counted from the hemodynamic evolution of the critically ill patient.



Figure 157.1 Peripheral and rectal temperatures are measured for calculating the delta Tcp.

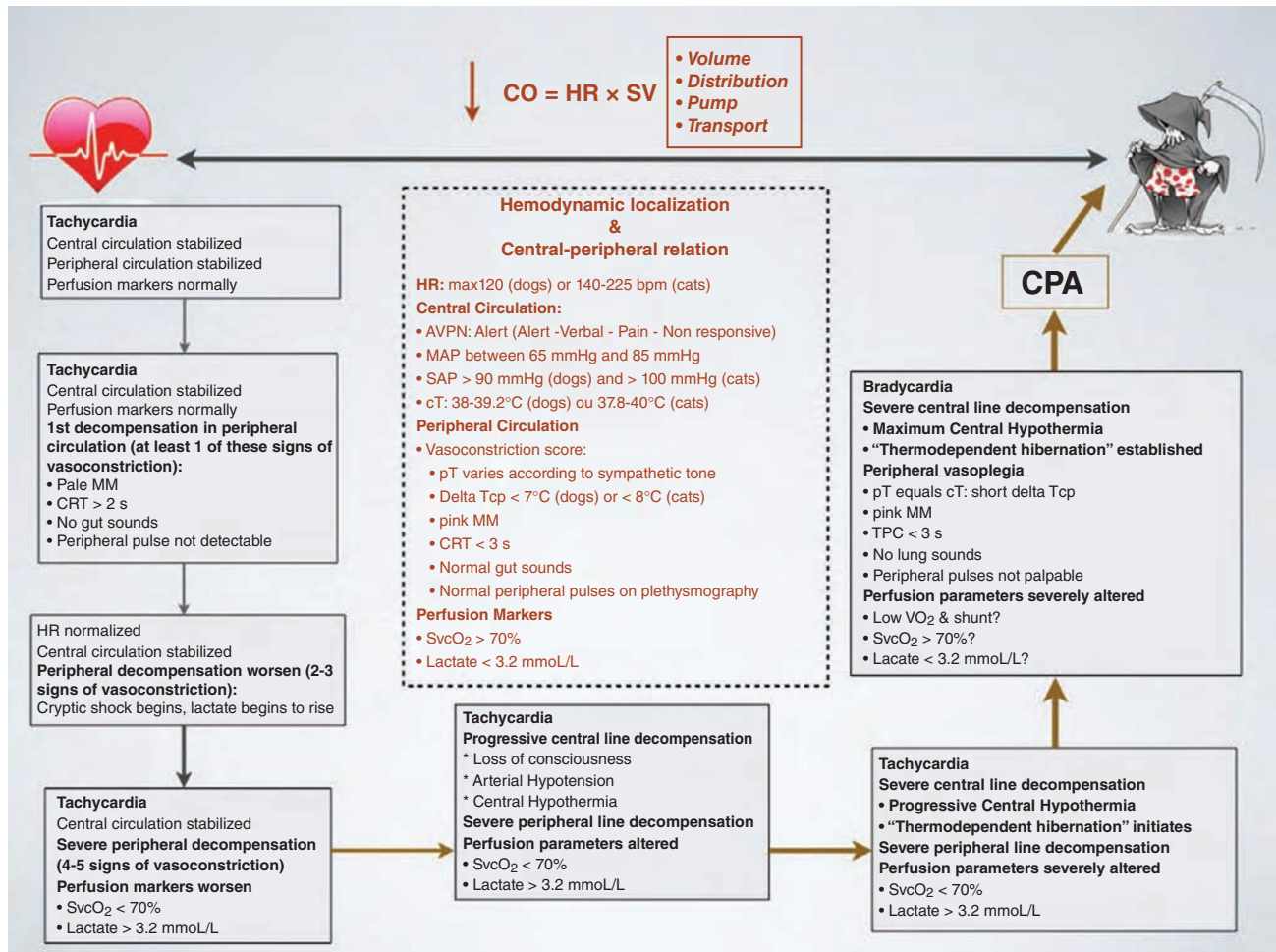


Figure 157.2 The Line of Life describes the hemodynamic evolution and the organic response to low cardiac output of the critically ill patient.

It is also important to stress that the values of 6.5°C and 7.5°C are alert indicators, based on the studies of Joly and Weil (1969), Kaplan (2001), and Lima and colleagues (2009) in human patients, and in our recent studies with populations of normal dogs and cats (unpublished data) [21,26,33]. More studies are in progress to improve the sensitivity and specificity of this parameter.

It is necessary to be attentive to the following information when assessing delta Tcp.

- The higher the peripheral vasoconstriction, the higher the core-peripheral temperature gradient.
- There is grave concern when the gradient is greater than 10°C or when the delta Tcp persists above the normal range for more than 24 hours.
- The peripheral sensor needs to be placed where there is production of heat and minimal movement (interdigital space of the left hindlimb is the standard).
- The presence of central hypothermia, an ambient temperature lower than 20°C and/or vasodilatory

shock tends to limit the use of this central-peripheral gradient.

- In cases of severe vasoplegia, the gradient tends to be shorter with an associated central hypothermia.

Evaluation of other temperature gradients can also be extremely useful for monitoring the peripheral circulatory state in the severely ill patient.

Delta Tskin-diff is the gradient obtained when the temperature sensor is directed to the interdigital space of the left forelimb compared to the medial aspect of the same limb in the region of the midradius. This technique is more suitable for environments where the temperature may vary (mainly the operating room, OR). Values of delta Tskin-diff greater than 4°C indicate severe vasoconstriction in anesthetized patients, and the normal would be a delta Tskin-diff close to 0°C [15,19].

When the gradient between the patient's skin (measured at the same point as described for delta Tcp) and the room temperature reaches a value lower than 4–6°C over 12 hours of hospitalization, there is a

correlation with a poor survival rate. The smaller this delta T_{pr} (peripheral–room temperature) value, the higher the lactate in people with cardiogenic shock, and a delta T_{pr} less than 5 °C is well correlated with lower cardiac indexes (the same did not occur in septic shock) [15,19,35].

Sublingual Capnometry

Sublingual capnometry should be used as a prognostic indicator and not as a guide for therapeutic interventions. The technique is recent and apparently promising but still require further clinical studies to support its routine use.

It is based on the knowledge that when there is local hypoperfusion and ischemia, there is a local increase in the production of H⁺ ions and lactate and an accumulation of CO₂. The CO₂ diffuses freely from the sublingual tissue to the tonometer, allowing its direct measurement (PgCO₂ or PsICO₂) and the calculation of the intramucosal pH (pHi) and the CO₂ gap (PgCO₂ – PaCO₂). The PgCO₂ and the CO₂ gap increase and the pHi decreases in situations of local hypoxia such as low flow conditions.

Sublingual capnometry has been shown to identify hemorrhagic shock and predict survival in several human studies, although it failed to identify hypovolemia in one human experimental study [36–38]. The reliability of sublingual PCO₂ as a marker of perfusion in clinical veterinary patients has not been determined. The advantages of sublingual capnometry include it being non-invasive, simple, easy to operate and with good correlation with gastrointestinal tonometry, serum lactate levels, and SvO₂. Its disadvantages include its newness, high cost, paucity of clinical experience with the method, a risk of infection (contamination of the solution with the capnoprobe) and it does not evaluate oxygenation. The PsICO₂ can only be correctly interpreted as an indicator of hypoperfusion in the light of PaCO₂ [39].

Hemodynamic Component of Pulse Oximetry

In addition to analyzing the respiratory component of pulse oximetry, the waveform generated by the pulse oximeter, the plethysmograph, permits the verification of some hemodynamic parameters especially relevant to the management of critical patients [40–42].

Even the systolic blood pressure can be measured with the aid of the oximeter. The system can be attached to a sphygmomanometer, and whenever the cuff is compressed, the plethysmographic curve will disappear. To deflate the cuff slowly, the first curve to appear on the

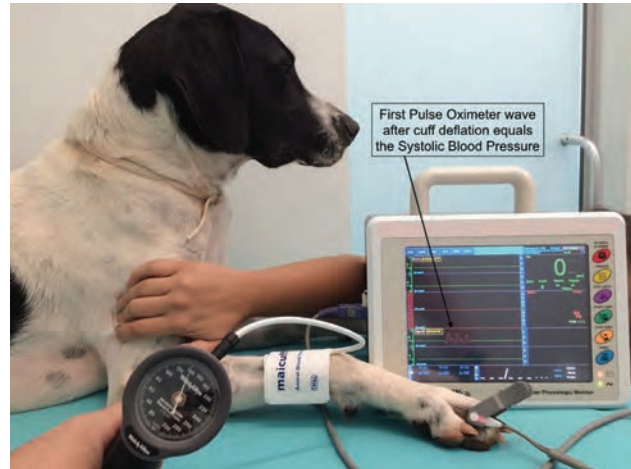


Figure 157.3 Pulse oximeter and sphygmomanometer used to check systolic blood pressure. Reproduced with permission of Pablo Ezequiel Otero.

monitor display will correspond to the systolic blood pressure, as shown in Figure 157.3.

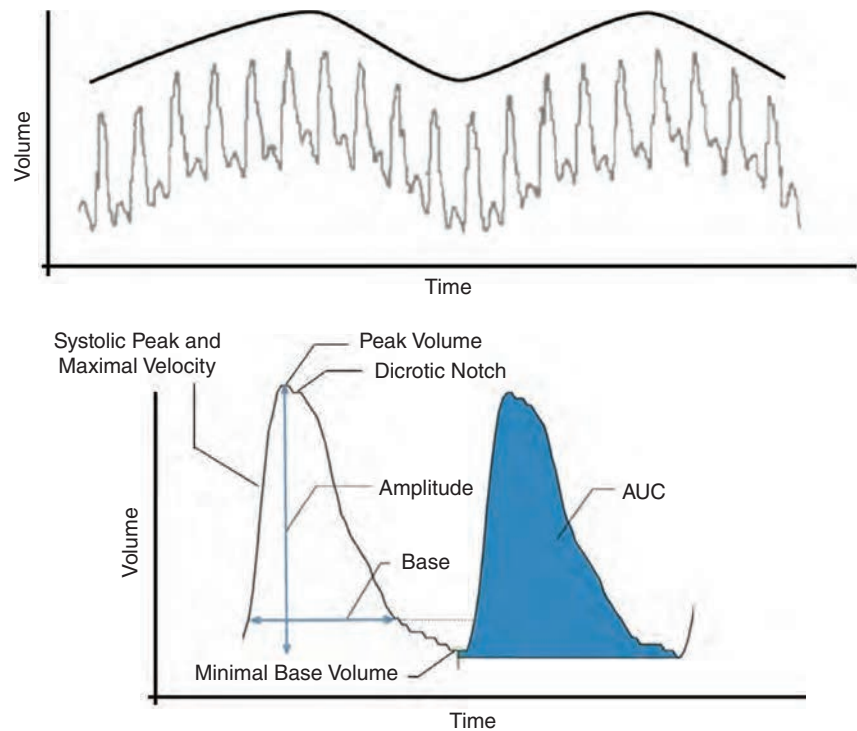
Even though it is similar, the pulse oximeter curve is only a virtual image and not a quantitative blood pressure curve. As the curve is constructed from the pulsation that generates the passage of blood through the tissue, it produces information about tissue flow. Since flow is a prerequisite for normal metabolic function, oximetry can be a relevant tool for emergency monitoring [43].

The plethysmograph draws two curves primarily. The pulse wave is a high-frequency curve that responds to pressure variations, becoming a specular image of the blood pressure curve. The low-frequency curve, which reflects the respiratory changes, the product of cyclical fluctuations promoted by the variations that experience the systolic discharge. Figure 157.4 identifies the two curves and describes the components of the plethysmograph's dynamics. The amplitude and the design of the curve (with its ascendant lift, the baseline and the area under the curve, AUC) will enable the correct interpretation of the whole system [43].

Plethysmogram Monitoring (Delta P_{pleth})

The changes in intrathoracic pressure that occur with the respiratory cycle are registered in a plethysmograph, by moving the baseline and modifying the amplitude of each wave. These variations are a reflection of the alterations of the central venous system during the respiratory cycle, directly affecting right atrial filling, which then affects the next volume to be

Figure 157.4 Components of the plethysmograph's dynamics. The amplitude and the design of the curve will enable the correct interpretation of the whole system. AUC, area under the curve.



ejected by the left ventricle, and reflected in time by the arterial pulse [44].

In spontaneous ventilation, during the inspiratory phase, the subatmospheric pressure produced in the thoracic cavity during inspiration draws both air and blood into the lungs. The blood is guided from the vena cava to the right circuit of the heart and then to the pulmonary vascular bed when a slight decline of peripheral venous pressure is registered. Simultaneously, the left ventricle decreases systolic ejection by 1–2 beats due to the retention of blood in the pulmonary circuit. In the expiratory phase, the positive pressure that occurs during expiration increases the systolic ejection, peripheral flow, amplitude, and peripheral venous pressure. Even if these changes are minimal, they can all be observed as a wave of lower frequency in the plethysmograph in association with inspiration [43,45–47].

During ventilation with positive pressure, changes recorded in the plethysmograph are exactly opposite to those observed during spontaneous ventilation.

The ΔP_{pleth} is determined by analyzing the plethysmographic curve obtained from the pulse oximetry during the respiratory cycle, under controlled mechanical ventilation, using the same principle of arterial pulse contour analysis [45,46]. As the plethysmographic curve

is obtained, the variation is calculated as a percentage of baseline amplitude obtained during apnea (without positive intrathoracic pressure):

Delta P_{pleth} Formula:

$$\Delta P_{\text{pleth}} (\%) = 100 \times (P_{\text{pleth}_{\text{max}}} - P_{\text{pleth}_{\text{min}}}) / [(P_{\text{pleth}_{\text{max}}} + P_{\text{pleth}_{\text{min}}}) / 2]$$

The ΔP_{pleth} should be 9–15% in normovolemic patients, and Figure 157.5 shows the relationship between the plethysmographic curve and breathing during mechanical ventilation [43,48].

In general, no dynamic indicator employed to identify which patients are responsive to fluid therapy should be considered reliable in patients with cardiac arrhythmias, as well as significant changes in the chest wall or pulmonary distensibility. Also, as previously mentioned, this type of measurement have been validated in human patients under mechanical ventilation and using the contour of the blood pressure curve as a guide, and will probably not be fully trusted in patients with spontaneous ventilation in the emergency setting. This technique should be used in association with all other available methods of hemodynamic monitoring [44,47,49].

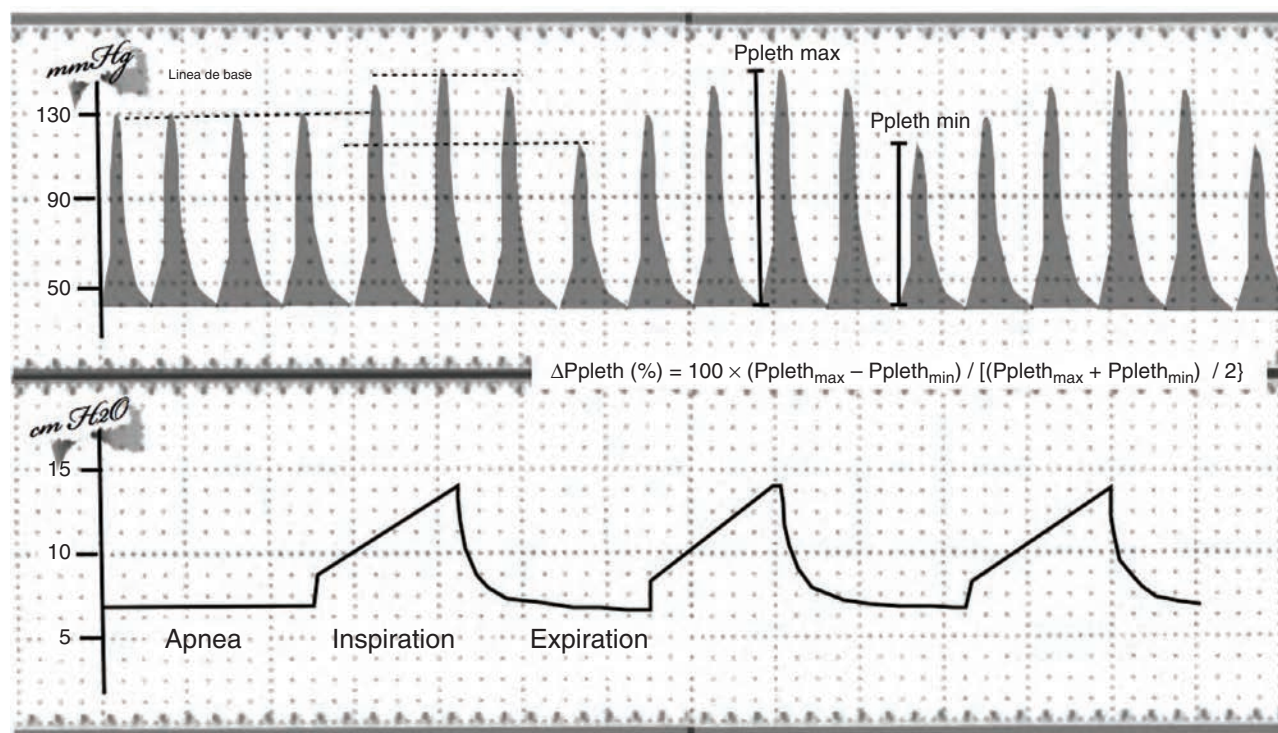


Figure 157.5 Relationship between the plethysmographic curve and breathing during a controlled ventilator cycle.

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Ischemia-Reperfusion Injury

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Pathophysiology

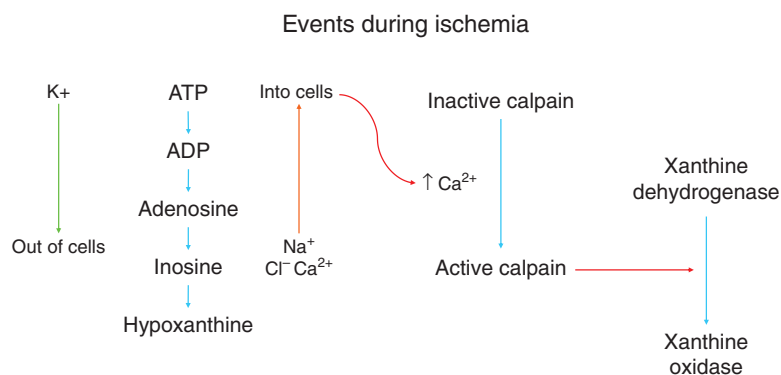
Ischemia-reperfusion injury (IRI) occurs secondary to an initial restriction or cessation of blood flow to an organ followed by a return of perfusion and oxygen delivery [1]. Ischemia reduces oxygen delivery resulting in tissue hypoxia, and initiates a series of events that prime cells for dysfunction and necrosis upon reintroduction of blood flow. During ischemia, anaerobic metabolism leads to accumulation of hydrogen ions, resulting in intracellular acidosis and subsequent enzyme dysfunction and damage to regulatory and membrane channel proteins. Failure of ATP generation and subsequent ATPase pump dysfunction result in potassium efflux and influx of sodium, chloride, and calcium [2]. Increased intracellular sodium concentrations induce water influx by diffusion, resulting in cellular swelling [3]. Cytoplasmic calcium concentrations increase through release from organelles and influx from extracellular fluid, facilitating reactive oxygen species (ROS) generation and initiating both apoptosis and necrosis [4].

During ischemia, available ATP is progressively degraded to adenosine, followed by inosine and then hypoxanthine (Figure 158.1). In health, hypoxanthine is

metabolized to urate by xanthine dehydrogenase (XD). In ischemic tissue, increased intracellular calcium concentrations activate calpain, which converts XD into xanthine oxidase (XO). Oxygen is required for XO-catalyzed metabolism of hypoxanthine. Thus in ischemic tissues, hypoxanthine cannot be metabolized normally and as hypoxia persists, both hypoxanthine and XO accumulate [2].

Reperfusion is necessary to restore oxygen delivery to ischemic tissues and increase ATP production, but it paradoxically worsens cellular injury and organ dysfunction. When oxygen is reintroduced, it enables XO to catalyze the conversion of water and hypoxanthine into urate and superoxide (Figure 158.2). A burst of ROS formation is seen within seconds of the onset of reperfusion wherein approximately 70% of the oxygen provided to the tissue is oxidized to superoxide by XO [3]. Xanthine oxidase is present in much higher amounts in dogs and rats compared to humans and rabbits, suggesting that it is a major player in canine reperfusion injury [2]. The superoxide formed can combine with nitric oxide to form peroxynitrite or be converted into hydrogen peroxide by superoxide dismutase (SOD). Catalase can then convert this hydrogen peroxide to water and oxygen, but hydrogen

Figure 158.1 During ischemia, ATP is sequentially hydrolyzed to hypoxanthine. The resultant reduction in available ATP leads to potassium efflux and movement of sodium, chloride, and calcium ions into cells. Increased intracellular calcium concentrations enable calpain activation which converts xanthine dehydrogenase to xanthine oxidase. These events cause cell dysfunction and swelling and set the stage for the damage that occurs following reintroduction of perfusion and an increased availability of oxygen and glucose. Reproduced with permission of John Wiley and Sons.



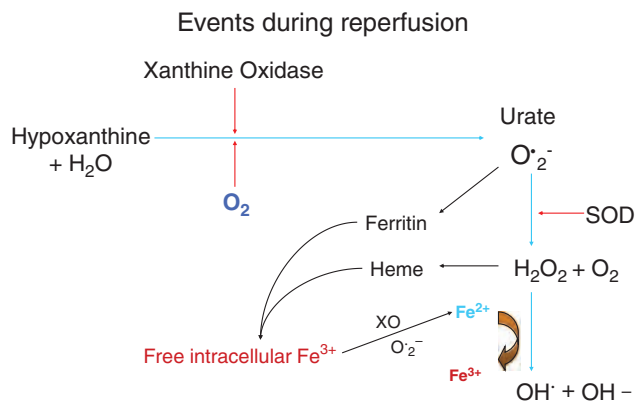


Figure 158.2 When oxygen availability increases following restoration of blood flow, the accumulated hypoxanthine is converted to urate and the superoxide radical by the action of xanthine oxidase. The superoxide radical can be converted into hydrogen peroxide by superoxide dismutase (SOD) or it can interact with ferritin to liberate intracellular ferric iron (Fe³⁺). The hydrogen peroxide produced by SOD is also able to liberate intracellular ferric iron from hemoglobin. This reduced iron species can be oxidized to ferrous iron (Fe²⁺). In turn, the ferrous iron enables the conversion of hydrogen peroxide into highly reactive hydroxyl radicals through a process that results in the regeneration of ferric iron that can continue to perpetuate the generation of further reactive oxygen species. Reproduced with permission of John Wiley and Sons.

peroxide can also combine with transition metals (usually free iron) to form the hydroxyl radical. Peroxynitrite and hydroxyl radicals are responsible for lipid peroxidation of cell membranes, oxidative damage to DNA, loss of membrane selective permeability, and degradation of structural proteins [2,5].

Neutrophils may mediate the majority of mucosal and microvascular injury with ischemia-reperfusion [1,6]. Neutrophils are attracted to ischemic tissue by XO and ROS and their infiltration is mediated by enhanced adhesion molecule expression. Activated neutrophils contribute to tissue injury in IRI through synthesis of additional ROS during the respiratory burst, with a 50–100-fold increase in oxidant production following exposure to micro-organisms or inflammatory mediators. Neutrophils also activate complement and release various proteolytic enzymes, including collagenases and elastases, that damage the vascular endothelium [7]. Neutrophils may also be responsible for the no-reflow phenomenon, characterized by diminished or absent blood flow in an area of tissue despite relief of prolonged vascular occlusion. This phenomenon may occur through neutrophils adhering to the endothelium and thereby inducing endothelial swelling, platelet activation, thrombus formation, and further neutrophil recruitment [8–10].

During episodes of ischemia, tissue hypoxia inhibits oxygen-sensitive enzymes, initiating signaling cascades

that control the transcription factor nuclear factor-kappa B (NF-kappa-B) [1]. Activation of NF-kappa-B leads to increases in inflammatory mediators and augmented expression of adhesion molecules, specifically intracellular adhesion molecule-1 and E-selectin [1,2]. During tissue ischemia-reperfusion, cyclo-oxygenase-2 (COX-2) is activated, leading to the formation of proinflammatory prostaglandins and ROS from arachidonic acid and the subsequent activation of phospholipase A₂. The cell death that accompanies IRI activates both the innate and adaptive immune systems via stimulation of the toll-like pattern recognition receptors (TLRs). During IRI, the TLRs are activated by interactions with damage-associated molecular pattern molecules including cfDNA, histones and high mobility group box 1 that are released from dying cells [1,11]. Activation of the TLRs results in production of inflammatory mediators, perpetuating tissue injury.

Tissues are protected from oxidative injury by antioxidant molecules, including proteins such as haptoglobin, ferritin, and ceruloplasmin [12], water-soluble compounds such as ascorbic acid (vitamin C) and glutathione [13], and fat-soluble molecules such as alpha-tocopherol (vitamin E), beta-carotene (vitamin A), and ubiquinol-10 [14]. Ultimately during IRI, however, the generation of ROS through the above mechanisms exceeds the capacity of the host antioxidant defenses. Lipid peroxidation, cell death, and accelerated inflammation result [15].

Disorders Associated with Ischemia-Reperfusion Injury

Ischemia-reperfusion injury likely contributes to the pathogenesis of a number of important emergent conditions of small animals (Table 158.1). A common cause is gastric dilation-volvulus (GDV) syndrome [16]. In animals with GDV syndrome, dilation and rotation of the stomach result in increased intragastric pressures and decreased venous return. This causes relative hypovolemia and obstructive shock as well as decreased gastric perfusion. Treatment of the condition involves restoration of intravascular volume, gastric decompression, and surgical correction. Irrespective of how these procedures are performed, reperfusion and hence IRI may result and can affect various organs including the stomach, intestines, spleen, liver, heart, and brain [17].

Reperfusion injury typically manifests within 3 hours of decompression [18]. In experimentally induced GDV syndrome, ATP concentrations in the fundus were not significantly different from baseline after 120 minutes of GDV, but were significantly reduced after 210 minutes. Interestingly, jejunal ATP concentrations were reduced

Table 158.1 Diseases in small animal emergency medicine associated with ischemia-reperfusion injury.

Disease process	Species affected	References
Arterial (aortic) thromboembolism	Cats > dogs	[21,22,24,26,88–97]
Cardiopulmonary arrest	Dogs, cats	[27,97]
Cardiopulmonary bypass	Dogs > cats	[98–106]
Crush injury	Dogs, cats	[33,107]
Diaphragmatic rupture with herniation	Cats > dogs	[108–111]
Gastric dilation-volvulus syndrome	Dogs	[17,81,112,113]
Intestinal incarceration/strangulation	Dogs, cats	[114,115]
Mesenteric volvulus	Dogs > cats	[116–118]
Myocardial infarction	Dogs, cats	[119,120]
Organ transplantation	Cats	[121–125]
Spinal cord injury	Dogs > cats	[126–129]
Traumatic brain injury	Dogs, cats	[130–133]

within 120 minutes of GDV syndrome induction, concomitant with more severe mucosal injury, suggesting that the intestine may be compromised at least as quickly as the stomach with GDV syndrome [19]. Biomarkers of oxidative stress and antioxidant status have been assessed clinically in patients with GDV syndrome [20]. Consistent with IRI occurring in these patients, there were significant reductions in concentrations of key antioxidants including tocopherol and ascorbate during hospitalization.

Arterial thromboembolism (ATE) is a debilitating and potentially fatal complication of critical illness. Typically with ATE, thrombosis or embolization interrupts blood flow to the iliac arteries, although other vascular beds can be affected. ATE occurs most commonly secondary to feline cardiomyopathy [21], although low plasma arginine concentrations have also been associated with ATE [22]. This is potentially significant, because low arginine levels may contribute to increased platelet aggregation and potentiate IRI [23]. Thrombolytic therapy has been attempted in feline patients with ATE, but the complication rate is high. Reported adverse effects include hyperkalemia, azotemia, neurological signs, arrhythmias, acidosis, and sudden death (see Chapter 62) [24–26].

Reperfusion injury contributes significantly to the challenges faced after return of spontaneous circulation (ROSC) following cardiopulmonary arrest (CPA) [27]. During CPA, blood flow ceases and widespread ischemia occurs. After ROSC is achieved, oxygenated blood returns to ischemic, vasodilated tissues. In this setting, normoxic reperfusion in CPA is less damaging than hyperoxic reperfusion [28].

Myocardial infarction (MI) is an uncommon condition in dogs compared to humans [29], although dogs have been commonly used as models for MI in people. Myocardial ischemia causes the release of chemotactic factors with subsequent neutrophil migration, lipid peroxidation, and antioxidant depletion [30]. The invading neutrophils generate ROS and result in further injury to the vessels of the heart. Experimental studies in canine models have shown that administration of superoxide dismutase plus catalase reduced infarct size if given up to 75 minutes after occlusion [30]. A follow-up study showed that SOD had an equivalent effect to the combination, suggesting that IRI with MI is mediated principally by superoxide [31].

Although infrequent, crush injuries can result in IRI from reperfusion of skeletal muscles after removal of the crushing force [32]. Given the potential for crush injury with bite trauma, it is possible that IRI may also contribute to the pathogenesis of bite injuries. Crushed, ischemic tissue is markedly inflammatory such that following reperfusion, neutrophils invade in large numbers. The inflammation generated by the crush injury activates these neutrophils, leading to generation of high ROS concentrations that result in myocyte lipid peroxidation, myoglobin release, and subsequent myoglobinuria [33].

Ischemia-reperfusion injury likely contributes to the pathogenesis of spinal cord injury (SCI), myelomalacia, and ischemic myelopathy [34]. Previous landmark clinical trials in people evaluated the use of high-dose methylprednisolone sodium succinate (MPSS) to mitigate lipid peroxidation in SCI [35]. Although these data remain controversial, MPSS had no meaningful beneficial impact on outcomes in SCI and is not currently recommended [36].

Traumatic brain injury (see Chapter 19) can cause IRI due to ischemia that results from primary brain injury or develops secondary to excitotoxic or vasogenic edema formation and subsequent alterations in cerebral perfusion [36]. Given the very high brain lipid content and the limitations of neuronal repair and regeneration, cerebral IRI can have profound consequences. During cerebral IRI, alterations of endothelial cell reactivity, coagulation system activation, and granulocyte–endothelial cell interactions have been shown to affect the microvascular of the brain [37].

Identification of Ischemia-Reperfusion Injury

While the detrimental downstream effects of IRI on organ function may be readily apparent [38], specific identification of IRI is challenging. Various methods have been reported including measurement of reaction products, markers of oxidative stress, endogenous antioxidants, or markers of inflammation [39]. Few are widely available, straightforward to use, or well validated [40]. Although ROS can be measured directly [41], their high reactivity results in a fleeting existence that precludes easy quantification. Therefore, most methods focus on the downstream effects of IRI and ROS generation.

Measurement of reaction products involves measurement of malondialdehyde (MDA) or isoprostanes. Malondialdehyde forms when endoperoxides combine with unsaturated fatty acids and free iron and indicates that lipid peroxidation (although not necessarily IRI) has occurred. Measurement of MDA can be performed with the thiobarbituric acid reactive substances test or by ELISA and has been used to evaluate oxidative stress in dogs with hemolytic anemia, heart failure, nephrotoxicity, and parvoviral enteritis [42–45]. Measurement of MDA as a marker of IRI is confounded by generation of the compound *ex vivo* and as a result of thromboxane synthesis [40].

Isoprostanes are prostaglandin-like compounds formed when ROS oxidize cell membrane arachidonic acid. Isoprostanes, particularly F₂ forms, are considered a more reliable measurement of lipid peroxidation *in vivo* than MDA [46]. Isoprostane measurement has been used to identify lipid peroxidation in dogs with spinal cord injury [47,48], lymphoma [49], and critical illness [50]. However, they are best measured by mass spectrometry [51], which limits their clinical utility.

Detection of low levels of endogenous antioxidants offers an alternative means to assess a patient’s oxidative stress. Glutathione occurs in the body in two forms: a reduced form (GSH) and an oxidized form (GSSG). In IRI, more glutathione will exist as the oxidized form, such that the ratio of the two forms can be used to determine the level of oxidative stress occurring [52]. This method is susceptible to spontaneous oxidation *ex vivo*, which artifactually increases the concentrations of GSSG. Measurements of glutathione have been used to identify oxidative stress in patients with GDV syndrome [20], critical illness [53], and various infectious and parasitic diseases [54–57]. Measurements of blood tocopherol concentrations also provide insight into IRI-induced oxidative stress. Abnormally low tocopherol concentrations have been identified in dogs with lymphoma [49], mast cell tumor [58], anesthesia [59], and in dogs enduring intense exercise [60]. In racing sled dogs, supplementing vitamin E prior to exercise can increase antioxidant

levels post race [61], although the clinical relevance of this is unclear.

Numerous additional biomarkers have been evaluated for assessment of IRI, including tumor necrosis factor-alpha, interleukin (IL)-1, IL-6, IL-8, transforming growth factor-beta and cell-free DNA (cfDNA) [62,63]. Concentrations of these biomarkers can vary greatly during the course of illness, however. Many of these substances are labile and for some, their measurement is time-consuming and expensive [64]. Point-of-care tests for cfDNA hold promise for assessing patients with traumatic brain injury, sepsis, and cardiopulmonary arrest [65–67], although more work remains to be done validating cfDNA in IRI patients before it can be considered an alternative to standard testing [68]. As with many complex processes, maximum diagnostic accuracy may be obtained through the measurement of a panel of assays including peroxidation reaction products, antioxidants, and inflammatory markers. Such in-depth analyses are expensive and time-consuming and currently remain predominantly in the research realm.

Management of Ischemia-Reperfusion Injury

Numerous drugs and therapies have been evaluated for the prevention and treatment of IRI (Table 158.2) [69].

Table 158.2 Proposed therapies for IRI.

Proposed therapy	Disease or model studied	References
N-acetylcysteine	Canine myocardial dysfunction post CPA	[74]
Allopurinol	Feline intestinal ischemia, canine GDV syndrome	[84,112]
Deferoxamine	Canine experimentally induced GDV syndrome	[81]
DMSO	Canine GDV syndrome, renal ischemia	[81]
Hypothermia	Canine myocardial ischemia	[134]
Ischemic preconditioning	Canine myocardial ischemia	[135]
Ketamine	Canine cerebral ischemia	[136]
Lazaroids	Canine stroke, subarachnoid hemorrhage, sepsis	[137–140]
Lidocaine	Canine GDV syndrome	[71,72]
Nicardipine	Canine cerebral ischemia	[141]
Vitamin C	Canine renal transplant	[142]
Vitamin E	Canine ischemic stroke	[143]

CPA, cardiopulmonary arrest; DMSO, dimethyl sulfoxide; GDV, gastric dilation-volvulus.

Many have demonstrated promise in preclinical evaluations that use model systems, but most have failed once applied to real-world situations in human and veterinary clinical trials. In some cases, the therapy is effective only if given before the IRI injury occurs – a scenario that is rarely possible in clinical medicine. Here we discuss the therapies for which there is some evidence of benefit or where more work appears warranted.

Lidocaine

Lidocaine is an attractive therapy for the treatment of IRI because of its multimodal effects [70]. Lidocaine is a use-dependent fast sodium channel antagonist used as a local anesthetic and a class Ib antiarrhythmic agent. Additionally, it is an antagonist of ATP-sensitive potassium channels, a scavenger of superoxide and hydroxyl radicals, an inflammatory modulator, and an inhibitor of granulocytes [70].

There is moderate evidence for the prophylactic use of lidocaine in patients with GDV syndrome. Two studies have been performed. The first, a retrospective study, evaluated IV lidocaine administered after medical treatment and decompression, but before surgery [71]. That study showed no difference in complication rate or mortality between treated and untreated groups. The second study was a prospective trial that implemented lidocaine prior to fluid therapy and gastric decompression [72]. When administered prior to decompression and hence before the likely peak of reperfusion injury, lidocaine treatment significantly decreased the incidence of kidney injury, cardiac arrhythmias and coagulation disorders and shortened hospitalization. There was no significant effect on mortality, although the study was not powered to detect such a benefit [71,72].

N-Acetylcysteine

N-acetylcysteine (NAC) is a glutathione precursor that penetrates into cells and acts to replenish intracellular glutathione concentrations. Such increases in glutathione availability may result in improved cellular antioxidant capabilities. In experimental models, NAC reduces cardiopulmonary bypass-induced lung injury, preserves systolic function, and reduces myocardial edema in cardiopulmonary arrest [73,74]. Administration of NAC to critically ill dogs significantly increased glutathione availability but did not affect illness severity or outcome, although the study was likely underpowered to detect such differences [50]. Although dogs with spinal cord injury have demonstrable oxidative stress, administration of NAC intravenously before hemilaminectomy has no effect on urinary isoprostane excretion or neurological outcome [75].

Currently, the evidence for safety of NAC is excellent, but the evidence for efficacy of clinically meaningful endpoints is equivocal. Until further studies are conducted, the use of NAC is a reasonable pragmatic choice.

Ischemic Preconditioning

Ischemic preconditioning is a process by which short, controlled episodes of ischemia and reperfusion prime tissues in an effort to protect them from subsequent damage during IRI [76]. Preconditioning has most frequently been studied in myocardial ischemia models, with promising early results. In dogs, preconditioned hearts appear to have improved antioxidant capacity with less severe IRI following subsequent ischemia [77]. At this time, preconditioning has not been clinically studied in veterinary medicine, but two recent human clinical trials suggest the benefits may not translate from bench to bedside [78,79]. The reason is unclear, but may relate to patient heterogeneity, intercurrent disease or the limited benefit attainable from any one novel intervention [80].

Deferoxamine

During ischemia, intracellular iron bound to ferritin is released. Superoxide and hydrogen peroxide generated during reperfusion also mobilize iron from ferritin and heme, respectively, resulting in large amounts of free iron following reperfusion. Ferric iron (Fe^{3+}) is required for the Haber–Weiss reaction that results in formation of the hydroxyl radical, a potent oxidizing agent principally responsible for lipid peroxidation [2,40]. Deferoxamine, an iron chelator, has been evaluated experimentally in the treatment of IRI associated with GDV syndrome and was shown to decrease mortality, but the safety and clinical efficacy of this treatment have not been assessed [81].

Allopurinol

Allopurinol is a potent XO inhibitor that has been shown to attenuate the IRI in canine liver [82] and myocardium [83], and feline intestine [84]. The evidence to date, however, suggests that allopurinol may only be efficacious when used as a pretreatment. Clinical studies in which allopurinol is administered after or during IRI are lacking, and hence there is currently little to support its use in veterinary patients.

Cyclosporine

Cyclosporine is a calcineurin inhibitor that decreases activity of lymphocytes, especially T-cells. Calcineurin mediates calcium-triggered apoptosis in cells deprived of growth factors and is likely to be involved in the

initiation of calcium-triggered apoptosis in IRI [4]. As such, there has been considerable interest in the potential use of calcineurin inhibitors to reduce IRI. Cyclosporine is also hypothesized to inhibit the opening of mitochondrial permeability-transition pores, and attenuate lethal myocardial injury associated with reperfusion in patients with myocardial infarction [29].

An initial small-scale prospective trial in people assessed the use of cyclosporine at the time of percutaneous coronary intervention, and demonstrated a reduction in the infarct size in the treatment group [85]. A larger follow-up study was unable to confirm this potential benefit, however [86]. The drug is widely used as an immunosuppressive in veterinary medicine and there are some experimental data suggesting efficacy in canine IRI model systems [82], but there are currently no studies investigating its use as an agent for IRI in veterinary patients.

Remifentanyl

Remifentanyl is a short-acting mu-agonist opioid that is degraded by plasma and tissue esterases. It has been investigated in mouse models as a preconditioning agent for IR injury with intestinal ischemia. Initiation of remifentanyl prior to reperfusion of mouse intestines

was associated with decreased destruction of villi and IR injury [87]. This therapy has not yet been investigated clinically in veterinary or human medicine.

Conclusions and Clinical Recommendations

In IRI, tissue injury results from both diminished blood flow (ischemia) and subsequent reperfusion. Ischemia damages cells and primes tissue for injury following restoration of blood flow wherein generation of reactive oxygen species and activation of the innate immune system occur. Commonly associated conditions include GDV syndrome, feline arterial thromboembolism, and brain and spinal cord injury. Reperfusion injury can be difficult to identify, and the necessary biochemical testing is rarely conducted in a clinical setting. It is reasonable to assume that IRI has occurred or will occur during the management of patients with associated conditions and hence therapy may be initiated on an empiric basis. Evidence of efficacy is lacking for the majority of available therapies. Evidence exists supporting the use of lidocaine in dogs with GDV syndrome and may support the use of N-acetylcysteine in GDV syndrome and in other disease processes associated with IRI.

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Systemic Inflammatory Response Syndrome, Sepsis, and Multiple Organ Dysfunction Syndrome

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Introduction

The systemic inflammatory response syndrome (SIRS) and sepsis are surprisingly common and associated with high morbidity and mortality in dogs and cats [1,2]. Dogs and cats commonly present to veterinary emergency rooms (ERs) with evidence of SIRS and it is vital for the emergency veterinarian to take an aggressive diagnostic and treatment approach to these patients in order to maximize the likelihood of a successful outcome. Identifying the underlying cause of SIRS and, specifically, differentiating infectious from non-infectious causes of SIRS, as well as recognizing organ dysfunction(s), are vital to guide appropriate and timely treatment.

Definitions

The current definitions for SIRS and sepsis used in veterinary medicine are derived from those originally published in human medicine [3,4]. Of note, revised definitions of sepsis and septic shock were recently introduced in human medicine (Sepsis-3) [5], so it is likely that the current veterinary definitions, used below, will ultimately be reconsidered.

Systemic inflammatory response syndrome is a clinical diagnosis, made on the basis of abnormalities in vital signs and white blood cell count. While specific criteria are published [6–10], there is no consensus in veterinary medicine; what denotes SIRS varies between species and publications (Table 159.1). Essentially, SIRS is considered present if the animal fulfills two (dogs) or three (cats) out of the four following SIRS criteria: (1) abnormal temperature, (2) abnormal heart rate, (3) tachypnea; and/or (4) a change in the leukon [6–10]. Sick cats with SIRS and sepsis are more likely to be hypothermic and bradycardic than dogs [9]. Since the primary aim of

having SIRS criteria is to flag patients that are systemically unwell and require prompt attention, the exact cut-off points for these parameters are less important than the overall assessment of the patient in light of their signalment, history, and physical examination findings.

Sepsis is the systemic inflammatory response to infection. Diagnosis of sepsis requires identification (or a high index of suspicion) of infection and fulfillment of SIRS criteria.

Severe sepsis is the presence of sepsis with decreased perfusion to the tissues and/or organ dysfunction(s). While there is no consensus definition for what denotes organ dysfunctions in veterinary medicine, various parameters have been suggested by different authors [1,5,11] (see Table 159.1).

Septic shock is said to occur in patients with sepsis and persistent arterial hypotension that is non-responsive to intravascular volume expansion; by definition, patients with septic shock are vasopressor dependent.

Multiple organ dysfunction syndrome (MODS) is defined as two or more dysfunctional organs in patients with SIRS or sepsis (Table 159.2) [1,5,11].

The changes in the Sepsis-3 definitions in human medicine occurred so as to remove an excessive focus on inflammation as the pathological process in sepsis, and move away from the misleading model that sepsis follows a continuum from sepsis, through severe sepsis, to septic shock, amongst other reasons [12].

As part of the new consensus definitions, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. With this change, the term *severe sepsis* becomes superfluous. Sepsis-3 also includes a lay definition of sepsis as a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs. In the new definition, organ dysfunction is identified as any acute change in total Sequential Organ

Table 159.1 Criteria for the systemic inflammatory response syndrome (SIRS) used in dogs and cats by various authors.

Criteria	Dogs (2/4 criteria)			Cats (3/4 criteria)	
	Hauptman et al. 1997 [13]	de Laforcade et al. 2003 [14]	Okano et al. 2002 [15]	Brady et al. 2000 [16]	DeClue et al. 2011 [17]
Temperature (°F/°C)	> 102.2 °F (>39 °C)	> 103 °F (>39.4 °C)	> 103.5 °F (>39.7 °C)	> 103.5 °F (>39.7 °C)	≥ 103.5 °F (>39.7 °C)
• Fever					
• Hypothermia	< 100.4 °F (<38 °C)	< 100 °F (<37.8 °C)	< 100 °F (<37.8 °C)	< 100 °F (<37.8 °C)	≤ 100 °F (<37.8 °C)
Heart rate (beats/min)	> 120	> 140	> 160	> 225	≥ 225
• Tachycardia				< 140	≤ 140
• Bradycardia					
Respiratory rate (breaths/min)	> 20	> 20	> 40	> 40	≥ 40
• Tachypnea					
White blood cell count (cells/μL)	> 16 000	> 16 000	> 12 000	> 19 500	≥ 19 500
• Leukocytosis	< 6000	< 6000	< 4000	< 5000	≤ 5000
• Leukopenia	> 3%	> 3%	> 10%	> 5%	≥ 5%
• Band neutrophils (% bands)					

Table 159.2 Specific treatment considerations for organ dysfunctions that can occur in patients with SIRS and sepsis.

Organ dysfunction	Possible manifestations of organ dysfunction requiring treatment	Objective characterization of dysfunction	Treatment considerations
Cardiovascular dysfunction	Septic shock	MAP < 65 mmHg despite IV fluid resuscitation	Vasopressor agents
	Decreased myocardial contractility/myocardial dysfunction	Vasopressor dependence Decreased fractional shortening, ejection fraction Biventricular dilation Increased cTnI	Positive inotropes
Coagulation dysfunction (DIC)	Malignant cardiac arrhythmias	Recognized on ECG	Antiarrhythmics
	Hypercoagulable state • Thromboembolic events possible	Hypercoagulable trace on viscoelastic testing Decreased endogenous anticoagulants (AT, aPC) Increased D-dimers	Antithrombotics (e.g. heparin, clopidogrel, aspirin)
	Hypocoagulable state/ consumptive coagulopathy • Bleeding possible	Prolonged clotting times (PT, aPTT) Thrombocytopenia (Plt count ≤ 100,000/μL) Hypocoagulable trace on viscoelastic testing	Blood product transfusion if hypocoagulable and bleeding or prior to an invasive procedure
Endocrine dysfunction	Hypoglycemia	BG < 60 mg/dL (3.3 mmol/L)	IV glucose supplementation
	Hyperglycemia	BG > 180 mg/dL (10 mmol/L)	Insulin therapy
	Critical illness-related corticosteroid insufficiency (CIRCI)	Low delta cortisol on ACTH stimulation test	Physiological hydrocortisone therapy

(Continued)

Table 159.2 (Continued)

Organ dysfunction	Possible manifestations of organ dysfunction requiring treatment	Objective characterization of dysfunction	Treatment considerations
Gastrointestinal dysfunction	Vomiting		Antiemetics (e.g. maropitant, ondansetron, dolasetron)
	Regurgitation, functional ileus, intolerance of enteral nutrition	Increased gastric residual volumes	Prokinetics (e.g. metoclopramide, erythromycin)
	Gastrointestinal ulcers		Antacids (e.g. PPIs, H ₂ RAs) Sucralfate
	Diarrhea		Generally no specific therapy indicated
	Constipation		Laxatives, enemas
Hepatobiliary dysfunction	Icterus	Hyperbilirubinemia (TBili >0.5 mg/dL)	No clear role for specific therapy
	Increased hepatic transaminases (esp. ALT)		
	Impaired synthetic function		
Neurological	Seizures		Antiepileptic drugs
	Encephalopathy/impaired level of consciousness		
	Delirium		
Pulmonary dysfunction	Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)	A-a gradient > 10 mmHg	Oxygen supplementation
		SpO ₂ < 95% (FiO ₂ 0.21)	Lung protective mechanical ventilation
		P/F ratio < 300 mmHg	
Kidney dysfunction	Acute kidney injury (AKI)	Oliguria, anuria	Consider diuretic therapy (e.g. furosemide, fenoldopam)
		Rise in [Creatinine] > 0.3–0.5 mg/dL, in the absence of prerenal or postrenal causes	Continuous renal replacement therapy or intermittent hemodialysis
Vascular/endothelial dysfunction	Endothelial glycocalyx damage, vascular leak		No specific therapy at this time

ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; BG, blood glucose; Cr, creatinine; cTnI, cardiac troponin I; H₂ RAs, H₂ receptor antagonists; MAP, mean arterial pressure; PPI, proton pump inhibitor; PT, prothrombin time; TBili, total bilirubin; UOP = urine output.

Failure Assessment (SOFA) score ≥ 2 points as a result of the infection. And finally, septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Based on the new definitions, patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mmHg and having a serum lactate > 2 mmol/L (18 mg/dL) despite adequate volume resuscitation. In addition, hospitalized patients can be screened for sepsis using a quick SOFA (qSOFA) consisting of an abnormal Glasgow Coma Scale Score, increased respiratory rate, and decreased blood pressure.

Pathophysiology

The SIRS, sepsis, and MODS share common pathogenic processes, although the clinical spectrum of disease is extremely varied. When inflammation in response to an insult has systemic effects, rather than remaining localized to the site of the insult, the resultant clinical manifestations are characterized as SIRS. Explained most simply, SIRS refers to a systemic proinflammatory state, inadequately controlled by endogenous anti-inflammatory responses. Although localized inflammation is a protective response to tissue injury, systemic inflammation is often deleterious. Sustained systemic inflammation can result in organ

dysfunctions, and it is generally MODS that causes mortality in these patients.

Systemic inflammatory response syndrome can be the result of a non-infectious or an infectious insult (sepsis). Table 159.3 displays common causes of SIRS and sepsis in dogs and cats. Non-infectious SIRS and sepsis can be challenging to differentiate clinically because their pathophysiology is almost identical, with the exception only of the initial insult [13]. In patients with sepsis, pathogen-associated molecular patterns (PAMPs), expressed by the pathogen, stimulate pattern recognition receptors (PRRs), such as the toll-like receptors (TLRs), in the host. PAMPs include motifs such as lipopolysaccharide on gram-negative bacteria. Although most clinicians commonly think of bacterial causes of sepsis, viruses, fungal organisms, and parasites also have PAMPs that

stimulate receptors of the host's innate immune system and can trigger SIRS. Stimulation of PRRs drives an intracellular signaling cascade that ultimately results in the upregulation of nuclear transcription of a variety of inflammatory mediators.

The inflammatory mediators of SIRS include cytokines, chemokines, vasoactive substances, and mediators of coagulation. Prototypical proinflammatory cytokines include tumor necrosis factor and interleukins-1 and 6; these cytokines contribute to the development of fever, leukocyte production and activation, cardiovascular instability, increased vascular permeability, and acute-phase protein synthesis. Chemokines induce neutrophil chemotaxis to sites of inflammation. Vasoactive substances released include inducible nitric oxide (NO), a potent vasodilator. Stimulation of inflammation also activates coagulation [14].

In non-infectious SIRS, tissue damage results in the expression or release of damage-associated molecular patterns (DAMPs) on/from host cells. DAMPs include cellular components such as heat shock proteins, high mobility group box 1 protein, ATP, and DNA. DAMPs also stimulate PRRs, initiating the same intracellular signaling cascades as PAMPs to produce SIRS.

Multiple organ dysfunction syndrome is a multifactorial phenomenon that occurs secondary to both non-infectious SIRS and sepsis. MODS refers to the presence of two or more dysfunctional organs in an acutely ill patient such that homeostasis cannot be maintained without intervention [3]. Organ dysfunctions result from inflammation, decreased tissue oxygen delivery (DO_2), energetic failure (impaired mitochondrial function), heterogenous microvascular flow, apoptosis, and microthrombosis.

Coagulation dysfunction and disseminated intravascular coagulation (DIC) in patients with systemic inflammation are due to the concurrent activation of coagulation, with an initial prothrombotic phase, followed by a consumptive coagulopathy (see Chapter 70) [14]. Endothelial activation also likely contributes to a hypercoagulable state *in vivo*. Microvascular thromboses and hemorrhage in turn can contribute to other organ dysfunctions (see Chapter 62). Cardiovascular dysfunction and septic shock are at least in part explained by the actions of NO. Additionally, critical illness-related corticosteroid insufficiency (CIRCI) causes vascular hyporeactivity [15,16]. Respiratory dysfunction is explained by leukocyte infiltration and fluid leak into alveoli, as well as impaired blood flow in the pulmonary circulation associated with thrombosis, leading to diffusion impairment and ventilation/perfusion mismatch (see Chapter 42) [17,18]. Other organ dysfunctions such as acute kidney injury (AKI) (see Chapter 94), and acute hepatic dysfunction are less well understood (see Chapter 90) [19].

Table 159.3 Commonly recognized causes of non-infectious SIRS and sepsis in dogs and cats. Some of these disorders are also covered in other chapters.

Non-infectious SIRS	Sepsis
Trauma <ul style="list-style-type: none"> • Blunt trauma (e.g. motor vehicle accident) • Penetrating trauma (e.g. gunshot wounds) • Surgical/iatrogenic trauma 	Peritonitis/abdominal sepsis <ul style="list-style-type: none"> • Gastrointestinal perforation • Septic bile peritonitis when an infected biliary tract ruptures • Rupture of infected urogenital tract
Neoplasia	Pneumonia
Pancreatitis	Pyothorax
Immune-mediated diseases	Pyometra
Submersion injury	Prostatitis/prostatic abscess
Electrocution	Pyelonephritis
Burn injury	Lower urinary tract infection
Heatstroke	Hepatic abscess
Ischemic diseases <ul style="list-style-type: none"> • Gastric dilation-volvulus (GDV) • Splenic torsion • Mesenteric volvulus • Colonic torsion • Thromboembolic disease 	Skin and soft tissue infections, including necrotizing fasciitis
Transfusion reactions	Rickettsial diseases <ul style="list-style-type: none"> • Babesiosis, ehrlichiosis, and others
Toxicoses and adverse drug reactions	Systemic mycoses
Anaphylaxis	Systemic viral infections
Envenomation	Systemic protozoal and parasitic infections

Diagnostic Approach to SIRS and Sepsis

The history and clinical signs of dogs and cats that present with SIRS and sepsis are often non-specific and vary depending on the underlying disease process. The presenting complaint of the animal may be quite vague, including symptoms such as lethargy, depression, and inappetence. Vomiting and diarrhea may be due to gastrointestinal tract disease or secondary to the systemic disease (i.e. extragastrointestinal in origin). As with any case presenting on an emergency basis, identifying clinical signs that localize the primary problem to a body system is invaluable, if possible, to guide the diagnostic process.

Physical examination of patients with SIRS and sepsis reflects the systemic inflammatory state with possible derangements in temperature, heart rate, and respiratory rate as discussed. Dehydration and/or evidence of shock are also common. Assessing perfusion parameters (level of consciousness, heart rate, pulse quality, oral mucous membrane color, and capillary refill time (CRT)) should be a priority of the initial physical examination, since treatment of shock should be initiated immediately (see Section 4B, Circulatory Shock). Dogs present most commonly in the early decompensatory phase of shock, with pale mucous membranes, prolonged CRT, and weak pulses. That being said, a hyperdynamic state of shock or vasodilatory shock can also be present in dogs with SIRS and sepsis, resulting in hyperemic mucous membranes, a rapid CRT (<1 sec), and strong or bounding pulses. Concurrent dehydration (if present) will manifest as abnormalities such as dry mucous membranes, increased skin tenting, dehydrated abdominal contents and sunken eyes, and should be addressed following resuscitation from shock (see Chapter 171).

Point-of-care diagnostic tests such as measurement of blood pressure, blood lactate (see Chapter 156), and venous blood gases are often performed concurrent with the initial physical examination and patient stabilization. Hypotension and/or hyperlactatemia may be present in patients with compromised perfusion, and should prompt an aggressive approach to improve DO_2 . Pulse oximetry and arterial blood gas analyses are usually performed in animals with evidence of respiratory compromise.

Screening diagnostic tests, including a complete blood count, blood smear, biochemistry profile, urinalysis, and coagulation tests, are also part of the initial diagnostic approach to a systemically unwell patient. Screening diagnostics are performed to assess for the presence of underlying disease, identify abnormalities requiring treatment, and assess for the presence of organ dysfunctions. Hematological and biochemical abnormalities typically reflect the underlying disease process and derangements in organ dysfunction secondary to SIRS. Hematological abnormalities may include abnormalities in the leukon (see Table 159.3) and toxic changes in leukocytes. Hemoconcentration consistent with hypovolemia

and splenic contraction (dogs) may be present, while anemia may reflect chronic underlying disease, blood loss or hemolysis. Thrombocytopenia is common.

Biochemical abnormalities may include hypoalbuminemia, dysglycemia, ionized hypocalcemia, and hyperbilirubinemia. Hypoalbuminemia is generally multifactorial but thought to be associated with albumin's status as a negative acute-phase protein (i.e. decreased hepatic synthesis), and increased loss (e.g. gastrointestinal, urinary or into body cavity effusions). Hypoglycemia tends to be a terminal finding in dogs and cats with SIRS and sepsis, reflecting increased consumption and/or decreased hepatic synthesis. Hyperglycemia is more common and may reflect decreased insulin sensitivity, and the effects of high circulating concentrations of cortisol and catecholamines (i.e. stress hyperglycemia). Ionized hypocalcemia is thought to be predominantly due to hypovitaminosis D [20]. Hyperbilirubinemia may be secondary to intrahepatic cholestasis or hemolysis [9,21]. Azotemia with isosthenuria may reflect underlying chronic kidney disease or AKI. Kidney injury may be direct and primary (e.g. pyelonephritis) or an organ dysfunction secondary to SIRS. Urine sediment evaluation should be performed and urine collected by cystocentesis should be submitted for culture and susceptibility testing to screen for a urinary tract infection.

Coagulation testing is also commonly performed in veterinary patients with SIRS and sepsis (see Chapter 70). The hypercoagulable phase of DIC may be detected by hypercoagulable tracings on viscoelastic tests. Increased D-dimers suggest the formation and subsequent degradation of fibrin clots. Reduced circulating concentrations of endogenous anticoagulants, such as activated protein C (aPC) and antithrombin, also suggest a hypercoagulable state [7]. A hypocoagulable state can also be documented using viscoelastic tests, but is more commonly characterized by prolongations in prothrombin time and activated partial thromboplastin time.

Identification of the SIRS criteria in a patient should prompt a search for the underlying cause, either non-infectious or infectious. In order to diagnose sepsis, a patient must fulfill SIRS criteria and have a confirmed (or highly suspected) infection. Definitive diagnosis of bacterial infection requires identification of bacteria by cytology, histopathology or culture, while definitive diagnosis of infections with other types of pathogens may involve ancillary diagnostics such as identification of pathogen antigen, DNA or RNA in the host, or an antibody response suggestive of acute infection. In some cases, the underlying cause of systemic inflammation is immediately obvious, while in others it is not and exhaustive diagnostics are required. The preliminary search for infection may include point-of-care infectious disease testing, screening ultrasound, thoracic radiographs, abdominal ultrasound, and urine sediment examination.

Further testing based on these initial diagnostics may include additional infectious disease testing, spinal radiographs, and echocardiogram.

Point-of-care infectious disease testing in an animal with SIRS should include testing for feline immunodeficiency virus and feline leukemia virus in cats, and tick-borne pathogens (*Borrelia burgdorferi*, *Anaplasma phagocytophilum*, and *Ehrlichia canis*) in dogs in endemic areas. Send-out testing for other rickettsial diseases, fungal, viral and other pathogens may also be indicated. Fecal diagnostics can be used to screen for pathogens in-house and are particularly indicated in patients with SIRS and diarrhea as a prominent clinical sign. Fecal immunoassays are available for canine parvovirus (which cross-reacts with feline panleukopenia virus), and *Giardia*. Routine fecal diagnostics such as fecal floatation, fecal cytology, and wet-prep may also be useful.

Ultrasound examinations can be used in the ER (see Chapter 182) to evaluate for cavitory effusion or other obvious abnormalities. Standard approaches to using ultrasound in the veterinary ER are described for the thorax (thoracic focused assessment with sonography for trauma, tFAST), abdomen (aFAST), and pulmonary parenchyma (Veterinary Bedside Lung Ultrasound Examination; VetBLUE) [22,23].

Three-view thoracic radiographs or thoracic computed tomography (CT) should be obtained, particularly in animals with respiratory abnormalities. Thoracic imaging may reveal evidence of pneumonia, pleural effusion (although this is usually detected on tFAST first), or primary or secondary neoplasia. Abdominal ultrasound or CT by a specialist radiologist can also be invaluable in the search for an underlying cause, particularly in a patient with clinical signs or laboratory abnormalities suggestive of intra-abdominal disease. Imaging findings can be used to guide surgical exploration of effusions, for example in patients with abdominal sepsis or pyothorax.

Any abnormal fluid accumulations identified during physical examination or diagnostic imaging should be sampled for cytology, culture, and susceptibility. This may include peritoneal effusion (see Chapter 87), pleural effusion or joint fluid. Biochemical tests on cavitory effusions may also be helpful [24–26]. Other specific fluid samples that may be obtained as part of the diagnostic process for a patient with SIRS or sepsis include blood, lower airway fluid (collected by endotracheal wash, transtracheal wash or bronchoalveolar lavage), cerebrospinal fluid, urine, joint fluid, and organ aspirates.

Obtaining samples for culture and susceptibility testing should be performed as promptly as possible. Ideally, samples are obtained before, but should not delay the administration of, antimicrobials in a septic patient [27]. Current recommendations for blood cultures are to obtain two samples 30 minutes apart from different vessels, generally one central (jugular vein) and one

peripheral, in an aseptic fashion. Generally, both aerobic and anaerobic cultures are submitted, perhaps with the exception of lower airway fluid culture where an anaerobic culture is less likely to be needed unless there is evidence of pulmonary abscessation.

Other diagnostic tests are based on signalment, history, clinical signs, and diagnostic findings in an individual patient.

Treatment Approach to SIRS and Sepsis

Treating Shock

The first and foremost consideration when stabilizing a patient with SIRS or sepsis is to ensure adequate DO_2 . Animals with SIRS and sepsis may have decreased stroke volume due to hypovolemia, maldistribution, obstructive shock, cardiogenic shock or a combination of these. Identifying the contributors to shock in a particular patient with SIRS or sepsis is important to ensure appropriate treatment. Septic patients with shock generally have hypovolemic and/or distributive shock (see Section 4B, Circulatory Shock).

Restoring adequate DO_2 is achieved by sequentially considering and normalizing each contributor to DO_2 . This is essentially the foundation of the early goal-directed therapy (EGDT) approach for the management of patients with severe sepsis and septic shock [27]. Although strict adherence to the published EGDT protocol has been questioned in human medicine, the principles of shock resuscitation that it embodies remain the same. Preload is addressed first, and the surviving sepsis guidelines suggest that boluses of isotonic crystalloids administered to predetermined endpoints should be the fluid of choice for restoration of intravascular volume [27]. Perfusion parameters and point-of-care tests are used to guide resuscitation to endpoints. Ideally, if the clinician uses resuscitation endpoints (e.g. mean arterial pressure ≥ 65 mmHg), the minimum amount of fluid needed to restore acceptable perfusion parameters will be administered. The use of synthetic colloids for increasing preload is no longer recommended in septic humans due to the risk of AKI and coagulation derangements, but there is some evidence of a beneficial effect of albumin [27].

The role of synthetic colloids and albumin for shock resuscitation in veterinary medicine is unclear (see Chapter 168). Packed red blood cell transfusions are indicated in those patients whose anemia is of sufficient severity to contribute to decreased DO_2 (see Chapter 176).

Treating Cardiovascular Dysfunction

In patients with septic shock, increasing preload alone is inadequate to restore DO_2 due to inappropriate peripheral

vasodilation and distributive shock. As such, vasopressor administration is often beneficial. Norepinephrine is the first-line agent in human medicine [27]. Vasopressin, epinephrine, and dopamine may also be used. Myocardial depression may require specific therapy with positive inotropes, such as dobutamine, levosimendan or pimobendan. In patients with vasopressor-dependent hypotension, physiological hydrocortisone therapy is recommended due to the likelihood of CIRCI.

Antimicrobial Therapy (see Chapter 200)

In addition to fluid resuscitation from shock, the mainstays of sepsis treatment are antimicrobial therapy, source control, and aggressive supportive care. Early appropriate use of IV antimicrobials is perhaps the single most important factor in stabilizing the septic patient. Evidence in people with severe sepsis and septic shock suggests that every hour delay in administration of appropriate antimicrobials increases mortality [28,29]. In veterinary medicine, there is good evidence that implementation of a sepsis protocol improved the time to first administration of an antimicrobial in dogs with abdominal sepsis [30], although currently there is no evidence that this affects outcome [31].

Giving an appropriate antimicrobial requires an understanding of the origin of sepsis, the likely pathogens involved, and local resistance patterns. Generally, the goal is to start with broad-spectrum antimicrobial coverage and later de-escalate based on the results of culture and susceptibility testing. For example, community-acquired, secondary abdominal sepsis of gastrointestinal origin may be treated with amoxicillin + sulbactam for gram-positive aerobic and anaerobic coverage, and enrofloxacin for gram-negative aerobic coverage. In animals with recent exposure to antimicrobials or a high local burden of fluoroquinolone-resistant *E. coli*, amikacin (if normal renal function) or cefotaxime (if azotemic) would be more appropriate empiric antimicrobials for treatment of gram-negative aerobes. For animals that develop hospital-acquired sepsis, empiric antimicrobial choices are usually based on the assumption of multidrug-resistant (MDR) organisms.

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Source Control

Following identification of the septic patient, sample collection, administration of IV antimicrobials, and resuscitation from shock, the next step of management is source control. Without effective source control measures, there is less chance of success, especially if infection is confined within a closed space (e.g. septic peritonitis, septic arthritis, pyothorax). Source control must be pursued as soon as is reasonably possible following initial patient stabilization. This often means emergency surgery. Provision of analgesia also becomes an important part of management when surgical source control is needed.

Supportive Care and Managing Organ Dysfunctions

The remainder of the therapeutic approach to dogs and cats with SIRS and sepsis focuses on treating the underlying disease, good supportive care, and managing organ dysfunctions (see Table 159.2). Close monitoring is also imperative. Parameters requiring serial monitoring include perfusion parameters, hydration parameters, heart rate, respiratory rate and effort, temperature, blood pressure, urine output, and electrolytes.

Prognosis for SIRS, Sepsis, and MODS

The prognosis for animals with SIRS, sepsis, and MODS varies markedly depending on the severity of illness and the specific nature of the underlying disease. It may not always be possible to provide pet owners with an accurate prognosis for a specific patient with SIRS or sepsis at the time of presentation to the ER; rather, daily reassessment, to assess response to treatment, is helpful for prognostication.

Some studies suggest that the more SIRS criteria an animal meets, the worse their prognosis [8], although this does not always hold true. There is also good evidence in dogs with septic peritonitis that the greater the number of organ dysfunctions, the worse the prognosis [1]. Septic shock carries a particularly grave prognosis. Nonetheless, given the confounding influence of euthanasia in veterinary studies assessing outcome, all efforts should be made for patient treatment when owners have intent to treat.

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C. Trauma

Trauma Overview

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Introduction

Trauma is defined as any tissue injury that occurs more or less suddenly as a result of an external force [1]. Injury to tissues may be classified by the type of forces applied to the body, such as blunt and penetrating, and can occur secondary to motor vehicle accidents, animal abuse, falls, gunshot wounds, and animal–animal interactions. Traumatic injuries may be minor, such as lacerations or single bite wounds that are easily addressed and fixed. However, trauma can be severe and life threatening with injuries to multiple body systems. These severely injured patients may die acutely due to overwhelming injury typically associated with severe blood loss, hypoxemia, or traumatic brain injury. Other severely injured patients may survive initially but subsequently die due to complications such as delayed hemorrhage, infection, or multiple organ dysfunction. Finally, other severely injured patients may be treated and survive to hospital discharge.

It is important for the veterinarian to understand the epidemiology of small animal trauma in order to rapidly evaluate for common life-threatening injuries. Rapid and accurate recognition of life-threatening injuries is key in the initial triage evaluation to institute life-saving therapy and improve the animal's chances of survival. Trauma scoring systems help to identify the more severely injured patients, evaluate hospital patient outcomes, and aid patient enrollment in clinical trials.

Overview of the Pathophysiology of Trauma

In polytrauma patients, hemorrhage, hypoxemia, and tissue injury may either directly or indirectly contribute to decreases in tissue perfusion and oxygen delivery. An accumulating oxygen debt and systemic release of inflammatory mediators are responsible for triggering the systemic inflammatory response syndrome (SIRS)

and multiple organ dysfunction syndrome (MODS), ultimately contributing to the death of the patient (see Chapter 159). Both SIRS and MODS have been identified in veterinary patients as a complication of both blunt and penetrating trauma and, similar to people, they are associated with non-survival [2,3].

In hemorrhagic shock, a decrease in cardiac output and mean arterial pressure is a key element leading to initial tissue hypoperfusion. Tissue hypoperfusion results in activation of the neuroendocrine stress response characterized by enhanced release of pituitary hormones, increased sympathoadrenal activity, pancreatic hypersecretion, and activation of inflammation [4]. When tissues and cells become deprived of oxygen, anaerobic metabolism is initiated, leading to increases in blood lactate and overproduction of oxygen radicals and other toxic metabolites [5]. Re-establishing effective circulation during resuscitation causes a steep increase in the levels of these toxic compounds, overwhelming tissue free radical scavengers and resulting in significant cellular injury (see Chapter 158). If oxygen delivery is not restored quickly, cell membrane pumps fail irreversibly and cell death occurs. The ischemic cell takes up interstitial fluid and swells, reducing perfusion to its neighbors [6,7]. Uncontrolled hemorrhage can lead to fatal shock characterized by a lack of contractile power of the heart and great vessels, inappropriate vasodilation, lack of response to catecholamines, and eventually brain death [6,7].

The systemic response to severe injury is characterized by a complex interaction across the hemostatic, inflammatory, endocrine, and neurological systems which may exacerbate the initial damage caused by hypoperfusion and reperfusion [8]. Following tissue injury, extracellular release of damage-associated molecular patterns (DAMPs) or alarmins from activated neutrophils or necrotic cells activates cells of the innate immune system (neutrophils and monocytes) and complement (C3a and C5a) [9–13]. Complement and inflammatory

cell activation triggers the production and release of inflammatory mediators such as interleukins (i.e. IL-6 and IL-8), generating the systemic response seen in SIRS [14]. Platelets activated by trauma and coagulation can also contribute to release of proinflammatory mediators and further promote SIRS [15]. Activated neutrophils migrate across the damaged vascular endothelium and become sequestered in “bystander” organs, leading to organ dysfunction [16]. Simultaneously, a compensatory anti-inflammatory response occurs characterized by increases in anti-inflammatory cytokines (IL-10 and TGF-beta) and cytokine antagonists (IL-1Ra) [17].

Depending on the balance of proinflammatory and anti-inflammatory factors, these responses may return to baseline or progress to persistent inflammation, immunosuppression, and increased risk for multiple organ dysfunction and sepsis [18].

Epidemiology of Small Animal Trauma

Trauma is common in small animal patients, accounting for 11–13% of emergency visits at Urban Teaching Hospitals [19,20]. In a large epidemiological study of approximately 75 000 North American dogs over a 20-year time period, trauma was the second leading cause of death in both juvenile and adult dogs [21]. To the author’s knowledge, a similar epidemiological study has not been done in cats.

A large retrospective study and one multi-institutional prospective study describe trauma patterns in dogs. These studies found that trauma is most common in young male dogs, with blunt trauma occurring in approximately 50% of dogs, followed by penetrating trauma (34%), unknown trauma (11%), and crush injury (~2.5%) [19,22]. Polytrauma secondary to blunt injury is common, occurring in up to 72% of dogs [2]. The prognosis following trauma is excellent in dogs, with survival to hospital discharge reported to be around 90% [22].

There are two large studies describing trauma patterns in cats [19,23]. In these studies, male cats were most commonly injured and the majority were indoor-outdoor cats. The causes of trauma were similar in both studies, with unknown trauma the most common cause (34–39.5%), followed by blunt trauma (16.3–17%), multiple bite wounds (~14%), crush injury (13–14%), non-bite penetrating wounds (4–10%), and falls (8.6–14%). The survival to hospital discharge rate in the most recent study in cats was 76% [23]. Present-day information regarding trauma patterns in both dogs and cats will soon be available as a result of data being collected from veterinary trauma centers through an international veterinary trauma registry overseen by the American

College of Veterinary Emergency and Critical Care (see Chapter 161).

Animals suffering from blunt trauma may sustain injuries to multiple parts of the body, including the chest, abdomen, head, soft tissues, and extremities, as a consequence of widespread energy transfer to the body. Table 160.1 outlines the type and incidence of blunt traumatic injuries that have been described in the veterinary literature. Factors in several studies identified with non-survival included recumbency at admission, development of hemothorax, cardiac arrhythmias, hemoperitoneum, body wall hernias, severe soft tissue injury, vertebral fractures, pneumonia, disseminated intravascular coagulation, acute respiratory distress syndrome, MODs, requirement for mechanical ventilation, use of vasopressors, and cardiopulmonary arrest [2,24].

A recent veterinary study evaluated injuries sustained in dogs and cats secondary to animal abuse [25]. In this study, cats were more likely to suffer from non-accidental injuries compared to dogs and both dogs and cats were significantly younger than a cohort of animals with blunt trauma secondary to motor vehicle accidents. Injuries significantly associated with non-accidental trauma

Table 160.1 Types and frequency of injuries sustained in blunt trauma in dogs.

Type of injury	Frequency reported
Thoracic injury	
Pulmonary contusions	44–83% [1–3]
Pneumothorax	7–47% [1–3]
Hemothorax	3–18% [1,2]
Rib fractures	9–14% [1–3]
Diaphragmatic hernia	2–6% [1–3]
Flail chest	2% [1]
Pulmonary bullae	2% [1]
Abdominal injury	
Hemoperitoneum	23–38% [1,3]
Abdominal hernias	5% [1]
Urinary tract rupture	2–3% [1–3]
Head trauma	25% [1,2]
Fractures	
Pelvic and sacral fractures/luxations	21–39% [1–3]
Other hindlimb appendicular fractures	17–36% [1,2]
Forelimb appendicular fractures	12–15% [1,2]
Spinal fractures	9–10% [1,2]
Skull fractures	5–11% [1,2]
Soft tissue injuries (lacerations, abrasions, degloving wounds)	81–90% [1,3]

included scleral hemorrhage, damage to the claws, skull fractures, vertebral fractures, and rib fractures (usually on one side of the chest). Older fractures are also often identified [25].

Penetrating wounds may result from animal–animal interactions or foreign objects such as gunshot wounds or impalements. In penetrating injuries, shearing, compressive, and tensile forces combine to damage soft tissue, bone, and viscera [26]. Often, the degree of skin damage in these cases does not predict the underlying tissue damage. Penetrating abdominal injuries from bite wounds, gunshot wounds, and impalements can result in significant internal organ injury and surgical exploration is typically recommended following patient stabilization. Bite wounds appear to occur more commonly in male dogs compared to female dogs, with small dogs more likely to suffer multiple injuries [27]. A majority of studies report that *Pasteurella* spp, *Staphylococcus* spp, and *Streptococcus* spp were the bacteria commonly cultured from bite wounds, but mixed infections with both aerobic and anerobic bacteria are also reported [28–32].

In a recent study evaluating severe extensive bite wounds in 94 dogs requiring ICU admission, the majority were small-breed dogs (<10kg) attacked by larger dogs (i.e. big dog–little dog interactions) and all dogs had surgical intervention [3]. Many dogs had evidence of SIRS, disseminated intravascular coagulation, and MODs and all were independently and significantly associated with mortality [3]. The most common organ dysfunction in this study was the respiratory system. Additionally, dogs with postoperative cardiovascular dysfunction (defined as a systolic arterial blood pressure <60 mmHg or requirement for vasopressors) or coagulation dysfunction were 29 times and 16 times respectively more likely to die [3].

Gunshot wounds can occur in both civilian and military working dogs. In two retrospective veterinary studies describing civilian gunshot wounds, injuries to the appendicular skeleton were most common, followed by the thorax (22%), head or neck (14%), and abdomen (14%) [33,34]. In a single paper describing gunshot wounds in 29 deployed military working dogs, the thorax was the most common site of injury (50%), followed by extremity wounds (46%) [35].

Trauma Scoring Systems

The Animal Trauma Triage Score (ATT) was developed for use in dogs to aid in identification of severely injured animals and for survival prediction [36]. In this scoring system, animals are scored on a 0–3 scale (0 = slight injury or no injury with 3 = severe injury) in six different

categories based on the initial physical examination: perfusion, cardiac, respiratory, eye/muscle/integument, skeletal, and neurological [36]. The ATT score assigned can range from 0 (an animal with only no or only slight injury in all categories) to 18 (an animal with severe injuries in all categories). In the initial prospective validation study, the survivors of trauma were found to have significantly higher mean ATT scores than non-survivors [36].

The utility of the ATT for predicting both severity of injury and outcome has been validated in several additional studies [22,24,35], with the most recent prospective study in traumatically injured dogs finding that an ATT >5 was 83% sensitive and 91% specific for predicting survival [22]. Although other variables have been evaluated for survival prediction, such as age, pre-existing disease, type of trauma, and number of injuries, the ATT score appears to be the best outcome predictor available to date [22,24].

The Modified Glasgow Coma Scale (MGCS) is another scoring system used for outcome prediction in animals with head trauma [37]. In this system, animals with head trauma are scored on a scale from 1 to 6 in three different categories: motor activity, brainstem reflexes, and level of consciousness. The MGCS can range from 18, an animal with normal or only slight evidence of head injury, to 3, an animal with the highest score in all categories. Similar to the ATT score, the MGCS has been evaluated in both retrospective and prospective studies [22,37,38]. In these studies, lower scores have been found to be associated with more severe injury and non-survival. In the most recent retrospective study evaluating prognostic indicators in dogs with head trauma, a MGCS of <11 was 84% sensitive and 73% specific for predicting non-survival [38].

It is important to note that although these scoring systems can be useful to identify animals that may require more aggressive intervention, to evaluate specific hospital trauma patient outcomes or for patient enrollment in clinical trials, they should be used very cautiously in the individual patient and should not be used solely to advise a pet owner on whether to pursue treatment for their pet.

General Approach to the Polytrauma Patient

Animals with significant trauma often have injuries to multiple body systems and a thorough physical examination should be performed. As stated previously, in traumatically injured patients an accumulating tissue oxygen debt, due to either decreased tissue perfusion and/or hypoxemia, can trigger processes that lead to SIRS and MODS. Therefore, the initial approach to the emergency stabilization and resuscitation of traumatically injured

patients should be aimed at improving and restoring tissue perfusion and oxygenation.

Initial assessment of cardiac output and circulating blood volume to evaluate for evidence of shock includes an evaluation of the patient's mucous membrane color, capillary refill time, heart rate, peripheral pulse quality, and rectal and extremity temperature (see Chapter 2). Pale mucous membranes, prolonged capillary refill time (>2 sec), tachycardia (or bradycardia in a cat), weak peripheral pulses, and hypotension indicate inadequate tissue perfusion. In the trauma patient, shock is typically the result of hemorrhage, but hypoxic, cardiogenic or septic shock may also occur [39]. Clinically significant hemorrhage secondary to trauma typically occurs in the thoracic cavity, peritoneum, retroperitoneal space, tissue compartments of the thigh (i.e. femoral fractures) and outside the body. These spaces should be investigated for the source of bleeding both during the physical exam and with diagnostic imaging (see below on abdominal FAST and thoracic FAST). External bleeding should be managed by application of direct pressure and ligation of exposed vessels. Generally, bleeding from the low-pressure pulmonary circuit resulting in a hemothorax will resolve spontaneously unless a major vessel has been injured or in cases of diaphragmatic hernia where hemorrhage originates from a displaced organ such as the liver.

In hemorrhagic shock, when only small volumes of blood are lost (10–12 mL/kg of blood or $<15\%$ of blood volume), there may only be mild changes in tissue perfusion parameters, such as a mild tachycardia, and arterial blood pressure may be normal or even elevated due to activation of compensatory mechanisms. These animals are at risk for ongoing hemorrhage and decompensation. As increasing amounts of blood are lost ($>15\%$ of blood volume), clinical signs of shock become more apparent. Absent pedal pulses is a very specific physical examination finding in hypotensive dogs and cats; the pedal pulses are no longer palpable when the blood pressure is less than 55 mmHg in dogs [40] and 70 mmHg in cats [41]. Arterial blood pressure should always be measured as many animals with hypoperfusion will have palpable peripheral pulses. This can be performed either directly through the placement of an arterial catheter or indirectly by Doppler or oscillometric techniques. Recently, the utility of the shock index (SI), which is the ratio of heart rate to systolic blood pressure, has been evaluated in dogs with hemorrhage. In this study, an $SI > 1.0$ was found to be 79% sensitive and 69% specific for diagnosing blood loss [42].

An electrocardiogram should be performed to assess heart rate and evaluate for the presence of sustained cardiac arrhythmias that may affect cardiac output. Arrhythmias may result from shock, myocardial contusions or

autonomic imbalance. Ventricular tachycardia and ventricular premature contractions (VPCs) are the most common cardiac arrhythmias in traumatically injured dogs, occurring in approximately 20% of cases [2,43,44]. Ventricular tachycardia may warrant therapy if sustained rates develop (see Chapter 53).

Injuries to the thorax may result in hypoxemia and decreased tissue oxygen delivery. In the veterinary literature, the incidence of blunt thoracic trauma is reported to be approximately 39–72% [2,45–48] (see Chapter 49). In one study of appendicular fractures in dogs, 25% were found to have concurrent hypoxemia [48]. Pulmonary contusions and pneumothorax are the most common thoracic injuries but other injuries that can occur include hemothorax, rib fractures, flail chest, and diaphragmatic hernia (see Table 160.1). Therefore, both the triage and serial physical examinations should include an evaluation of the animal's respiratory rate, respiratory effort, and a thorough thoracic auscultation.

Patients that are not breathing should be intubated and positive pressure ventilation initiated. Oxygen supplementation should be provided by mask or flow-by during the initial patient assessment (see Chapter 181). A pulse oximetry reading and/or arterial blood gas analysis can also be done to assess for hypoxemia. Dull lung sounds or an inverse or asynchronous breathing pattern should alert the clinician to the possibility of pleural space disease secondary to a pneumothorax, hemothorax, or diaphragmatic hernia [49] (see Chapters 44, 45, and 47). Moist lung sounds or fine pulmonary crackles, coughing, and/or blood in the mouth without evidence of oral or facial trauma may be seen in animals with pulmonary contusions.

In dyspneic patients in which pleural space disease is suspected, a needle thoracocentesis can be a life-saving intervention. A thoracic focused assessment with sonography for trauma (tFAST) examination could be done prior to needle thoracocentesis to confirm the presence of pleural space disease as indicated by an absent glide sign in patients with pneumothorax or the presence of echogenic effusion in animals with a hemothorax (see below and Chapter 180). For animals with suspected hemothorax, a needle thoracocentesis should only be done to relieve dyspnea as blood in the thoracic cavity will be reabsorbed by the lymphatic circulation, with 65% of red blood cells re-entering the systemic circulation within 2 days [50] (see Chapter 183).

In animals with abnormalities in thoracic auscultation or with penetrating thoracic injuries, thoracic radiography and/or computed tomography (CT) should be done to assess for intrathoracic injury. However, these diagnostic tests should be delayed until the patient has been stabilized. Of note, thoracic radiographs may be initially normal in dogs with pulmonary contusions, especially if

radiographs are taken immediately after the traumatic event [51,52]. In general, pulmonary lesions develop within the first 4 hours following the traumatic event but it can take up to 24 hours for radiographic changes to occur [51,52].

Following evaluation of the cardiovascular and respiratory systems, an evaluation of the neurological system should be performed to evaluate for evidence of traumatic brain injury or spinal cord injury (see Chapters 19 and 24). A full neurological examination should be delayed until life-threatening conditions of the respiratory and cardiovascular systems have been addressed. Animals with injuries to the neurological system, including animals with traumatic brain injury, may have an abnormal level of consciousness, brain-stem reflexes, and motor responses. Non-ambulatory patients should be evaluated for both spinal cord injury and pelvic fractures. Movement of these animals should be restricted until injury to the spinal cord can be excluded.

Evaluation of traumatic injury to the urinary system should include an admission and serial evaluation of blood urea nitrogen (BUN) and creatinine to assess renal function and monitoring of urine output. A normal urine output should be at least 1–2 mL/kg/h in a normotensive, euhydrated patient. Urinary ultrasound, urinary contrast studies, and/or CT can be performed to evaluate for integrity of the urinary tract if urinary tract rupture is suspected.

Finally, the patient should be assessed for fractures and wounds. Pelvic fractures are extremely common in dogs suffering from blunt trauma and may be identified during a rectal examination. Long bone fractures should be immobilized with a soft padded bandage initially and wounds should be clipped of hair, copiously flushed to remove debris, aseptically prepared and covered with a sterile dressing until further evaluation or definitive treatment can be performed.

During the triage evaluation, an intravenous catheter should be placed immediately in any animal with significant trauma, including animals with cardiovascular or respiratory instability or if there is evidence of traumatic brain injury. The intravenous catheter can be used for administration of intravenous fluid therapy for intravascular resuscitation and/or for administration of medications such as analgesia. Blood should be drawn at the time of intravenous catheter placement for packed cell volume (PCV), total protein (TP), lactate, blood gas analysis, blood electrolytes, blood urea nitrogen, and creatinine. In animals with significant hemorrhage, coagulation testing (PT, PTT, and/or thromboelastography) should be performed to evaluate for acute traumatic coagulopathy (see Chapter 163). In dogs with acute hemorrhage, the PCV may be initially normal due to release

of red blood cells from splenic stores, and therefore a low TP should raise suspicion for hemorrhage.

A recent study investigating transfusion practices in dogs following trauma found that PCV of 39% and total solids of 4.5 g/dL were specific (92% and 89%), but insensitive (43% and 55%) predictors of the need for blood transfusion [53]. In a different study of 52 dogs with blunt trauma, admission base excess of -6.6 was 88% sensitive and 73% specific for predicting the need for a blood transfusion [54].

Animals with cardiovascular or respiratory instability should have both an initial and serial abdominal and thoracic FAST ultrasound examinations to evaluate for peritoneal, retroperitoneal, and thoracic effusions, diaphragmatic hernia, pneumothorax, and the presence of a urinary and gall bladder (see Chapter 182). During the thoracic FAST examination, an evaluation for pericardial effusion, cardiac chamber size, and contractility should also be done. These minimally invasive examinations can be done at the cage side and immediately following the triage physical examination (see Chapter 182). Serial FAST ultrasound examinations should be done especially in an animal with signs of shock in which fluid is not initially identified or in animals with unresponsive or recurrent shock following intravenous fluid resuscitation. In one study of dogs with blunt trauma, 17% of dogs were found to have an increasing volume of abdominal effusion on serial aFAST examinations [55].

If abdominal fluid is identified, an abdominocentesis should be performed to obtain a sample of fluid for analysis. For hemorrhagic effusions, a PCV and TP should be performed on the effusion. In acute hemorrhage, the PCV and TP of the effusion should reflect the patient's venous PCV and TP. In non-hemorrhagic or serohemorrhagic effusions, a creatinine and potassium of the effusion should be compared to a venous creatinine and potassium. An effusion-to-serum creatinine concentration >2.0 and an effusion-to-serum potassium >1.9 in cats and >1.4 in dogs are diagnostic for uroabdomen (see Chapter 103) [56,57]. Uroabdomen as a complication of trauma has been reported to occur in approximately 1.6–3% of dogs [2,24,58,59]. Bile peritonitis, although a rare condition, results from rupture of the gall bladder or bile ducts from either penetrating or blunt trauma [60,61]. Bile pleuritis has also been reported occurring secondary to a bilopleural fistula, diaphragmatic hernia, or movement of peritoneal fluid across the intact diaphragm [62,63] (see Chapter 87). Both conditions can be diagnosed by an effusion bilirubin that is at least twice the serum bilirubin and/or the presence of bile pigments on microscopic evaluation of the effusion [60].

While both biliary rupture and uroperitoneum require surgical intervention, it is rare that surgery is indicated in fluid-responsive patients with traumatic

hemoperitoneum caused by blunt trauma. In one study, only three of 53 dogs (6%) with hemoperitoneum secondary to blunt trauma required surgical intervention [2]. In most of these animals, hemorrhage is likely originating from the liver or spleen and the intact abdominal wall and the limited space within the peritoneum allow for compression limiting ongoing hemorrhage. However, indications for surgical intervention in blunt traumatic hemoperitoneum include animals that are unresponsive to intravenous fluid resuscitation (i.e. uncontrolled hemorrhage) or that have recurrence of bleeding and increased requirements for blood products. Animals with penetrating abdominal and thoracic injury secondary to bite wounds and impalements should be managed surgically once the patient has been hemodynamically stabilized. Surgical intervention is also indicated for abdominal gunshot wounds due to a high rate of peritonitis but thoracic gunshot wounds can often be managed conservatively with intermittent needle thoracocentesis or a tube thoracostomy to evacuate air and fluid [33].

Considerations for Intravenous Fluid Resuscitation in Trauma

The goal of intravenous fluid resuscitation in the traumatically injured patient is to restore tissue perfusion and oxygen delivery, thereby preventing organ failure. Intravascular volume replacement with crystalloids, colloids, hypertonic saline or blood products is the mainstay of treatment in hemorrhagic shock until hemorrhage ceases or is controlled. However, despite significant research in this field in both experimental animal studies and traumatically injured people, the optimal fluid resuscitation strategy in trauma remains elusive. In several randomized controlled trials comparing the safety and efficacy of different fluid therapy strategies in people with trauma, no clear benefit of one type of fluid therapy was found [64–66] (see Chapters 167–170).

Crystalloid fluid therapy with a balanced electrolyte solution such as Normosol-R or Plasmalyte is generally recommended as the first-line treatment in hemorrhagic shock (see Chapters 167 and 170). Intravenous boluses of 10–30 mL/kg of a balanced electrolyte solution given over 20–30 minutes should be administered until endpoints of resuscitation have been met (i.e. normalized tissue perfusion parameters, urine output, lactate clearance). The potential deleterious effects of aggressive crystalloid administration include the development of tissue edema, coagulopathy, and diluting the oxygen-carrying capacity of the blood. Tissue edema results from the redistribution of crystalloids into the extravascular space within minutes following administration, with only about 10–25% or less of the volume infused

remaining in the circulation after 1 hour [67]. Vascular endothelial injury as a result of the trauma can lead to increased permeability, and dilution of plasma proteins with crystalloids can aggravate the SIRS and interstitial edema [68]. Additionally, hemodilution of clotting proteins and platelets may impair coagulation.

Synthetic colloids, such as hydroxyethyl starch, are another intravascular volume replacement option and remain in the intravascular space for longer compared with crystalloids (see Chapters 168 and 169). Boluses of 5–10 mL/kg over 15–30 minutes are generally used and it is not recommended to exceed the maximum daily dose of 20 mL/kg. In a study that compared the use of crystalloids to hydroxyethyl starch (HES 130/0.4) in severely injured people with penetrating trauma who had already received 2 liters of crystalloids, those who received hetastarch had a faster resuscitation and lactate clearance without evidence of renal injury than people who received additional crystalloids [69] (see Chapter 169). However, synthetic colloids can impair coagulation and their use has been associated with acute kidney failure in people with sepsis [64]. High molecular weight hetastarch reduces factor VIII and von Willebrand's factor and will cause a coagulopathy [70,71]. The nephrotoxic effects of colloids are believed to be secondary to osmotic nephrosis, a condition in which the renal proximal tubular epithelial cells take up colloids, ultimately causing swelling and cellular dysfunction.

In the veterinary literature, there are few studies evaluating whether the administration of colloids is associated with acute kidney injury. In a recent retrospective study of critically ill dogs, the majority of which had septic peritonitis, neoplasia and gastrointestinal tract disease, the use of 6% tetrastarch (hydroxyethyl starch 130/0.4) was not associated with an increase in acute kidney injury as indicated by an increase in creatinine [72]. In people, a recent Cochrane systemic review of 78 randomized controlled trials comparing crystalloids to colloids in critically ill people concluded that there is no evidence to suggest that colloids reduce the mortality risk compared with crystalloids in patients with trauma or burns or following surgery [64]. Although colloids likely still have a role in trauma resuscitation in animals, consideration should be given to the increased cost and possible detrimental effects prior to their administration.

Hypertonic saline (7.2–7.5%) causes a marked osmotic fluid shift from the intracellular space to the extracellular space, leading to an increase in intravascular volume many times the volume infused [67,73]. An infusion of hypertonic saline causes an increase in heart rate and contractility, and a reduction in peripheral vascular resistance, and may improve microcirculatory hemodynamics [74]. Additionally, hypertonic saline may exert an anti-inflammatory effect by reducing proinflammatory

cytokines and increasing anti-inflammatory interleukins in hemorrhagic shock, which may limit SIRS [75]. The addition of a colloid to hypertonic saline will extend its intravascular persistence. Studies in people and experimental animal studies have shown that similar to both crystalloids and colloids, the use of hypertonic saline can lead to impaired hemostasis [76–80]. Proposed mechanisms include a dilutional coagulopathy, platelet dysfunction, diminished clot propagation, and clot strength as well as impaired fibrin formation [76–80].

Administration of 3–5 mL/kg of hypertonic saline +/- a colloid intravenously may be particularly useful in animals with severe cardiovascular collapse, either before or during a crystalloid bolus. Additionally, hypertonic saline may be the preferred initial fluid resuscitation choice in hypotensive animals with traumatic brain injury due to its simultaneous effects of expanding intravascular volume and reducing intracranial pressure (see Chapter 19).

In people without traumatic brain injury, different fluid resuscitation strategies for shock have been evaluated due to concerns that aggressive crystalloid resuscitation strategy in uncontrolled hemorrhage results in increased intra-abdominal bleeding and worse outcomes. These strategies include “hypotensive,” “controlled,” and “limited volume” resuscitation, almost all of which refer to strategies in which the blood pressure is allowed to remain lower than normal during resuscitation compared with conventional resuscitation. Generally, when employing these types of strategies, smaller amounts of balanced isotonic crystalloids, colloids, hypertonic saline, and/or vasopressors are administered to a lower target blood pressure (i.e. 70–100 mmHg). The goal is to avoid artificially elevating the blood pressure and displacing tenuous blood clots after bleeding stops or diminishes in the hypotensive trauma patient.

Evidence from both experimental animal studies and human clinical studies has shown that an aggressive fluid resuscitation strategy results in increased intra-abdominal bleeding and a worse outcome compared to a hypotensive resuscitation strategy. In experimental animal studies, aggressive fluid resuscitation in hemorrhagic shock associated with penetration injuries led to hydraulic disruption of the thrombus, dilution of coagulation factors, and lowering of blood viscosity which was associated with a risk of rebleeding [81–83]. In a landmark study, Bickell et al. demonstrated that in people with penetrating torso injuries, prehospital aggressive fluid administration was associated with lower survival and higher complication rates compared with fluid therapy that was delayed and initiated at the time of surgery [84]. It should be noted that the time to surgical treatment in this study was <30 minutes, a time frame that is generally not achievable in most veterinary practices and therefore limits the applicability of this approach in veterinary

medicine. However, in another clinical trial evaluating different in-hospital fluid resuscitation strategies in traumatically injured people, there was no difference in mortality in people who received conventional fluid therapy compared to a hypotensive resuscitation strategy [85].

To date, the use of a hypotensive fluid resuscitation strategy and blood pressure targets has not been investigated in veterinary trauma patients with hemorrhage. To the author's knowledge, there is only one veterinary study investigating the use of a limited volume fluid strategy protocol compared to conventional resuscitation with large volumes of crystalloids in dogs with hemorrhage secondary to spontaneous hemoperitoneum. In this study [86], dogs in the limited volume fluid resuscitation group were given up to 8 mL/kg of hypertonic saline and 10 mL/kg of hydroxyethyl starch until endpoints of resuscitation were met (HR <120 bpm, RR <40 bpm, and SAP >90 mmHg). Dogs in the conventional resuscitation group received up to 80 mL/kg of crystalloids with the same resuscitation goals. Dogs in the limited volume group reached resuscitation goal endpoints significantly sooner than dogs in the conventional group. However, there was no difference in survival nor a significant difference in red blood cell transfusion requirements, although the study did not have the power to detect a difference in transfusion requirements between the two groups of dogs [86].

In this author's opinion, a limited volume resuscitation strategy may be useful in hemorrhagic shock secondary to trauma but to date, it has not been definitively shown to have a benefit over conventional resuscitation with crystalloids in animals with trauma. A fluid resuscitation strategy that targets a lower than normal blood pressure should be used cautiously (if at all) and only in animals without evidence of traumatic brain injury and in which surgical control of hemorrhage is being emergently pursued.

Administration of blood products (whole blood, packed red blood cells, fresh frozen plasma) may be used as part of the resuscitation strategy of a traumatically injured patient with hemorrhage (see Chapter 176). The benefits of packed red blood cells (pRBCs) and fresh frozen plasma transfusions include intravascular volume expansion while concurrently increasing oxygen carrying capacity and reversing coagulopathy. Accumulating evidence in the human trauma literature suggests that a cumulative ratio of fresh frozen plasma to pRBCs of at least 1:2 is associated with improved survival in people with massive hemorrhage, with some authors recommending a 1:1 ratio until hemorrhage has been controlled [7,87]. However, blood products are expensive, generally in short supply, and can lead to transfusion reactions. Therefore, the administration of blood products is generally reserved for animals with severe

hemorrhage unresponsive to conventional fluid resuscitation or those that initially respond to fluid resuscitation but have recurrence of bleeding and shock. Dogs with penetrating trauma may be more likely to require transfusion and approximately 15–36% of dogs will require a pRBC transfusion [2,53,54].

Finally, the syndrome of acute traumatic coagulopathy may contribute to ongoing hemorrhage and need for blood transfusion. This condition is not simply a dilutional or consumptive coagulopathy as a result of intravascular fluid resuscitation and initial hemorrhage, but is thought to also occur secondary to an imbalance of the equilibrium between procoagulant factors, anticoagulant factors, platelets, endothelium, and fibrinolysis. In people, this syndrome may be characterized by factor V inhibition, dysfibrinogenemia, systemic anticoagulation, impaired platelet function, and hyperfibrinolysis [88,89]. Therefore, the early use of antifibrinolytics, such as tranexamic acid or ϵ -aminocaproic acid, to prevent clot dissolution and additional hemorrhage in trauma patients is intriguing given the limited availability and cost associated with blood transfusions in veterinary medicine (see Chapter 68). This interest stems from the results of the CRASH-2 trial that found that the administration of tranexamic acid to traumatically

injured people who were bleeding or at risk of bleeding within 8 hours of injury reduced the risk of death from hemorrhage and decreased overall mortality as compared to placebo [90]. Interestingly, there was no difference in blood transfusions or the number of blood products transfused between the two groups, calling into question the mechanism of the beneficial effect of tranexamic acid [90].

Both tranexamic acid and epsilon-aminocaproic acid (EACA) are lysine derivatives that block the lysine site on plasminogen, thus preventing binding of tPA and preventing fibrinolysis. In veterinary medicine, there have been two clinical studies evaluating EACA in greyhounds undergoing either ovariohysterectomy or limb amputation, both of which demonstrated significant reductions in postoperative bleeding compared to a control group [91,92]. There have also been two recent veterinary retrospective studies describing the use of EACA and tranexamic acid in dogs [93,94]. It is difficult to reach conclusions regarding whether these medications reduce hemorrhage as there was no control group in the EACA study and in the tranexamic study, there were very few dogs with traumatic hemorrhage. However, based on the current data, these medications appear to be safe although tranexamic acid can cause vomiting.

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Trauma Center Registry

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Veterinary Trauma Initiative

Cats and dogs sustaining traumatic injury present frequently to hospitals, and have an overall very high survival rate [1–4]. Despite a high frequency of positive outcomes, trauma is the second leading cause of death in dogs and there remains an acute drop-off in survivability for more severely injured animals [4–6]. Data support a significant drop-off in survivability of dogs with an Animal Trauma and Triage (ATT) score greater than 5 [4,5,7]. There is enormous opportunity to improve outcome and reduce co-morbidities in the veterinary trauma population.

Established in 2010, and subsequently recognized as an *ad hoc* committee by the American College of Veterinary Emergency and Critical Care (ACVECC), the Veterinary Committee on Trauma (VetCOT) has a vision to create a network of lead hospitals that seed development of trauma systems. These hospitals work collaboratively to define high standards of care and disseminate information that improves trauma patient management efficiency and outcome. In order to achieve this vision, veterinary trauma centers (VTCs) contribute to a trauma registry that allows for continued advancement of trauma patient care.

The four aims of the trauma initiative are:

- enhancement of trauma patient care
- enhancement and promotion of research collaborations
- expansion and formalization of education on veterinary trauma
- enhancement of the visibility of veterinary specialty colleges.

Trauma Registries: History and Purpose

In the United States, formation of trauma centers and systems for human trauma patient care was initiated in the 1970s through the American College of Surgeons

Committee on Trauma (ACS-COT). Trauma registries began development at the same time. In its first large-scale study (Major Trauma Outcome Study), 139 North American hospitals submitted data on >80 000 cases over a 5-year period (1982–1987). This study became the springboard for further development of trauma registries, and established the importance of utilizing trauma registries for individual hospital and trauma system quality assurance as well as informing performance improvement programs [8]. Today, the National Trauma Data Bank (NTDB) houses the largest aggregation of trauma registry data ever assembled and is utilized by hospitals and researchers alike to improve trauma patient care [9].

The objectives of trauma registries are to [10]:

- assess and improve patient care
- identify opportunities for injury prevention initiatives
- document the medical, economical, and social effects of trauma
- develop and test research hypotheses.

In 2013, the VetCOT-Registry Subcommittee (VetCOT-RS) recommended the use of REDCap [11] to house the first ever multicenter veterinary trauma registry. In September of that year, nine VTCs started entering prospectively obtained data on trauma cases presenting to their hospital. In the first year, data from >3000 trauma cases were entered into the database. With 13 additional VTCs entering their trauma cases beginning January 2015, and five additional centers in August 2015, the veterinary trauma registry grew to >10 000 cases by October 2015. This makes the VetCOT-housed trauma registry the largest trauma-specific medical database in veterinary medicine.

Trauma Registry: The Future

In January 2015, the VetCOT Registry subcommittee, in collaboration with the full VetCOT and VTC leads,

finalized the “Registry Guidelines for Data Use and Authorship,” outlining the mechanisms for accessing and evaluating data from the veterinary trauma database [12]. As of this writing, the first two projects that were approved are in process, and a further calls for applicants are expected. It is anticipated that the results of these, and future studies, will be presented at the annual Veterinary Trauma and Critical Care Conference and published in peer-reviewed journals. Studies of this magnitude are rare in veterinary medicine, and the ability to apply findings to improve current patient care and inform development of future clinical research is enhanced by the statistical power possible with large, multicenter study cohorts.

The VetCOT-RS anticipates publishing an open-access annual summary of the epidemiological data in the veterinary trauma registry modeled after the NTDB annual report [9]. It is hoped that this information will inform development of interventional clinical research, which is particularly sparse in veterinary trauma literature. Volume resuscitation of the severely hemorrhaging patient, damage control surgery, management of traumatic brain and spinal injury, maximizing triage tool application, improving survival for the most severely injured patients and cost-effective care for all patients are just a few of the areas where opportunity exists in

improving veterinary trauma patient care. Additionally, given the similarities between human and canine trauma, opportunity exists to utilize naturally occurring trauma in dogs as a pre-phase I and pre-phase II model for interventions being evaluated for human trauma patient care [13]. This advantage, supported by registry data, can potentially help researchers obtain funding for clinical trials and research that would ultimately benefit both veterinary and human trauma patients.

Acknowledgments

Significant admiration, gratitude, and appreciation to the VetCOT members and particularly the Registry Subcommittee (Manuel Boller, Soren Boysen, Jamie Hoffberg, Marie Holowaychuk, Maureen McMichael, Marc Raffe, Lauren Sullivan) as well as the VTC leads and teams, ACVECC Regents, and collaborating allied specialty groups.

Excerpts of this chapter were paraphrased from similar resources generated by the author (Hall) and collaborators:

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High-Rise Syndrome

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Definition and Pathophysiology

High-rise syndrome (HRS) refers to the constellation of injuries sustained after falling from a certain height. By convention, in veterinary medicine a high-rise injury is defined as vertical fall from two stories or higher, which is a distance of about 24 feet. Animals that reside in urban areas are particularly predisposed to this condition. It appears to be a disease of young animals, likely due to the fact that they are more curious and more likely to explore, but all ages have been represented [1,2]. Sexually intact animals may be more likely to suffer from HRS, potentially due to increased propensity for roaming [1,2]. HRS has been reported to occur in warmer months, as it is likely the time when most people open windows, providing the animals with access to the outdoors [1,2].

During a fall from a height in atmospheric environment, the velocity of the fall is dependent on the distance fallen, as well as body mass and shape due to air resistance. These are likely the major determinants of injury severity. Distance fallen is a major predictor of injury severity and mortality in people [3], with head and chest injuries being significantly associated with mortality. Other factors that may play a role are objects encountered during the fall, the surface type encountered upon impact, as well as the body parts that hit the surface first [1,2,4].

It appears that dogs and cats behave differently when falling from a height. Dogs behave more like humans in that injury severity and life-threatening injuries were directly proportional to the height of the fall [2]. Conflicting evidence exists in cats. Some studies report that survival is negatively associated with the height of the fall [5], and injury scores increase in animals that have fallen over seven stories [6]. Others conclude that the injury rates ceased to increase and fracture numbers decreased in cats that fell from a height of over seven stories [1]. It is

speculated that during the fall, due to air resistance, their small size, natural dexterity and ability to stretch their body to increase the surface area, thus enhancing drag, cats achieve a terminal velocity of 100 kilometers per hour after a fall of about five stories, after which acceleration ceases and they continue falling at a constant speed [1]. Prior to reaching terminal velocity, it is postulated that cats reflexively extend their limbs, and if the fall is under five stories, the limbs absorb the impact of the fall. After the terminal velocity is reached, the cat assumes a more horizontal position, flexes its limbs, and if contact happens at any point during that time, the impact of the deceleration is more evenly distributed, potentially leading to more truncal injuries [1,5]. This is corroborated by the study by Vnuk, in which the percentage of fractures decreased and the percentage of thoracic injuries went up in falls higher than seven stories [6]. Other studies do not report any particular pattern, but uncover a complex relationship between the number of floors fallen and the types and extent of injuries sustained by cats [5]. This is likely due to the multifactorial nature of the cause of damage to the body in HRS.

The landing surface may play a significant role in the morbidity of cases of high-rise injury. In addition, objects encountered during the fall may enhance or mitigate sustained trauma. One study evaluated injury association with the landing surface and did not detect a difference in the severity of injury for cats [1]. However, landing onto spiked metal railings resulted in severe life-threatening penetrating injuries to three cats in one case series [4]. Gordon et al. reported that dogs landing on hard surfaces suffered more total injuries [2].

Clinical Signs

The first priority upon triage and initial assessment of the patient that has experienced HRS is establishing

whether any life-threatening injuries have occurred (see Chapter 2). The stabilization effort should be directed to rapidly identifying and addressing these. A complete physical examination is imperative; previous reports of HRS identified that head, thoracic, and extremity injuries have been reported most commonly [1,2,6], and an effort should be made to thoroughly inspect those areas.

A substantial number of animals present in shock, which could be due to hemorrhage, distributive shock secondary to massive tissue damage, or hypoxia [1,5,6] (see Chapters 152, 153, and 155). Signs of shock may include dull mentation, poor pulse quality, and pale mucous membranes. Hypothermia may be associated with poor perfusion and has been documented in cats with shock in one study [5]. It is of the utmost importance that animals in shock are identified as such, so immediate resuscitation can be initiated.

Acute traumatic coagulopathy (ATC) is a condition described in both severely injured human and veterinary patients and is characterized by impairment of hemostasis that can ensue independent of exogenous factors, such as fluid resuscitation, acidemia, and hypothermia [7–10] (see Chapters 70 and 163). The exact etiology is not well described, but is likely in part due to endogenous hyperfibrinolysis and elevated levels of protein C [7,9]. It is probable that acute traumatic coagulopathy exists in the subset of more severely injured high-rise cases, particularly those with massive tissue damage and shock on presentation [7]. These animals are possibly more likely to experience ongoing hemorrhage. Therefore, it is prudent to identify the patients most at risk for ATC, so that careful monitoring and re-evaluation may be implemented.

Thoracic trauma is an essential component of the HRS in dogs and cats [1,2,5,6] (see Chapters 48 and 49). Respiratory signs range from normal exam and auscultation to severe dyspnea. Pneumothorax and pulmonary contusions are very frequent findings in both dogs and cats and may be present in cats that are eupneic on physical examination [1] (see Chapter 44). Diaphragmatic hernia is an infrequent but significant sequela of HRS, and has been documented in about 2% of feline cases in several case series [1,6] (see Chapter 47). Thoracic auscultation may reveal increased lung sounds or crackles in the event of pulmonary contusions or decreased lung sounds in the event of pneumothorax, hemothorax or diaphragmatic hernia. Palpation of the chest may reveal pain or crepitus, if rib fractures are present.

Injuries to the head and face are a significant cause of morbidity in dogs and cats affected by HRS, and up to 67% patients may have these injuries [1,2,5,6] (see Chapter 19). Common signs include facial swelling, abrasions and wounds, epistaxis, pain upon manipulation of the jaw and possible bony instability if the fractures have

occurred. A complete evaluation of the facial area, palpation for fractures and thorough evaluation of the oral cavity for wounds, fractured or displaced teeth and fractures, including the hard palate for fractures and soft palate for tears, is paramount (Figure 162.1). Ophthalmological examination is important to rule out ocular injury, specifically intraocular hemorrhage, which may result in loss of sight (see Chapter 12).

Even though facial injuries are common in animal HRS, the incidence of significant traumatic brain injury is significantly smaller than that in people, with reported numbers of 7% in cats and 5% in dogs [2,5]. However, a detailed neurological examination should be undertaken as the patient's condition permits, and the animal should be frequently reassessed after stabilization to gain a more complete clinical picture and detect any changes.

Abdominal injuries are not as common as thoracic injuries in HRS but represent a significant threat to life and may require extensive care. Physical examination may reveal body wall defects, if a traumatic body wall hernia occurred. Pain upon palpation of the abdomen may be present with abdominal injury and should prompt a closer investigation of the abdominal cavity [5]. Hematuria may be present as well [1,2]. Studies that evaluated abdominal injuries found that 15% of dogs and 1–17% of cats had significant abdominal injuries, including hemoperitoneum secondary to splenic rupture (see Chapter 84), uroperitoneum secondary to rupture of the urinary bladder or other conduits (see Chapter 103), and diaphragmatic hernia [1,2,5,6]. Moreover, pancreatic rupture and traumatic pancreatitis are rare complications of HRS that have been documented in cats and may result in severe systemic inflammation, multiorgan failure and death [8,9] (see Chapter 86). Clinical signs of pancreatic rupture may not be evident immediately upon evaluation and may take several days after initial injury to fully manifest [11,12].

Skeletal injuries are a major component of HRS in both dogs and cats, with up to 50% of animals sustaining at least one fracture or ligamentous injury [1,2,5,6]. Reported distributions of injuries vary slightly, but generally are similar in frequency between forelimbs and hindlimbs. Animals with skeletal injuries may present with a range of symptoms ranging from lameness to non-ambulation with elicited pain upon manipulation of the affected site. Some injuries may be readily apparent, while others may require a thorough examination to pinpoint. In addition, cardiovascular and respiratory instability may delay diagnosis of the skeletal injury, and a thorough physical exam should be undertaken after the patient is stable.

Spinal cord and canal injuries are reported in 2–13% of cats suffering from HRS and up to 15% of dogs [1,2,5] (see Chapter 24). Signs may be similar to animals with other skeletal injuries and include difficulty ambulating

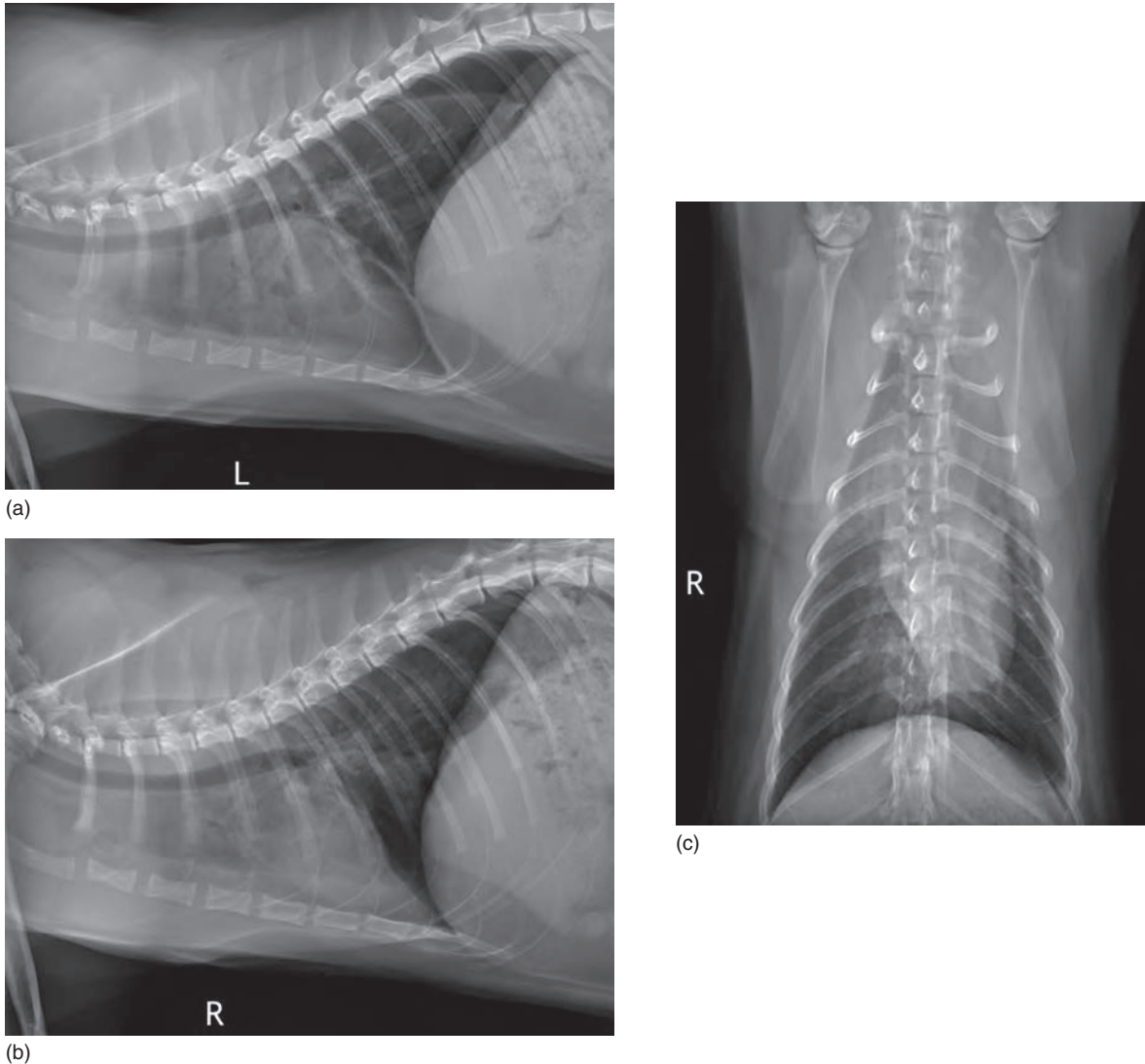


Figure 162.1 (a–c) Pulmonary contusions and a mild pneumothorax in a cat who suffered from HRS but appeared eupneic on presentation to the hospital.

or inability to ambulate, ataxia and neurological deficits, dependent on the anatomical location of the injury. As the focus tends to be on the more obvious abnormalities and fractures of the extremities, spinal injuries may be easily missed, but can change the prognosis and alter the course of treatment, if significant. Similarly to evaluation of skeletal injuries, a full neurological examination should be undertaken once the patient is stable.

Diagnostics

In addition to a thorough physical examination, the initial diagnostic database should be tailored to the needs of the individual animal and the severity of injuries sustained.

Most commonly, values collected upon triage should include a rectal temperature, a blood pressure measurement, pulse oximetry, electrocardiogram and point-of-care bloodwork, which includes a packed red blood cell volume (PCV), blood glucose and ideally a venous blood gas with a lactate (see Chapter 2). Serial evaluations of physical exam parameters, PCV, and lactate measurements will be useful in guiding resuscitation.

Due to the high incidence of thoracic injuries, imaging of the chest cavity (see Chapter 182) should be undertaken in all animals exhibiting signs of respiratory tract dysfunction. Animal stability should never be compromised to obtain imaging; if severe dyspnea is present, stabilization measures should be undertaken first, including oxygen supplementation, minimizing stress, adequate

pain control and possibly diagnostic thoracentesis, in case clinically significant pleural space disease is present (see Chapters 181, 183 and 193). Variable incidence of thoracic trauma has been documented, and the need for thoracic radiographs in animals without obvious abnormalities referable to the respiratory tract is questioned. Some animals, notably cats, have been documented to be eupneic while thoracic injuries were present [1] (see Figure 162.1). Many of these animals will be sedated or anesthetized for additional procedures and surgeries, and therefore routine imaging of the thorax may be advisable.

Veterinary abdominal and thoracic focused assessment with sonography for trauma (FAST) has been increasingly utilized and can be an invaluable bedside tool in evaluation of high-rise patients, especially those that are too unstable to be moved for radiographs [14] (see Chapter 182). aFAST is a rapid non-invasive way of evaluating for abdominal effusion, and tFAST may be used for evaluation of pleural effusion, as well as for pneumothorax, although the learning curve for recognition of pneumothorax is higher than for fluid recognition. Ultrasound may aid in timely diagnosis of hemorrhage and rupture of the urinary or gastrointestinal tracts, and could be instrumental in better stabilization and treatment of high-rise patients.

Blood analysis should be considered in high-rise patients, especially if they are scheduled to undergo general anesthesia for repair of any of the sustained injuries. Complete blood cell count may reveal an elevated neutrophil count and possibly anemia, if significant hemorrhage has taken place. Serum chemistry may reveal a number of abnormalities, including elevated liver enzymes, azotemia, and altered protein levels in the event of significant shock, hypoxemia, and hemorrhage. Azotemia may also be present if rupture of the urinary tract has occurred. In cats, species-specific pancreatic lipase monitoring may be advisable, especially in animals with evidence of significant abdominal injuries [11,12] (see Chapter 86). Coagulation testing, including thromboelastography, should be considered in severely traumatized animals with or without clinically apparent hemorrhage to rule out hemostatic disturbances, including coagulopathy of trauma.

After initial stabilization and treatment, evaluation of the facial and orthopedic injuries should be undertaken, if the patient's condition dictates. Orthopedic radiographs may be able to be performed with good pain management and possibly light sedation; however, for full evaluation of the facial and dental injuries, dental radiographs may be necessary, which typically require general anesthesia. Such procedures should be delayed as long as necessary for stabilization of the cardiovascular, respiratory and nervous systems, which may take up to several days of hospitalization.

Treatment

Treatment of animals with HRS should firstly focus on achieving acceptable ventilation, oxygenation, and cardiovascular stability. This is referred to as the primary survey and initial resuscitation (see Chapter 2). Airway patency should be evaluated and established immediately upon presentation, with intubation if necessary. Breathing and circulation should be evaluated and addressed next. Oxygen supplementation should be provided, and immediate thoracocentesis should be performed as a diagnostic and therapeutic step in severely dyspneic patients.

Cardiovascular stabilization is achieved via intravenous catheterization and administration of intravenous fluids, which may include isotonic crystalloids, colloids and a combination of blood products for hemorrhagic shock (see Chapters 167–169, and 176). Judicious but not restrictive fluids should be used in patients with pulmonary contusions to limit fluid extravasation and worsening hypoxemia [15]. Higher ratios of plasma to red blood cells are recommended in human medicine and should be considered; however, this is controversial [16]. Antifibrinolytic medications may be considered in animals with suspect acute traumatic coagulopathy [7] (see Chapter 163).

Pain management is imperative in animals with significant injuries, and may include systemic and local analgesia, as well as a multimodal approach using different types of analgesics, such as a combination of opioids and non-steroidal anti-inflammatory drugs when appropriate and safe (see Chapter 193).

If traumatic brain injury is suspected, hyperosmolar solutions should be used to improve cerebral blood flow (see Chapter 19). Hypertonic saline may also be used as small-volume resuscitation in polytrauma patients to improve perfusion.

After initial stabilization, a full physical examination and definitive repair should be pursued, if indicated. This is called the secondary survey. Any imaging or full bloodwork is performed at this juncture. Depending on the type of injury requiring repair, definitive fixation could be delayed up to several days after the initial insult to allow for organs like the brain and pulmonary parenchyma to return to normal or near-normal function. This may not be possible if surgical intervention is necessary for intractable hemorrhage or severe thoracic or abdominal wounds that require urgent exploration. Rupture of the urinary conduit can be managed with an abdominal drain prior to pursuing surgery for definitive repair (see Chapter 103).

When anesthesia is deemed to be safe, repair of the orthopedic and facial injuries should be pursued. Vertebral and appendicular skeleton fractures



Figure 162.2 Mandibular symphyseal and left body fracture in a cat.

can be managed conservatively or surgically, according to imaging, clinician discretion, and individual animal characteristics, such as age, disposition and co-morbidities, as well as owner compliance and finances. Facial soft tissue injuries and fractures may be treated conservatively or surgically, depending on clinician preference and the nature of the injury (Figure 162.2). Hard palate fractures are a hallmark of HRS in cats, and significant controversy exists over whether

they should be managed medically or if surgical repair should be pursued (Figure 162.3). Oronasal fistula is a complication of untreated and medically managed hard palate fractures and may be a challenge to address once it develops. Therefore, some authors recommend surgical closure of the initial defect [17] (Figure 162.4).

Prognosis

Overall prognosis for animals with HRS is good, with mortality ranging from 6% to 17%, including both euthanized cases and those that died [1,2,5,6]. Two studies in cats reported 100% survival in animals surviving the first 36 hours of hospitalization [1,6]. Animals that require surgery predictably have longer duration of hospitalization (median 2.7 days without surgery, 5 days with surgery in one study in dogs) [2]. Severity of injuries is directly proportional to the number of floors in most studies [2,5,6]. In many studies of feline HRS, mortality was associated with thoracic injuries and shock [5]. One study found that hypothermia at presentation was positively associated with death, and likely with shock [5]. In addition, this study found that mortality of cats with abdominal injuries was 2.5 times higher compared to the other cats with HRS. The authors concluded that presence of abdominal trauma signifies more severe injury and should be regarded as a negative prognostic indicator in feline HRS.



Figure 162.3 Hard palate fracture in a cat due to HRS.



Figure 162.4 Surgical fixation of a hard palate fracture in a cat.

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Trauma-Associated Coagulopathy

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Introduction

Acute hemorrhage is the most important reversible cause of death in people following trauma [1–3]. The consequences of acute hemorrhage, including cardiovascular collapse, compromised tissue oxygen delivery, impaired organ function, and secondary sepsis, are widely recognized [4]. Until recently, therapeutic strategies for patients with acute traumatic hemorrhage involved restoration of intravascular volume with crystalloid and colloid fluids and augmentation of oxygen-carrying capacity via red blood cell transfusion [5,6] efforts have been made to optimize resuscitative and operative strategies for the management of traumatic hemorrhage [7,8]. Our understanding of the role hemostatic dysfunction plays in exacerbating traumatic injury has grown significantly over the last 15 years, such that two major contributors to traumatic hemorrhage are now recognized in people – the trauma and resultant shock itself and our resuscitation efforts [9,10]. There has been a consequent paradigm shift in the way human trauma patients are resuscitated in the prehospital setting, in the emergency department, and in operating rooms [11–13]. A corresponding evolution of understanding and management is also in veterinary trauma.

Pathogenesis

Trauma-associated coagulopathy (TAC) is the preferred term for any coagulopathy identified in traumatized patients. TAC encompasses both the endogenous coagulopathy that develops early in severely traumatized individuals with concurrent tissue hypoperfusion – acute coagulopathy of trauma-shock (ACOTS) – and the syndrome that occurs later and is exacerbated by

resuscitation practices – resuscitation-associated coagulopathy (RAC).

Resuscitation-Associated Coagulopathy

Until recently, coagulopathy in trauma patients was considered to result from the “bloody vicious cycle” of dilution, acidosis, and hypothermia secondary to the effects of tissue damage, hemorrhage, hypoperfusion, and crystalloid resuscitation [14–16]. In the clinical setting, the additive effects of dilution, acidosis, hypothermia, and hypocalcemia on coagulation status are likely more important than any individual component alone. Indeed, using thromboelastography, it has been shown that acidosis in isolation has minimal impact on coagulation, while more profound hypocoagulability ensues with combined acidosis and hypothermia [17].

The administration of crystalloid fluids contributes to TAC via clotting factor dilution and induction of hypofibrinogenemia [18,19], thereby directly impeding clot formation and lowering resultant clot strength. The degree of coagulopathy may be dose dependent, but large-volume resuscitation has not consistently resulted in coagulopathy development in people [20,21]. The choice of resuscitation fluid undoubtedly has significant consequences for trauma patients [22]. In particular, the inhibitory effects of hydroxyethyl starch solutions on coagulation factor activity, platelet function, and hemostasis have been extensively documented in humans and small animals, raising important questions about their use in fluid resuscitation [23] (see Chapter 168) Although the impact on canine trauma patients is unknown, dilution does occur in traumatized dogs following resuscitation. In one study, volume resuscitation resulted in a 10% reduction in packed cell volume (PCV) and a 1.0 g/dL fall in serum protein concentration [24].

The development of acidosis in traumatized patients is multifactorial. Hyperlactatemia associated with high concentrations of circulating catecholamines and impaired tissue oxygenation, the administration of chloride-rich fluids, and accumulation of citrate from blood products could act individually or in combination to induce metabolic acidosis [16]. The presence of hypoalbuminemia following hemorrhage and fluid resuscitation may also hinder traditional interpretation of acid–base status, increasing the likelihood that the presence and potential impact of acidemia on coagulation will be overlooked [25]. Simplistically, the coagulation cascade involves sequential activation of enzymes leading to the generation of thrombin. Enzymes function optimally within a narrow range of environmental conditions (e.g. pH and temperature), and any deviations from normality adversely affect enzyme function. In the context of hemostasis, this could lead to impaired thrombin generation and a hypocoagulable phenotype. A reduction in pH from 7.4 to 7.0 reduces the activity of factor VIIa by more than 90%, and the FXa/FVa complex by 70%, and hence impairs thrombin generation [26].

Acidosis has also been associated with enhancing fibrinogen breakdown and impairing the interaction between coagulation factors and the surface of activated platelets [27]. Although severe acidemia was uncommon in one canine trauma retrospective [24], two studies have documented that metabolic acidosis and hyperlactatemia are associated with outcome in traumatized dogs [28,29]. While causation cannot currently be confirmed, there is an association between hemorrhage and acidosis in traumatized dogs, since those dogs requiring a packed red cell transfusion have significantly larger base deficits [29].

Hypothermia can occur in people after trauma due to environmental exposure, large-volume resuscitation with room temperature fluids, soft tissue exposure during surgery, and administration of vasodilating anesthetic agents that impair thermoregulation. Hypothermia may negatively affect hemostasis by inducing platelet dysfunction [30], reducing coagulation factor activity [31], slowing clot formation [32], and limiting thrombin generation [33]. Fibrinolytic activity appears to be minimally affected by hypothermia, however, which may contribute to development of a fibrinolytic phenotype [34]. Hypothermia appears to be an uncommon finding in dogs with trauma [24,35] but may occur in more severely injured dogs and those requiring massive transfusion [36–38]. This mirrors the human situation, where the degree of heat loss varies with injury severity and patient age [39,40].

The downstream effects of unintentional hypothermia should always be considered in any traumatized

patient requiring urgent anesthesia and surgery [41]. Given the potential impact of hypothermia on hemostasis, some advocate performing hemostatic assays at a temperature equivalent to the patient's core body temperature, in addition to the conventional 37°C, in an attempt to uncover the true *in vivo* hemostatic potential [42].

Calcium is an important co-factor for hemostasis *in vivo*, so ionized hypocalcemia could induce hemostatic dysfunction [43]. Hypocalcemia is commonly identified in dogs receiving massive transfusion, likely associated with excessive administration of citrate in blood products [38]. The level at which hypocalcemia interferes with coagulation is unclear, however, with one human study suggesting hemostatic function is preserved with ionized calcium concentrations as low as 0.56 mmol/L [44].

Acute Coagulopathy of Trauma-Shock

Although the iatrogenic effects of trauma resuscitation undoubtedly contribute to TAC, it is now clear that people suffer a separate and early coagulopathy characterized by hypocoagulability with hyperfibrinolysis that occurs independent of and prior to resuscitation [9,10]. Patients that develop ACOTS have higher transfusion requirements, spend longer in the hospital, develop multiple organ dysfunction more frequently, and are four times more likely to die [9,10]. The exact mechanism underlying the development of ACOTS is debated, but its development requires both the presence of severe tissue injury and hemorrhagic shock [45,46].

Central to the current hypothesis of ACOTS development is increased generation of anticoagulant activated protein C by high concentrations of the thrombin-thrombomodulin complex (Figure 163.1). The activation of the protein C pathway requires the combination of severe injury, tissue hypoperfusion, and sympathoadrenal activation, hence the term ACOTS [47,48]. In patients with mild-to-moderate trauma where increases in catecholamines are minimal, increased systemic thrombin generation and blood hypercoagulability are balanced by catecholamine-induced release of tissue-type plasminogen activator (tPA) and activation of the protein C (PC) pathway, such that ACOTS does not result [49,50].

Following severe trauma, widespread tissue injury and excessive plasma catecholamines cause generalized endothelial activation (Figure 163.2). Consequently, there is expression and release of thrombomodulin [45], systemic coagulation activation, and consumption of clotting factors and platelets [51]. Procoagulant thrombin, once bound to thrombomodulin, activates protein C

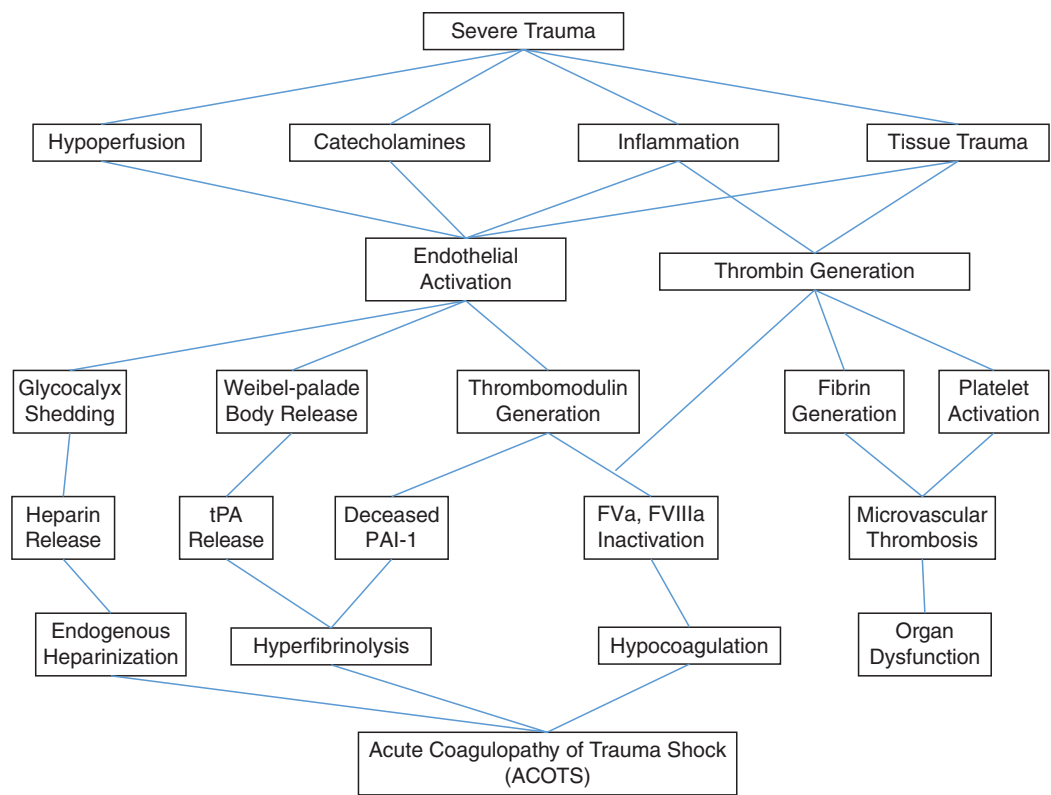


Figure 163.1 The pathogenesis of the acute coagulopathy of trauma-shock. An initial severe injury causes tissue trauma and blood loss that result in hypoperfusion, inflammation, and a sympathoadrenal response. In turn, these generate thrombin to aid hemostasis and activate the endothelium. If the injury and the body’s responses are sufficiently profound then the high concentrations of thrombin-thrombomodulin mediate the inhibition of FVa and FVIIIa and the inhibition of PAI-1. This results in hypocoagulation and potentiates fibrinolysis, while endothelial activation and damage releases endogenous heparin-like compounds. The result of these three processes is the acute coagulopathy of trauma-shock.

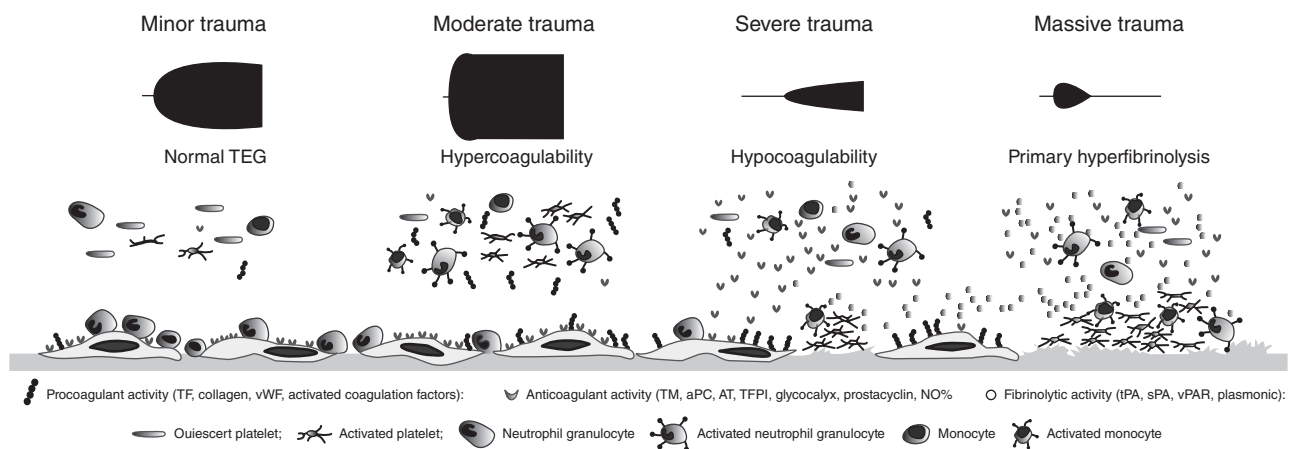


Figure 163.2 A schematic illustration of the hemostatic response to increasing trauma severity as assessed by thromboelastography (TEG). The variable hemostatic responses occurring in the bloodstream with increasing trauma severity are depicted. The hypothesized pathogenesis is that the combined effects of tissue injury, associated shock, and the catecholamine responses promote a switch from hypercoagulability to hypocoagulability and hyperfibrinolysis, generating the acute coagulopathy of trauma-shock (ACOTS). Source: Adapted with permission from Johansson PI, Ostrowski SR. Medical Hypotheses 2010;75:564–567.

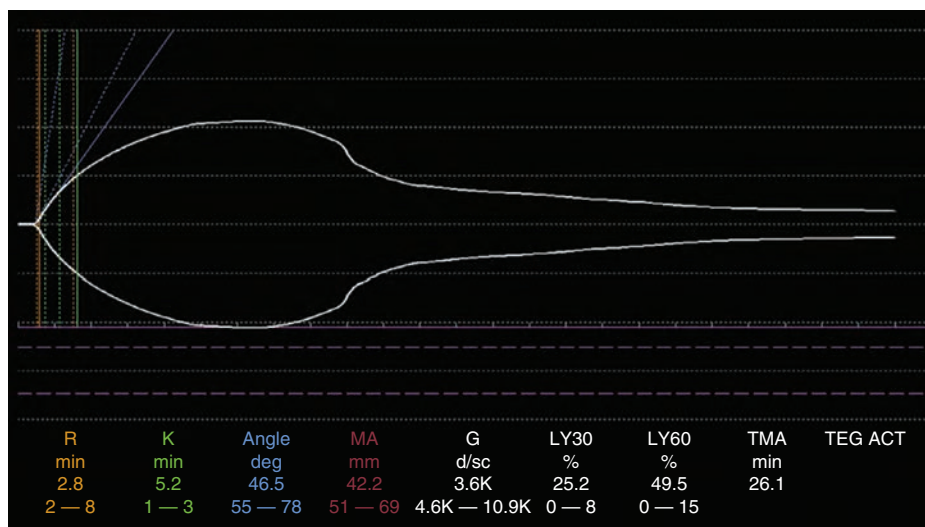


Figure 163.3 Kaolin-activated thromboelastography (TEG) tracing from a 20 kg 3-year-old CM pit bull mix dog hit by a car 60 minutes before; the dog had received 500 mL of lactated Ringer's solution prior to obtaining blood for this assay. The TEG tracing demonstrates a hyperfibrinolytic profile, suggesting that this dog has suffered significant injury.

[50,52], a potent endogenous anticoagulant that inhibits factors Va and VIIIa. Activated protein C also inhibits plasminogen activator inhibitor 1 (PAI-1) and thrombin activatable fibrinolytic inhibitor concurrently, inducing hyperfibrinolysis [53–55]. Soluble thrombomodulin inhibits further thrombin generation [56], tipping the scales further in favor of hypocoagulability. The sympathoadrenal response following trauma is also integral to ACOTS development. Severe trauma can induce a catecholamine surge that can damage the endothelial glycocalyx [57]. This glycocalyx damage results in a shift towards a local procoagulant effect, with shedding and release of endogenous anticoagulants (e.g. heparan sulfate) and profibrinolytic agents (e.g. tPA) into the systemic circulation. This results in systemic anticoagulation and hyperfibrinolysis.

There is equipoise regarding the differentiation of ACOTS from disseminated intravascular coagulation (DIC) characterized by a fibrinolytic phenotype [58]. The Educational Initiative on Critical Care Bleeding in Trauma (EICBT) concluded that ACOTS is distinct from DIC [59] while the Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Haemostasis (ISTH) suggests that ACOTS represents a variation of DIC [60]. Traditionally, early DIC has been considered a hypercoagulable condition with *de novo* tissue factor expression favoring thrombin generation and PAI-1-mediated inhibition of fibrinolysis. Over time, this early prothrombotic and antifibrinolytic tendency wanes and progresses to a consumptive hypocoagulable and fibrinolytic state characterized by clinically relevant bleeding. In simpler terminology, the early stages of DIC can be considered non-overt/thrombotic/antifibrinolytic and the latter stages are overt/hemorrhagic/fibrinolytic. In contrast, ACOTS

may be considered as a process that limits thrombin generation early on in its course via the action of thrombomodulin/activated protein C pathway. Some human trauma victims exhibit hypercoagulability identified using thromboelastography prior to resuscitation (Figure 163.3), a finding that complicates our mechanistic understanding of ACOTS and suggests that further work is required to clarify the similarities and difference between DIC and ACOTS [61].

Platelet dysfunction occurs in some people shortly after trauma and may also contribute to ACOTS [62–64]. The origin of platelet dysfunction in naturally occurring trauma is also multifactorial. In people following trauma, retention of hypofunctional platelets may occur, contributing to hemostatic dysfunction [65]. Widespread release of ADP following tissue trauma in patients with shock may prematurely activate platelets, leading to their exhaustion and then retention in the circulation [66]. This phenomenon may also occur in dogs. In a canine hemorrhage model, where dogs were bled to 80% and 60% of their blood volumes, a progressive but mild hypocoagulability identified using traditional and viscoelastic coagulation tests. Platelet dysfunction can also be identified in this model using impedance aggregometry despite largely unchanged platelet counts [67]. Further work focused on the incidence and impact of platelet dysfunction in naturally occurring canine trauma is warranted, since this may offer a therapeutic solution in some situations (e.g. platelet-containing transfusions).

Trauma-Associated Coagulopathy in Dogs

To date, there are only a handful of publications in the veterinary literature focused on the coagulation defects in

dogs following trauma [24,35,36,68,69]. Prior to evaluating the evidence provided by these studies, the potential impact of analysis timing in relation to resuscitation should be considered. Hemostatic defects identified before fluid administration may more closely resemble the ACOTS phenomenon described in people, while in comparison, coagulopathy identified in dogs after treatment may more accurately reflect RAC or a combined phenomenon.

Several publications have specifically evaluated coagulation status in traumatized dogs prior to fluid administration. One study aimed to evaluate severely injured dogs by utilizing an Animal Trauma Triage (ATT) score ≥ 5 to stratify patients [36]. In this study, 33% of dogs were considered hypercoagulable based on the thromboelastography-derived G value; no hypocoagulable or hyperfibrinolytic tracings were obtained. The finding of hypercoagulability in these dogs echoes some studies in people [70–72] but the lack of convincing evidence for hypocoagulability and hence ACOTS begs the question about the true injury severity of these dogs. Since most dogs in the study had ATT < 10, the inclusion criteria may have been too liberal to identify ACOTS in dogs. Further work on severely injured dogs with evidence of shock prior to fluid administration will be necessary to characterize TAC in dogs and to determine if ACOTS does indeed occur in our patients. In this regard, we must recognize that the most severely injured dogs may be euthanized or die naturally before an opportunity arises to analyze their coagulation status, which may hinder our progress in identifying ACOTS in this species.

Two studies report comprehensive coagulation analyses of 30 dogs that sustained trauma prior to treatment [68,69]. The analyses performed included platelet enumeration and measurement of prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, FDP concentrations, and activities of coagulation factors, protein C, antithrombin, plasminogen and alpha-2 plasmin inhibitor. Thrombocytopenia and factor deficiencies were commonly identified, as were increased soluble fibrin concentrations, reflecting intravascular thrombin generation. Resonance thrombography, a viscoelastic method of coagulation assessment, was also performed. The resonance thrombography results were suggestive of delayed fibrin formation, but there was overlap with controls sufficient to make it insensitive compared to conventional tests.

Two further studies reported data from traumatized dogs that received treatment prior to blood collection for coagulation testing. A large retrospective study of blunt trauma reported coagulation tests performed commonly in emergency practice [24]. Mild-to-moderate prolongations of PT and aPTT were identified in 20.8% and 47.2% of dogs tested, respectively.

Coagulation parameters were not significantly different in dogs that survived to discharge compared to non-survivors. Disseminated intravascular coagulation was only recognized in 2% of the dogs in this study. In a second study involving 40 dogs treated at two institutions, 70% of dogs received crystalloids before blood sampling, making an iatrogenic influence on hemostasis likely. Mild-to-moderate coagulation abnormalities were recognized commonly in these dogs, with hemostatic abnormalities impacting the likelihood of survival, presence of body cavity hemorrhage, and outcome [35]. In this study, coagulation deficits also correlated with indicators of tissue hypoperfusion (i.e. lactate and blood pressure) [35].

Hemostatic Testing for Trauma

The availability of hemostatic assays in emergency practice is hospital dependent. Based on review of the veterinary literature, there is useful information to be gleaned from traditional coagulation tests, including platelet count, PT, and aPTT, when evaluating dogs that have sustained trauma. In human medicine, there are compelling data to suggest a clinical utility for viscoelastic monitoring in the assessment of trauma victims and, in particular, in the prediction of transfusion requirements [73,74]. In veterinary medicine, an additional potential advantage of viscoelastic monitoring is the ability to recognize hyperfibrinolysis, since this offers a potential therapeutic intervention (antifibrinolytics) [75], but more work is required in veterinary patients to establish whether antifibrinolytic drug administration to trauma patients will impart the survival advantage identified in people [76].

Conclusion

Trauma-associated coagulopathy has been described in dogs, but the mechanisms of the observed phenomena are less certain. Currently, there is little evidence to suggest that ACOTS occurs in dogs presenting to emergency rooms following trauma but more work is required to characterize the coagulopathy present in severely injured dogs prior to treatment. The emergency clinician should be cognizant of complicating iatrogenic factors, including dilution, acidosis, and hypothermia, that may worsen pre-existing coagulopathy and negatively affect outcome. Resuscitation strategies for veterinary patients should be based on available data from dogs and until further evidence is available, we can rationally incorporate the early hemostatic transfusion principles developed for people.

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Metabolic Consequences of Trauma

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Introduction

Trauma is defined as tissue injury caused by violence or accident that occurs suddenly and includes physical damage to the body [1]. Traumatic injury is a common occurrence in veterinary medicine. Kolata et al. reported that the incidence of patients seen for trauma at an urban veterinary teaching hospital was approximately 11–13% [2]. Trauma may result from penetrating wounds or blunt forces.

The metabolic consequences of trauma have been well documented in human medicine but less so in veterinary medicine. Several have described the “ebb and flow” phenomenon following trauma [3]. After the traumatic insult occurs, there is initially a decrease in metabolism secondary to a hypovolemia and hypoperfusion. This results in activation of several compensatory physiological mechanisms which attempt to restore hemodynamic stability. As treatment ensues and restoration of volume status takes place, the “flow” state occurs and hypermetabolism and inflammatory changes are seen. These metabolic changes occur via multiple mechanisms which are discussed in more detail below.

Sympathoadrenal Activation

Catecholamine activation after traumatic injury can occur via different mechanisms. One mechanism occurs via loss of blood or fluids leading to hypovolemia. This decrease in blood volume is sensed via baroreceptors located in the carotid bodies and aortic arch. Also, pain can cause catecholamine activation by stimulation of the hypothalamus. Once sympathetic nervous system activation occurs, the adrenal medulla is stimulated and epinephrine and norepinephrine are released. These catecholamines mediate several functions including increasing heart rate, increases in cardiac contractility,

and peripheral vasoconstriction. These effects result in increased cardiac output and help to restore blood pressure.

Neuroendocrine Activation

After the initial sympathetic activation occurs, an additional hormonal response is seen. This response is more long standing and slower in activation but strives for the same goals as the sympathetic response with increased hemodynamic parameters. This response is mediated via release of adrenocorticotrophic hormone (ACTH) and growth hormone. Antidiuretic hormone (ADH) is also released in times of hypovolemia. These hormones result in antidiuresis and help to restore vascular volume. In addition, decreased cardiac output detected by baroreceptors and/or increased sodium levels sensed by chemoreceptors result in activation of the renin-angiotension-aldosterone system. Renin is transformed to angiotensin in the liver and causes vasoconstriction of the peripheral vasculature, shunting blood centrally to more vital organs. Angiotensin activation also stimulates the release of aldosterone, as does sodium concentration and ACTH levels. Aldosterone acts to retain sodium and minimize water loss with additional antidiuretic effects.

Hyperglycemia

Glucose is the main nutrient source for the neurons and red blood cells and results from carbohydrate breakdown [4]. Circulating glucose levels are normally balanced via the interaction of insulin and glucagon. Any excess in carbohydrates is converted to glycogen and stored within the liver. When the level of carbohydrates decreases below normal, moderate quantities of glucose can be formed from amino acids, the glycerol portion of

fat, and lactate; this process is called gluconeogenesis [4]. Glycogen breakdown also helps maintain normal levels of glucose. This process is known as glycogenolysis [4].

After trauma, patients will have elevation in blood glucose secondary to the release of counterregulatory hormones, such as glucagon, cortisol, growth hormone, and catecholamines. Epinephrine leads to proteolysis, glycogenolysis, and inhibition of insulin-mediated glucose uptake by the muscle [5], whereas cortisol release promotes gluconeogenesis, inhibits insulin activity, and exacerbates the effects of glucagon and epinephrine [4,5].

Hyperglycemia has been associated with outcome in human patients. In veterinary medicine, elevated blood glucose has not been associated with outcome, but dogs and cats with hyperglycemia after head trauma did have more significant injury [6]. In these patients, elevated blood glucose levels can increase free radical production and excitatory amino acid release and worsen cerebral edema and acidosis.

Hyperlactatemia

Hyperlactatemia is described as an increase in plasma lactate. Post trauma, lactate levels become elevated as a result of poor tissue perfusion and anaerobic metabolism secondary to hypovolemia and fluid losses. In normal aerobic conditions, pyruvate is converted into ATP via the tricarboxylic acid cycle (TCA), resulting in 36 moles of ATP. During anaerobic metabolism, pyruvic acid is converted into lactic acid; during this process 2 moles of ATP are formed. Even though this seems like a small amount of ATP, glycolysis is fast enough that this may satisfy tissue demands temporarily. The production of NADH^+ and lactate promotes metabolic acidosis and subsequent vasodilation. This alternative energy pathway is essential for preserving cellular function during times of shock and hypoxia. As the shock state resolves and aerobic metabolism returns, lactate is recycled into the TCA cycle and the hyperlactatemia resolves.

Acid–Base Disorders

The most common acid–base disorder seen in trauma patients is metabolic acidosis [7]. Metabolic acidosis is identified in a venous blood gas sample via the presence of low bicarbonate, low CO_2 and blood pH less than 7.35. Metabolic acidosis occurs secondary to the presence of hydrogen ions, lactate, uremic acid, ketoacids, phosphates, and other unmeasured anions. Acidosis is one component of the “triad of death” seen in trauma patients; the other components are hypothermia and coagulation disturbances. Metabolic acidosis can

contribute to coagulopathy and cellular and enzymatic disruptions (see Chapter 163). The degree of acidosis has been shown to be prognostic in some human patients.

The ideal crystalloid for correction of metabolic acidosis is a balanced electrolyte solution (see Chapter 167). Drobatz and Cole revealed a faster correction of acid–base in severely acidotic cats with urethral obstruction when a balanced electrolyte solution was implemented [8]. Sodium chloride has an acidifying effect and it is not recommended in cases with severe metabolic acidosis. Also, fluids with high chloride volume may worsen metabolic acidosis via the Stewart method, resulting in a hyperchloremic metabolic acidosis. Rarely, bicarbonate is necessary to correct the metabolic acidosis (see Chapter 174). The bicarbonate provided will be converted to CO_2 which later needs to be exhaled. If the patient has concurrent respiratory disease then CO_2 will build up, which may result in worsening hypercapnia and acidosis. Fluid therapy to address underlying hypovolemia is usually sufficient to correct acidosis.

Body Temperature

Decreases in body temperature are commonly seen after traumatic injury. The cause of this decrease may be the traumatic injury and exposure or it may occur during initial resuscitation. The hypothermia may be the result of loss of vasomotor tone and subsequent vasodilation. Also, traumatic injury may alter central thermoregulation and affect the body’s ability to respond to decreased temperatures. The shivering response often does not take place in states of hypotension and has been shown to occur at lowered temperatures in injured animals [9].

As hypothermia persists, the renal system becomes affected (see Chapter 148). The primary effects are known as cold diuresis, which is triggered by the sense of increased blood volume induced by peripheral vasoconstriction [10,11]. Also, there is a decrease in response to antidiuretic hormone, which results in poor water reabsorption. The water loss contributes to further hypovolemia, which further reduces cardiac output and renal perfusion, leading to azotemia and renal dysfunction. The decreased renal perfusion results in accumulation of hydrogen ions and metabolic acidosis.

The decreases in temperature can affect coagulation systems and can also contribute to traumatic coagulopathy (see Chapter 163). Decreases in body temperature affect platelet function by decreasing production of thromboxane B_2 and platelet adhesion molecules. Also, lowered temperature can affect coagulation enzymatic activity and fibrinolysis.

Hypothermia, despite its many potential adverse reactions, has also been shown to improve outcome in

certain populations. Hypothermia has been advocated in patients with traumatic brain injury due to decreases in metabolic rate, thereby decreasing oxygen consumption and improving ischemic injury to the brain (see Chapter 19). Also, patients undergoing cardiac and transplant surgery have had similar potential improved outcomes with hypothermia. Despite these reports, evidence remains conflicted and due to the potential detrimental consequences, further research is needed to confirm any beneficial effects of hypothermia in trauma.

Gastrointestinal Injury

Secondary to the shock state, hypoperfusion of splanchnic tissues occurs due to shunting of blood in order to preserve perfusion to more vital structures such as the heart, brain, and lungs. This decrease in blood supply leads to cell injury and death and increased gastrointestinal permeability is seen. This increase in intestinal permeability may result in bacteria translocation, leading to exacerbation of inflammation, and possibly predispose to multiple organ failure and death.

Studies have been performed in both people and dogs showing increases in intestinal permeability up to 48 hours after trauma that improve as recovery from the insult occurs [12,13]. While this change has been documented, not all patients with increases in intestinal permeability go on to develop sepsis or systemic inflammation (see Chapter 159). These discrepancies in pathological changes and clinical effects likely represent differences in immune system ability to clear offending organisms.

Gastrointestinal injury manifests as vomiting, diarrhea, ileus, gastrointestinal ulceration, and bleeding. Prevention is aimed at improvement in shock states. Early enteral nutrition has also been shown to improve GI tract viability and health [14–16]. Enteral feeding should be instituted in trauma patients as soon as possible. Prophylactic antibiotics are controversial and should be used only in cases of confirmed sepsis (see Chapter 200). Use of other medications, such as H₂ blockers, proton pump inhibitors, etc., is also controversial. While these may improve intestinal health, prevent stress ulcers, and decrease incidence of bacterial translocation, altered intestinal flora may also occur and predispose to resistant infection if bacterial translocation takes place. Evidence regarding many of these therapies is conflicting.

Systemic Inflammation

In most traumatic injuries, tissue disruption occurs. This cellular injury, in addition to ischemia and vascular

disruption, can lead to an inflammatory response. The activation of cytokines and release of inflammatory mediators such as interleukin (IL)-6, TNF alpha, and IL-1B occur following the tissue injury. Once released into the bloodstream, these mediators can cause widespread inflammation and possible organ failure. Vascular activation can also occur, leading to coagulation abnormalities as well.

In many patients, this inflammatory response may be mild and self-limiting with appropriate support of vascular and respiratory systems. In other patients, it may be more severe and lead to more widespread complications. One possible contributor to the disparity in degrees of inflammation may be the “two hit” theory. In this explanation, the initial inflammatory response seen after trauma predisposes to a severe inflammatory response. In patients with a second inflammatory trigger, such as surgical repair of the original injury, systemic inflammatory response syndrome (SIRS) and possible multiple organ failure can result (see Chapter 159). In a recent publication reviewing organ dysfunction and mortality in dogs with bite wounds, patients with prolonged anesthesia were more likely to develop multiorgan dysfunction syndrome (MODS) and disseminated intravascular coagulation (DIC), and had a higher mortality rate [17]. Also patients with extensive wounds have a significant risk of developing SIRS.

Treatment or prevention of systemic inflammatory activation is aimed at support of cardiovascular and respiratory systems with appropriate intravenous fluid resuscitation, oxygen therapy, and other vascular support if needed.

Activation of the Coagulation Cascade

Trauma patients commonly have alteration of normal coagulation pathways (see Chapter 163). This change is multifactorial and occurs via several mechanisms. The inflammatory response, as discussed above, can lead to activation of the clotting cascade and initially a hypercoagulable state. As coagulation factors and platelets are consumed, a hypocoagulable state can then follow. This syndrome (disseminated intravascular coagulation or DIC) has been associated with significant increases in morbidity and mortality in both human and veterinary populations [17–19].

Traumatic injury can result not only in DIC and resultant coagulopathy but coagulopathy via other mechanisms. In trauma patients, acute traumatic coagulopathy (ATC) has been seen (see Chapter 163). Acute traumatic coagulopathy can develop within 30 minutes post trauma and may be seen even before fluid therapy is initiated. In the past, hemodilution was suspected to

be an important factor in development of this condition but over the last 10 years it has been demonstrated that ATC is independent of dilution or consumption of coagulation factors and thrombocytopenia [20,21]. Tissue injury and hypoperfusion appear to be the two main initiators of ATC, which can worsen patient outcomes and impair response to treatment. Early identification and correction of coagulopathy, acidosis, hypothermia, and hypovolemia are essential for successful treatment of ATC.

Conclusion

Trauma is a common occurrence in veterinary medicine and these injuries can trigger widespread metabolic changes. Understanding the pathophysiology behind these changes is essential in determining the appropriate therapies used for successful patient outcomes. Also, knowledge of these metabolic changes helps to guide the clinician in selecting appropriate monitoring and treatment goals for patients with traumatic injuries.

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165

Traumatic Orthopedic Emergencies

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General Considerations for the Trauma Patient

Orthopedic emergencies include a small group of traumatic injuries and joint infections. Most orthopedic injuries are not an immediate threat to life, the exceptions being skull and vertebral trauma.

While addressing immediate life-threatening concerns based on initial triage (see Chapter 2), a covering and/or immobilizing bandage can be applied to the affected limb(s). After the patient is hemodynamically stable, the animal should be helped to a standing position. If possible, the patient is walked and general proprioception assessed, followed by a complete orthopedic examination. Gentle palpation of the limbs, along with assessment of range of motion and stability of the joints, should allow localization of fractures or luxations. A digital rectal examination is done to assess pelvic integrity. A complete neurological examination should be performed to assess for concomitant neural injury, which may help dictate prognosis for repair. Radiographs of bones should be delayed until the animal is stable.

Analgesics should be administered but the potential adverse effects of analgesics should be considered in light of the patient's overall condition (see Chapter 190).

Fractures

Under normal circumstances, bones are subjected to multiple forces during daily use. When forces applied to a bone exceed its physiological capacity, traumatic orthopedic injury results, often in the form of a fracture.

Different types of forces or loads applied to bones can result in differences in fracture configuration and energy release. When loaded in compression, bone fails along the lines of the highest shear stress. This leads to

an oblique fracture of a long bone. Tensile forces tend to result in simple transverse fractures perpendicular to the load applied. Bending forces combine both compressive and tensile forces. When a bending force is applied, the convex side of the bone is under tension and the concave side is under compression. Because bone is weaker in tension, the bone fractures perpendicular to its long axis and the fracture propagates towards the compressive side of the bone. Torsional forces generally result in spiral fractures. When multiple forces are applied concurrently, combinations of fracture configurations occur.

Due to the viscoelastic properties of bone, the rate at which a load is applied influences the fracture configuration. Rapid loading results in high-energy storage and much greater damage to the bone in the form of comminution. Whether a fracture is closed or open is determined by the energy released and the amount of soft tissue surrounding the bone. High-energy fractures in the proximal region of the limb, where soft tissues are more plentiful, tend to be closed, while a similar injury toward the distal part of the limb, where soft tissues are less robust, may result in an open fracture. Both regions, however, may sustain substantial soft tissue trauma associated with the fracture.

Closed Fractures

Closed fractures are not addressed initially and repair should be delayed until the patient is stable for general anesthesia. Fractures of the distal extremities may be temporarily splinted. This allows for fracture immobilization, prevents further swelling, keeps a closed fracture from becoming an open fracture, and helps prevent additional soft tissue trauma. Fracture immobilization also increases patient comfort and facilitates movement. Immobilization is best accomplished by including the joint above and below the fracture in a splint. Effective

coaptation of fractures involving bones proximal to the elbow and stifle joints is difficult and requires placement of a spica splint for immobilization of the shoulder and hip, respectively.

Open Fractures

Open fractures are typically the result of high-energy trauma. Open fractures with associated severe wounds should receive initial therapy to control blood loss and limit further contamination (see Chapter 166). Significant bleeding vessels should be isolated and ligated to stop ongoing hemorrhage. The primary goal of open fracture management is to limit acute infection and prevent osteomyelitis. Tissue should be collected or deep tissues swabbed for initial culture and sensitivity to help direct initial antimicrobial therapy. Early use of broad-spectrum antimicrobials is warranted in the treatment of open fractures [1].

Open fractures are classified into groups that describe the degree of soft tissue damage present. The most commonly used in veterinary medicine is the Gustilo–Anderson classification scheme (Table 164.1) [2,3]. Wound care with daily evaluation serves as important management of open fractures because bone healing is associated with soft tissue health and overall wound healing. Gross tissue contamination should be removed as soon as possible to avoid continued bacterial growth [4]. If the wound will be managed open, an absorbent bandage should be used. A splint can be incorporated into the bandage to limit bone movement if it can be applied without further compromise to the injured tissues; alternatively, external skeletal fixation allows wound treatment while providing bone stability. Once the debridement stage of wound healing is completed, non-adherent bandages should be placed over the wound.

Table 165.1 Gustilo–Anderson open fracture classification scheme.

Type	Classification
I	Open fracture with wound <1 cm; mild to moderate soft tissue bruising
II	Open fracture with wound >1 cm without extensive soft tissue damage
III	Open fractures with extensive soft tissue damage
IIIa	Extensive trauma with adequate tissue covering remaining, irrespective of wound size
IIIb	Extensive trauma with soft tissue loss, periosteal stripping, and bone exposure
IIIc	Extensive trauma associated with arterial blood supply injury

The decision to close a wound is dependent on a variety of factors including time from injury, wound appearance, bacterial load, and mechanism of injury (see Chapter 166). Early closure of infected tissue may worsen cellulitis, lead to systemic sepsis, and/or result in osteomyelitis. The time from initial injury to definitive surgical repair of open fractures varies; definitive fracture repair should be postponed until the patient is a good anesthetic candidate and the soft tissues are sufficiently healthy for closure, grafting, or continued open wound therapy.

Decision Making for Fracture Repair

Fracture repair is performed only after concomitant injuries are treated and the patient is considered a stable anesthetic candidate. Goals of repair include anatomical alignment, fragment apposition, fracture stabilization, prevention of infection, repair of soft tissue damage, and restoration of normal function.

Closed reduction and external coaptation of incomplete or closed simple fractures can be performed under general anesthesia. This is rarely an option for open fractures as daily wound evaluation is needed. Radiographs are necessary after coaptation to verify adequate fracture reduction.

Open reduction is the treatment of choice for most fractures. Both internal and external skeletal fixation methods have been used for the treatment of open and closed fractures in veterinary medicine [5–10]. In general, the simplest method that maximizes the stability of fracture fragments while allowing access to soft tissue injuries and minimizing disruption to the soft tissues and blood supply should be chosen. The surgical approach for open reduction of open fractures should be selected in an area away from the initial wound if possible.

Internal fixation with bone plates, pins, cerclage wires, and interlocking nails has been used successfully in the treatment of closed and type I open fractures. Type II open fractures, when managed appropriately, can also be treated with a variety of internal fixation methods. The use of internal fixation is questioned, however, in areas of contamination or infection, particularly with type III open fractures. Articular fractures usually require internal fixation to achieve anatomical alignment, fragment apposition, and fragment stabilization. If damage is too severe to allow reconstruction and stabilization, salvage procedures (joint replacement or arthrodesis) or amputation may be preferred treatment options.

Fractures involving the growth plate of young dogs should be evaluated immediately. If possible, such fractures should be repaired within 3 days of the injury [11]. Although not evident at the time of injury, owners should be made aware that disturbance in growth of long

bones can lead to future angular limb deformities and joint incongruity.

Advancements of internal fixation include minimally invasive techniques that incorporate the theory of biological osteosynthesis. This theory places less emphasis on mechanical factors and greater emphasis on preservation of blood supply and tissue biology during fracture repair. Employing this theory, there is little disruption at the fracture site in efforts to promote rapid secondary bone healing. Both biological osteosynthesis and traditional methods of open reduction and internal fixation have been used in the management of open and closed fractures in veterinary medicine [5–16].

External skeletal fixation is an option to avoid implants adjacent to potentially contaminated or infected areas. External skeletal fixation can be performed with minimal disruption of the surrounding soft tissues and can be removed once fracture stability is achieved. This helps avoid long-term implant-associated complications. Placement of an external skeletal fixator allows easy access for open wound management, which is particularly useful when treating an open fracture [17]. Complications of this technique include pin loosening, drainage from the area around transfixation pins, pin tract infection, implant failure, delays in fracture healing, and non-union.

After repair, patients should be strictly prohibited from strenuous activity for 6–8 weeks. Additional radiographs are recommended at 4–8-week intervals to assess fracture healing. Patients with open wounds should be assessed regularly until wound closure is complete. Alternatively, skin reconstruction techniques can be used to facilitate wound healing (see Chapter 166).

Traumatic Joint Injuries

Penetrating Injuries

Injury involving entry into the joint space should be treated promptly in a manner similar to treatment of open wounds involving bone. Delay of treatment can lead to deep infection and septic arthritis. Although cases of infective arthritis may occur from penetrating traumatic injuries, infective arthritis can also develop from hematogenous spread, or local spread from adjacent tissues, especially after a previous surgery. Arthrotomy or arthroscopy is indicated for complete joint exploration, removal of foreign debris or devitalized bone or cartilage, and lavage. The integrity of intra- and extra-articular structures should be assessed. Tissue samples should be obtained and submitted for bacterial culture and susceptibility testing. Severe injuries should remain open, packed with sterile gauze, and immobilized for daily

wound care and coaptation prior to closure. Very mild penetrating joint injuries with minimal soft tissue damage warrant joint exploration with irrigation and may be closed primarily. Patients should be placed on empiric antimicrobial therapy until targeted antimicrobial selection can occur based on culture and susceptibility testing results (see Chapter 200).

Traumatic Joint Luxation

Joint luxation occurs as a result of damage to the supporting ligaments, tendons, joint capsule, and other soft tissue structures surrounding the joint. Reduction of a joint luxation should occur as soon as possible after the patient is adequately stabilized from the initial trauma. Orthogonal radiographic views are required to determine the degree of injury as well as the direction of luxation and to allow visualization of concurrent fractures. When chosen as the treatment method, closed reduction should be performed under general anesthesia for patient comfort and to allow adequate muscle relaxation; however, occasionally heavy sedation is adequate. Indications for open reduction are listed in Box 165.1.

After reduction, immobilization or support of the joint to limit weight-bearing forces is generally indicated for several weeks until the support structures surrounding the joint are healed or until periarticular fibrosis develops.

Hip Luxation

The hip joint is the joint most commonly luxated in small animals, with the femoral head luxated in the craniodorsal direction. When craniodorsal luxation occurs, the affected limb may appear shortened, adducted, and externally rotated. Radiographs should confirm the presence and direction of luxation and identify concurrent acetabular fractures, slipped capital epiphysis, femoral head and neck fractures, and the presence of hip dysplasia. The presence of hip dysplasia precludes success with most closed and open reduction techniques. In those circumstances, a salvage procedure (e.g. total hip

Box 165.1 Indications for open reduction after traumatic joint luxation.

- Unsuccessful attempts at closed reduction
- Joint relaxation
- Chronic luxation
- Concurrent intra-articular fractures
- Internal stabilization is necessary for adjacent long bone fractures
- Neurological injury suspected and exploration warranted

replacement or femoral head and neck ostectomy) is recommended.

Closed reduction is ideally performed within 12–48 hours of injury, prior to muscle contraction and further cartilage damage. Once reduced, the joint should be manipulated through a full range of motion to displace blood clots and other soft tissues from the joint space. Joint stability is assessed during manipulation. An Ehmer sling should be applied for 1–2 weeks for cranio-dorsal luxations to limit movement and prevent reluxation (Figure 165.1). Reduction should be documented radiographically with orthogonal views before and after sling placement. Reported failure rates following closed reduction may be as high as 50% [18–20]. Failures should be treated with open reduction techniques or salvage joint procedures.

Elbow Luxation

Luxation of the elbow joint occurs most frequently with the olecranon displaced in the lateral direction due to the size and shape of the humeral condyle. Patients are generally non-weight bearing with the elbow joint held slightly flexed with the antebrachium abducted and externally rotated. Orthogonal radiographic views are needed to confirm the diagnosis and rule out additional fractures involving the humerus, radius, or ulna.

Closed reduction is generally successful when performed soon after injury. After reduction, the joint should be tested for collateral ligament stability. External

coaptation (e.g. spica splint; Figure 165.2) with the elbow joint in 140° of extension can be maintained for 7–10 days depending on the severity of the injury. Orthogonal radiographic views are obtained to document reduction. If ligament integrity is questionable and instability persists, internal fixation is recommended.

Miscellaneous Joint Injury

Shear injuries to the carpus, tarsus, and digits are common and often treated with open wound therapy with or without the need for internal fixation, arthrodesis, digit amputation, and/or skin reconstructive techniques.

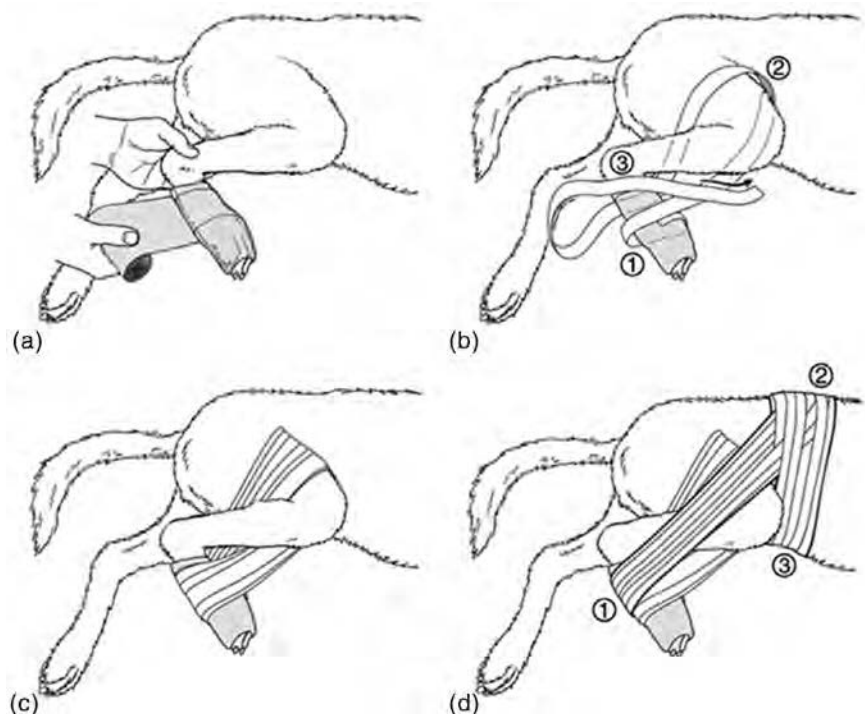
Traumatic stifle derangements and luxations have been reported [21,22]. Salvage procedures or ligament reconstruction techniques can be performed. Temporary stabilization and referral to an orthopedic specialist are recommended.

Skull and Maxillofacial Trauma

Most skull, maxillofacial, and mandible fractures are a result of traumatic injury such as blunt trauma from a vehicular accident, high-impact forces or kicks, or falling from high elevations [23]. These injuries require prompt diagnosis and treatment due to concurrent life-threatening injury to the central nervous system and the reader is referred to Chapter 19 for additional

Figure 165.1 Ehmer sling application.

(a) Begin with application of cotton padding on the plantar metatarsal surface of the foot. (b) Use roll gauze or adhesive tape wrapped from medial to lateral around the metatarsus to cover the soft cotton padding. Next, bring the bandage material from the lateral aspect of the metatarsus to the medial aspect of the flexed stifle (1) and bring the bandage over the cranial aspect of the thigh (2). In a figure-of-8 pattern, continue the bandage towards the medial aspect of the distal tibia and around the plantar aspect of the paw (3). The hock and stifle joints should be flexed with the limb internally rotated at the level of the hip joint. (c) This process is repeated with additional layers of adhesive tape onto the skin or hair. (d) Modification of this bandage includes incorporation of the bandage with adhesive tape around the caudal abdomen. Avoid the preputial sheath in male dogs and shave the hair if necessary to keep bandage from slipping. Reproduced with permission of Elsevier.





(a)



(b)



(c)

Figure 165.2 Thoracic spica splint application. (a) Several layers of cast padding with a layer of roll gauze are placed to incorporate the distal extremity. The bandage is continued over the dorsum to include the thorax in front of and behind the limb. (b) A fiberglass splint is made that begins at the digits and extends over the dorsum. (c) The splint should be broad enough to cover the craniolateral aspect of the shoulder joint. The splint is held in place with an additional layer of roll gauze and an outer protecting layer. Reproduced with permission of John Wiley & Sons.

recommendations. In addition to neurological injury, patients with mandible and maxillofacial trauma should be thoroughly assessed for compromise of the upper airway due to facial and oral swelling. Adequate patient stabilization is necessary prior to definitive fracture repair.

Many skull fractures are amenable to conservative management. The exception is when fracture fragments compromise cerebral blood flow and function or brain parenchyma. When such injuries occur, the surgical

goal is to decompress the surrounding tissue through removal of comminuted fragments. Internal fixation with miniplates has been reported for advanced reconstruction of skull fractures [24].

Fractures involving the mandible and maxilla can be assessed with radiographs or computed tomography for evaluation of fracture configuration, location, and involvement of tooth roots. Most mandible fractures are open to the oral cavity and the discontinuity in the

gingiva or bone is easily palpated or visible on physical examination.

Proper dental occlusion is the goal of fracture stabilization. Removal of teeth is not advised unless involved teeth are fractured, loose, or cannot be stabilized [25]. Removal of teeth may disrupt the blood supply, cause damage to adjacent tissues, further displace fracture fragments, eliminate occlusal landmarks, and/or eliminate available structures for fixation. If the viability of the tooth is uncertain, continue with fracture repair and have the tooth re-evaluated during and after fracture healing.

Fixation techniques include intraosseous and interdental wiring, plates, and external skeletal fixation [26,27]. Interdental wiring and intraoral splinting with acrylic or other composite material is a useful non-invasive technique for alignment of relatively stable fractures rostral to the first molar. Maxillomandibular fixation (bonding the maxilla to the mandible) can be applied to the teeth to maintain alignment and occlusion of minimally displaced fractures of the mandible caudal to the canine teeth.

Symphyseal separation or fracture of the mandible is commonly seen in cats and can be repaired with circumferential wiring using orthopedic wire (Figure 165.3). The wire is generally re-evaluated and removed in 4–6 weeks.

Incomplete fractures or minimally displaced fractures with little effect on occlusion can be managed with support using a muzzle. The muzzle is applied tight enough to maintain occlusion and dental interlock, but loose enough to permit tongue movement for prehension of gruel or liquid food and water. If concurrent injuries will delay definitive treatment of unstable fractures, nutritional support should be provided via an esophagostomy or gastrostomy tube.

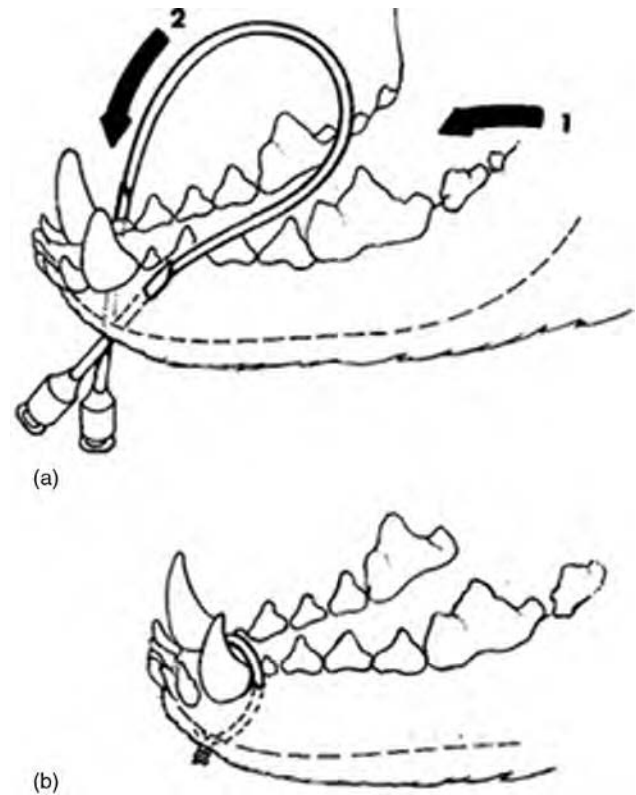


Figure 165.3 Circumferential symphyseal wiring. (a) Direct two 16 gauge hypodermic needles from the ventral midline through the gingival soft tissues to exit lateral to the right and left mandibular bodies. Stay against bone to avoid incorporation of excess tissue. Direct 20 gauge cerclage wire through one needle (1) and redirect the wire to exit the needle on the opposite site (2). (b) Both needles are removed and with the wire seated behind the canine teeth, it is tightened ventrally until no vertical shearing motion can be produced. Close the mouth to ensure adequate dental occlusion prior to final tightening. Reproduced with permission of Elsevier.

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Wound Management Principles

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Introduction

Trauma patients frequently have external wounds of varying degrees of complexity. Oftentimes, these wounds must be addressed after more life-threatening injuries are managed to (see Chapter 2). However, prompt attention to wounds and early appropriate wound management can make the difference between uncomplicated healing and a protracted course of wound complications. What the emergency doctor does to treat an acutely acquired traumatic wound can make a huge difference in the course of wound healing. A comprehensive review of wound management is beyond the scope of this chapter, and can be found in standard surgical textbooks [1–3]. The purpose of this chapter is to guide the emergency clinician in wound management decisions that will optimize healing and minimize patient morbidity. To that end, a basic understanding of wound healing is reviewed as a basis for making treatment decisions. Then, a step-wise organized approach to early wound management is described, incorporating probing questions to stimulate a problem-solving effort in wound management.

Phases of Wound Healing

Wound healing is the process by which tissue continuity is re-established, and this process occurs through coordinated cellular and biochemical events. These events can be explained in phases where activation of different cellular elements and specific signaling molecules takes place. The reader is referred to surgical texts [1–3] for detailed information of the cellular and biochemical processes of wound healing, but a basic understanding of wound healing phases, as follows, is important for decision making in wound management.

Wound healing processes are interwoven and a distinct point of transition from one phase to another is not identifiable but, for discussion purposes, the three

broad phases of wound healing are: (1) inflammation and debridement, (2) repair (also called proliferation), and (3) maturation.

Inflammation and Debridement Phase

Immediately after injury, the wound fills with blood and the clot becomes the first barrier to the outside environment. Transient (5–10 min) local vasoconstriction occurs in response to catecholamines and mast cell products (serotonin and bradykinin) to temporarily decrease blood loss. Then, local vasodilation occurs in response to histamine and interleukin-8 (IL-8), allowing plasma and intravascular cellular components to reach the extravascular space. Platelets and clotting factors gain access to the wound via the damaged blood vessels and are activated to generate fibrin, forming a blood clot. The extracellular matrix created by fibrin in association with fibronectin and activated factor XIII provides a scaffold for cell migration and early collagen deposition in the next phase of wound healing.

Inflammation ensues via migration of leukocytes from the intravascular space into the wound bed. Initially, neutrophils populate the wound, but their numbers are soon exceeded by macrophages. Tissue macrophages and mast cells activated at the time of injury promote the release of prostaglandins and leukotrienes, which attract neutrophils to the wound. Macrophages also produce IL-1, which stimulates endothelial cells to produce IL-8, another chemoattractant for neutrophils. The neutrophils and macrophages gain access to the injured tissue by margination, attachment, and diapedesis. At the wound site, neutrophils release superoxide radicals that kill bacteria and proteinases that help degrade necrotic tissue. Although these actions are important, neutrophils are not essential for wound healing. The neutrophils degenerate and die very soon and, mixed with degraded tissue and wound fluid, form the wound exudate known as pus.

Monocytes from the blood differentiate into macrophages in the wound, and it is the macrophage that is the essential inflammatory cell for wound healing. Macrophages produce cytokines that enhance the immune response. They also produce fibronectin and growth factors that stimulate mitosis and are essential for cell proliferation. Growth factors and cytokines produced by macrophages stimulate fibroblasts to produce and eventually modify the provisional matrix which becomes granulation tissue in the next phase of wound healing. Because macrophages are capable of phagocytosis of large particles, they are also vital to the debridement process.

As the wound becomes free of bacteria and necrotic tissue, the number of macrophages decreases. Fewer macrophages result in lower production of prostaglandins, leukotrienes, and cytokines and, therefore, fewer cells are attracted to the wound bed. However, macrophages will persist in chronic wounds, especially those containing foreign material. These macrophages can coalesce and become very large and multinucleated (referred to as epithelioid macrophages).

The duration of the inflammatory phase of wound healing is generally considered to be 48–72 hours, but the amount of injured tissue and bacterial load can influence the need for neutrophils and macrophages. Greater injury and higher bacterial contamination can prolong this phase, delay the next phase, or result in greater overlap of the phases. Some areas of the wound might have prolonged inflammation while other areas progress to the repair phase.

Repair (Proliferative) Phase

The four prominent processes in the repair phase of wound healing are angiogenesis, fibroplasia, wound contraction, and epithelialization. The end of the inflammatory phase and beginning of the repair phase are marked by the appearance of increased numbers of fibroblasts. One of the hallmarks of the repair phase of open wound healing is the presence of granulation tissue, which is typically evident by 3–5 days after initial wounding. The large numbers of fibroblasts combined with the formation of new capillaries give the granulation tissue its red fleshy and granular appearance. Granulation tissue markedly increases the wound's resistance to infection, serves as a surface for epithelial cell movement, and provides myofibroblasts for wound contraction.

Angiogenesis, the formation of new capillaries from vessels present at the limits of the wound, results from the migration and proliferation of endothelial cells in response to cytokines and growth factors produced by macrophages. This is regulated by the extracellular matrix. Proteins present in the extracellular matrix are responsible for apoptosis of endothelial cells and the

decrease in the number of capillaries as wound healing progresses. As capillaries die, the wound takes on a pale appearance characteristic of old granulation tissue.

Fibroplasia is the proliferation of wound fibroblasts and the resultant production of collagen. Fibroblasts are attracted to the wound by growth factors, and fibroblast migration is influenced by proteins (integrin receptors) in the extracellular matrix. Integrin receptors expressed on the cell's surface guide the movement of both fibroblasts and epithelial cells to cover the wound. Fibroblasts produce collagen and change the predominant type of collagen in the wound. Initially, collagen type III predominates, but collagen type I takes over as the most common type of collagen when the new fibroblasts fill the wound. The height of collagen deposition occurs between 7 and 14 days after wounding. Then, as the numbers of fibroblasts and new capillaries decrease, the collagen content stabilizes and the granulation tissue becomes a relatively acellular scar. The wound continues to gain tensile strength over time as collagen fibers align according to the tension of applied forces during the next phase of wound healing, although the scar tissue never achieves the strength of the original unwounded tissues.

Wound contraction, the process primarily responsible for decreasing the size of a wound, is achieved by the migration of myofibroblasts towards the center of the wound. As the wound contracts, the surrounding skin stretches and the wound changes configuration, often taking on a stellate appearance. Contraction of the wound ceases when the tension on the surrounding skin equals the contracting forces or when epithelialization is complete. The end result of contraction is usually beneficial by decreasing the diameter of the wound and making closure less reliant upon epithelialization. If the opposing forces limit the amount of wound contraction, incomplete closure or an extremely thin layer of epithelium may result. When excessive contraction occurs around tubular structures and joints, strictures and gait abnormalities, respectively, may result. The result of excess wound contraction is termed contracture. Early closure of wounds around tubular structures and joints is desired to avoid contracture and its consequences.

Epithelialization, the covering of the wound with new epithelial cells, begins with mobilization and migration of epithelial cells from the wound edges. Epithelialization begins almost immediately in partial-thickness skin wounds with mobilization of epithelial cells from the wound edges and skin appendages. In full-thickness skin wounds, granulation tissue is necessary for epithelialization to take place. Epithelial cells at the wound edges change their phenotype and disconnect from neighboring cells to migrate across the wound surface. When migrating cells come in contact with each other, movement ceases (contact inhibition), the phenotypic changes

reverse, and a new basement membrane is formed. Concurrent wound contraction minimizes the amount of epithelial migration needed to close the wound, but in large open wounds, where complete contraction does not occur, epithelialization continues. In such cases, a thin layer of epithelial cells covers the wound. This thin layer of epithelium is easily traumatized, and repetitive trauma may prevent epithelialization from being complete.

The duration of the repair phase of wound healing varies because of variable depths and dimensions of wounds, but one might expect this phase to last 1–3 weeks in most cases. Overlap of phases may occur at this juncture, just as there is overlap between inflammatory and repair phases. Some portions of the wound may begin to mature before all repair is complete.

Maturation Phase

Maturation, the phase of wound healing characterized by progressive gain of tissue strength, revolves around collagen deposition. Collagen deposition and gain in tissue strength are marked in the first 7–14 days after wounding, and then the rates of deposition and strength gain decrease. Despite the initial rapid gain in strength, most wounded tissues achieve only 20% of their final strength in the first 3 weeks after wounding. Tissue strength improves by rearrangement and increased cross-linkage of collagen fibers. Maturation may take months or years, but still, the final tensile strength of the scar is only 70–80% of normal tissue. In fact, the process of wound maturation continues for the life of the animal, with only two tissues (urinary bladder and bone) capable of returning to 100% of the tissue's unwounded strength.

Wound Closure

Local wound factors, concurrent injuries, co-morbidities, and time elapsed since the creation of the wound must be considered prior to wound closure in order to increase the chances of uncomplicated healing. Knowledge of how the wound was induced (incision by a sharp blade, gunshot, car accident, etc.) is of the utmost importance in determining the expected amount of tissue trauma and degree of wound contamination and necrosis.

Wounds can be managed by primary closure, delayed primary closure, secondary closure, and second intention healing. First intention healing refers to surgical closure of a wound with the intent of having the apposed wound edges heal to each other without the need for epithelium to migrate across a granulation bed. All three of the above-mentioned closures are performed to achieve first intention healing, whereas second intention healing does not involve surgical apposition of wound edges.

Primary closure is closure of a wound soon after it is created. A planned surgical incision is the most obvious example of a wound suitable for primary closure. Clean wounds can be managed by wound cleaning and primary closure if within a few (preferably 6) hours of wound creation. In such wounds, there should be minimal, if any, need for debridement. At wound evaluation, the veterinarian must decide that the chances of additional loss of tissue viability and infection will be minimal after closure. In addition, primary closure should result in minimal tension on wound edges in order to minimize the chances for dehiscence.

Delayed primary closure is closure of a wound after a delay to determine wound viability but before the onset of granulation tissue. Delayed primary closure is employed when there is minimal to moderate tissue damage, but the chances of contamination progressing to infection are significant. Cleaning, debridement, and bandaging are performed until the wound is suitable for closure. Delayed primary closure is performed within 3 days after wound creation, prior to the presence of granulation tissue. Local or distant tissue (tissue flaps) may be required for wound closure.

Secondary closure is wound closure after the onset of granulation tissue. Wounds with extensive tissue loss or necrosis, severe contamination, or marked presence of debris are good candidates for secondary closure. In such wounds, extensive cleaning is usually necessary due to the presence of large amounts of foreign material (dirt, asphalt, feces, etc.). Debridement of necrotic tissue should be performed daily until additional necrosis is not detected and a healthy bed of granulation tissue covers the wound (usually at least 5 days after wounding). Advancement of local skin with walking sutures, skin flaps, or skin grafts may be required for closure.

Second intention healing is non-closure of a wound. Closure is achieved naturally as previously described. Second intention healing is dependent on wound contraction and epithelialization. Small uncomplicated wounds or wounds where local or distant tissues are not available for closure may be suitable for second intention healing. Second intention healing should be avoided in wounds adjacent to tubular structures (perianal wounds) and in periarticular wounds, due to the risk of stricture and decrease in range of motion, respectively.

Management of Acute Traumatic Wounds and Deciding When and How to Close Them

Emergency practitioners are often presented with wounds that have just occurred, and what veterinarians do to initially manage these wounds may dictate

the ultimate outcome of the definitive treatment. The remainder of this chapter is written to stimulate the reader to think about the decisions involved in acute wound management and accompanying antibiotic therapy that may (or may not) be indicated. Answers to the questions posed below are somewhat incomplete in order to promote an active thought process when managing any particular wound.

Initial Wound Care

Early management of acutely inflicted wounds greatly influences healing and ultimate outcome. When shock or other injuries take priority over wound management, an attempt should be made to quickly cover wounds with clean (preferably sterile) material to provide a barrier to the environment until the wounds can be addressed. As soon as patient conditions permit, the following procedures should be carried out in order, to promote optimal results: prompt and efficient wound inspection, lavage, appropriate debridement, and aseptic bandaging. It is debatable whether topical medications are indicated and, if so, what topical medications should be used. Generally speaking, topical medications, other than lavage solutions, are rarely needed in acute wound management. A “cookbook” approach to the steps in wound management discussed below will inevitably result in an undesirable outcome at an unexpected time. Therefore, thoughtful consideration of the questions below should be part of the wound management process each time a veterinarian is presented with an acute wound to manage.

Wound Inspection

A thorough examination of the wound is essential for determining the immediate course of action, the possibilities for closure, and initial prognosis for success of treatment. Consider the necessity of the various components of wound inspection. Why is adequate clipping of hair around the wound important? How does one protect the wound from clipped hair during the process of clipping, and why is it important to provide this protection? Why are sterile gloves and sterile instruments used to inspect acute traumatic wounds? Is it really necessary that the gloves and instruments are sterile given that these wounds are already contaminated?

Here are some answers: Generous hair removal is important for adequate visualization, optimal decontamination, and general hygiene. Protection of the wound from clipped hair is accomplished by packing the wound with sterile gauze and/or sterile jelly. This protection is necessary to avoid foreign body (hair) contamination of the wound. Sterile gloves and instruments are used to avoid iatrogenic contamination. The wound needs to be protected from contamination by micro-organisms

in the hospital environment that could lead to serious nosocomial infection by resistant bacteria.

Lavage

It is generally accepted that wounds should be irrigated (laved) during inspection and treatment, but why should this happen? And what solutions are appropriate for wound lavage? List one advantage and one disadvantage of pressurizing the lavage. What is the optimal lavage pressure and how can this pressure be achieved? Should puncture wounds be lavaged? Why or why not?

Here are some answers: Wounds are lavaged to hydrate them. Remember the old adage that “moist tissues are happy tissues.” Also, another old adage states that “dilution is the solution to pollution.” As such, lavage is performed to remove small debris and to “dilute” the bacteria that are likely present. Removal of all foreign matter, even the particulate variety, will make the wound environment less conducive to bacterial growth, and copious lavage will help “wash away” bacteria as well. Depending on the solution used for lavage, some bacteria may even be killed.

A number of solutions have been used to lavage acute traumatic wounds. A balanced electrolyte solution with a physiologically acceptable pH (such as lactated Ringer’s solution) is ideal. Other solutions that have been successfully used for wound lavage include normal saline, 0.05% chlorhexidine, 0.1% povidone-iodine, and tap water, the latter typically reserved for wounds that are excessively covered with environmental dirt and grime. When antiseptics are used, solutions should be used; scrubs (detergents) should not be applied to wounds.

Some prefer to pressurize the lavage to facilitate removal of foreign matter in the wound. A disadvantage of pressurized lavage is the potential to drive bacteria into the tissues rather than washing them away. The optimal lavage pressure has been taught to be 7–8 psi achieved using an 18 or 19 gauge hypodermic needle attached to a 35 mL syringe. However, in one study a 35 mL syringe and 16 gauge hypodermic needle produced approximately double that amount of pressure [4]. Lavage of puncture wounds can be detrimental. Doing so could introduce fluid into the subcutaneous tissues, and it is likely that all of the introduced fluid will not be retrieved, ultimately resulting in “iatrogenic” edema. Therefore, it is recommended to not lavage puncture wounds, but rather to surface cleanse them.

Surgical Debridement

Debridement is the “removal of debris,” the removal of dead tissue and foreign material. The proper English pronunciation (dī-brēd’mənt) is recommended to emphasize that debris, not living tissue, is being removed. How does debridement differ from “freshening wound edges”? Why would “freshening edges” ever be indicated?

Describe appropriate anesthesia/restraint for surgical debridement. Why are sterile drapes, instruments, and gloves important for debridement?

Here are some answers: The technique of freshening wound edges involves incision until bleeding is witnessed; therefore, freshening removes viable tissue. Debridement does not remove viable tissue. Freshening edges has no role in surgical debridement of wounds. Freshening is occasionally done during wound closure (see “Freshening Wound Edges” below), but only when necessary for cosmesis or to avoid burying epithelium. The most appropriate restraint for surgical debridement is general anesthesia (see Chapter 190). The actual protocol should be tailored to the individual patient but in most cases, thorough debridement is best done with an intubated patient and inhalant anesthesia. Sterile drapes, instruments, and gloves are important for surgical debridement to avoid iatrogenic contamination.

Aseptic Bandaging

Bandaging a wound after surgical debridement can be beneficial, if appropriately applied, or detrimental, if errantly applied. What wounds require bandaging? What wounds require splinted bandaging? What wounds do not require bandaging? Why is it important for the contact layer of the bandage to be sterile? What is the purpose of a wet-to-dry dressing? When is a dry-to-dry dressing used? When is it appropriate to switch from an adherent to a non-adherent dressing?

Here are some answers: Ideally, all wounds should be bandaged after surgical debridement. Unfortunately, bandaging is not always practical. Essentially, all wounds in hospitalized patients should be bandaged if at all possible in order to minimize the chance of nosocomial wound infection. Splinted bandages are required for wounds around joints or wounds that are otherwise subjected to excessive movement. Wounds that can be safely left unbandaged are those that are covered by healthy granulation tissue and are going to be managed at home and not in the hospital environment. The contact layer of bandages is sterile in order to protect against iatrogenic contamination. Wet-to-dry dressings are used when continued debridement is required. A dry-to-dry dressing is used when the wound is already wet due to exudation, and, like the wet-to-dry dressing, the dry-to-dry dressing is used for debridement. Wet-to-dry and dry-to-dry dressings are adherent to the wound. A switch from adherent to non-adherent dressing is done once there is a granulation bed to protect the granulation tissue from being disrupted during bandage changes.

Negative pressure wound therapy (also called vacuum-assisted wound closure) [5,6] is a nice option for

open wound management in preparation for secondary wound closure. However, this option is frequently delayed 12–24 hours after acute wounds have been managed as described above. This delay is to ensure that no additional surgical debridement is necessary.

Topical Medications/Ointments

There seems to be an innate tendency for veterinarians to apply medications to wounds, and wound care products seem to be widely available. What ointments are appropriate for application to wounds? What ointments may delay wound healing? What ointments may enhance wound healing? List the reason(s) for using any justifiable ointment (is the ointment used for antimicrobial effect, enzymatic debridement, and/or direct enhancement of healing?).

Here are some answers: Any of a number of available topical wound medications may be deemed appropriate. Some for which the author has found appropriate use include triple antibiotic ointment, gentamicin ointment, silver sulfadiazine cream, sugar, and unpasteurized honey. However, the author typically avoids topical wound treatments unless a specified purpose is desired and likely to be achieved with the ointment. Further, one must consider potential detrimental effects of ointments. For example, some ointments will trap exudates in the wound, thereby contributing to bacterial growth rather than combating it. And many ointments will have some negative effect on wound healing. Petrolatum, a base found in some ointments, delays the epithelial stage of wound healing. On the other hand, some topical wound medications enhance wound healing. Notable examples of products that optimize wound healing are sugar and unpasteurized honey. Whenever a topical agent is applied to a wound, a justifiable reason (antimicrobial effect, enzymatic debridement, and/or direct enhancement of healing) should be evident.

Deciding on Wound Closure

Options for wound closure (as detailed above) are primary closure, delayed primary closure, secondary wound closure, and second intention healing. Primary wound closure is closure performed immediately after wounding (within the first few hours). Delayed primary closure is closure of the wound after allowing enough time to ascertain vascular compromise (usually 18–24 hours, but definitely before the onset of granulation tissue). Secondary wound closure is closure after the appearance of granulation tissue within the wound. The presence of granulation tissue signals that the wound is reasonably resistant to infection and therefore safe to close. Second intention healing is non-closure where, instead of closing

the wound, the processes of contraction and epithelialization are allowed to progress naturally to afford eventual closure.

Deciding which method of closure is best for any individual patient requires analysis of multiple factors, such as wound classification, timing of the injury, cause of the injury, and the owner's financial limitations. Relying only on any one of these four factors for determining the method of wound closure is flirting with failure. Box 166.1 gives an outline of the four factors used to determine the most appropriate type of wound closure and discussion of each factor.

Wound Classification

Clean wounds are rare with acute injury. The best example of a clean wound is a surgical incision in aseptically prepared skin that does not penetrate a contaminated lumen such as the alimentary or respiratory tract. Clean-contaminated wounds are wounds with minimal contamination. The best example of a clean-contaminated wound is a surgical incision in an aseptically prepared patient in which the alimentary or respiratory tract is entered. Acute traumatic wounds with minimal environmental debris and absence of necrotic tissue may also be considered to be clean-contaminated wounds. Primary wound closure can be performed with minimal risk of ensuing infection in clean and clean-contaminated

wounds (after appropriate wound inspection and lavage). Contaminated wounds are non-surgical wounds (or surgical wounds with major breaks in aseptic technique) where large bacterial load is likely, but there are no gross signs of infection. Contaminated wounds can be closed by primary or delayed primary wound closure if they are converted to clean-contaminated wounds through the processes of lavage and debridement (Figure 166.1).

Dirty/infected wounds are wounds with foreign debris and/or gross evidence of infection (such as purulent exudate). These wounds might also contain necrotic tissue. For a wound to be infected, enough time must have passed to allow proliferation of bacteria to the concentration of 10^5 bacteria per gram of tissue (or per mL of tissue fluid). Primary wound closure is rarely performed for dirty/infected wounds, but theoretically could be done if the wound can be converted to a clean-contaminated state through the processes of lavage and debridement.

Timing of Injury

Assuming all other factors support primary wound closure, such closure is safer if performed within 6 hours of the injury, because by 6 hours bacteria have had enough time to multiply to numbers capable of causing infection (10^5 bacterial organisms per gram of tissue or per mL of tissue fluid for most bacteria). Wounds older than 6 hours would ideally be managed as open wounds and have delayed primary or secondary wound closure once it is certain that infection is not developing or after an infection that develops is eliminated.

Cause of Injury

Puncture wounds are not typically closed because the amount of subcutaneous trauma is difficult to determine, and the punctures allow for drainage. In general,

Box 166.1 Four factors used to determine appropriate type of wound closure.

Wound classification

1. Clean
2. Clean-contaminated
3. Contaminated
4. Dirty/infected

Timing of injury

1. Within 6 hours of injury
2. Beyond 6 hours of injury

Cause of injury

1. Puncture wound
2. Sharp laceration
3. Sharp laceration with tissue loss (anatomical degloving)
4. Blunt injury (physiological degloving)

Owner's financial limitations

1. Is second intention closure really more economical than surgical closure?
2. Is primary closure ever warranted if dehiscence is likely?



Figure 166.1 Acutely acquired wound on the right flank of 4-year-old female mixed breed dog. The wound was presumably sustained by running into a fence in the owner's back yard a few hours prior to presentation. Because of the unwitnessed and therefore unknown exact nature of the injury, delayed primary closure was performed approximately 8 hours after presentation to the emergency service to allow time to assess tissue viability.

puncture wounds are not surgically explored unless there is a known foreign object that must be retrieved. Probing of puncture wounds is warranted during the inspection stage of wound management in order to determine if the wound should be extended or modified in some way to facilitate drainage.

Sharp lacerations offer the best opportunity for primary wound closure (see Figure 166.1), whereas sharp laceration with tissue loss (anatomical degloving) and open wounds due to blunt injury (physiological degloving) require some time to determine the health of the tissue. Delayed primary closure is more appropriate than primary closure for anatomical and physiological degloving wounds. In some cases, secondary wound closure is best for degloving wounds. If there is any doubt about the degree of tissue injury or bacterial load, waiting for the onset of granulation tissue before closure (i.e. secondary wound closure) is wise (Figure 166.2).

Owner's Financial Limitations

The owner's desire for a fiscally conservative approach may make second intention healing or primary wound closure more appealing than delayed primary or secondary wound closure. However, the wrong closure choice could result in more financial burden than if the wound was managed most appropriately in the first place. Second intention healing may necessitate wound management and bandaging for a protracted period of time, resulting in accumulation of more financial investment than if surgical closure (at the appropriate time) was

performed. Likewise, closing a wound before it is ready could result in infection and/or dehiscence and the added costs of dealing with those complications.

"Freshening Wound Edges"

During wound closure, one is often tempted to "freshen the wound edges." This is contraindicated because it offsets the advantage of the secondary wound phenomenon (i.e. accelerated healing due to already present and active fibroblasts). When might one justify "freshening the edges" of a wound? Perhaps edges should be trimmed if an exquisite cosmetic effect is desired (and in the best interests of the patient). During secondary wound closure, epithelium that has begun migration over the granulation bed may require excision to prevent its burial under the surgically advanced skin edges. One might consider excision of this advancing epithelium to be "freshening of the wound edge." Freshening is not indicated in acute wound management because discarding viable tissue may complicate ultimate wound closure by removing skin that would have been useful to achieve a tension-free closure. Of course, selective trimming of wound edges might facilitate some closures when the shape of the wound is inopportune.

Managing Wound Drainage

Wound drainage can be expected in most traumatic wounds. How is wound drainage managed in open



(a)



(b)

Figure 166.2 Acutely acquired wound (a) prior to and (b) after wound inspection and lavage on the upper right flank of a 6-year-old female Llewellyn setter. The wound was sustained as the dog was running under a trailer less than 6 hours prior to presentation to the emergency service. Despite the ability to quickly address this wound, secondary wound closure was chosen because of the depth of the wound and suspected physiological degloving associated with the blunt trauma. (Caudal is to the lower left and cranial is to the upper right in both images.)

wounds? Drainage must be controlled in wounds that are surgically closed. Methods for drainage control include obliteration of dead space and incorporation of a passive or active wound drain. Describe a wound in which no surgical drain is necessary. Describe the proper method of dead space obliteration. When would a passive or active wound drain be indicated? Identify some particular types of passive drains. Identify some particular types of active drains. What are the advantages and disadvantages of a passive wound drain? What are the advantages and disadvantages of an active wound drain?

Here are some answers: Drainage in open wounds is achieved through the wounds themselves. Ideally, open wounds are bandaged so that wound fluids are absorbed into the bandage material and removed during bandage changes. With negative pressure wound therapy, wound fluid is drawn through the wound contact material (gauze or open cell polyurethane ether foam) and collected in a canister. Drains can be omitted in surgically closed wounds if dead space is obliterated. Dead space is obliterated with careful placement of sutures similar to walking sutures. It can also be obliterated with bandaging, but bandage obliteration of dead space is more readily achieved on limbs than on other areas of the body.

When it is not possible to effectively obliterate dead space with suture or bandage, a passive or active wound drain is recommended. A commonly used passive drain is the Penrose drain. A commonly used active drain is the Jackson–Pratt drain. Passive drains are economical and easily placed, but ideally should be bandaged to collect drainage and protect from ascending infection. Also, passive drains must be maintained for 5 days before removal to ensure that the tissues have sealed to obliterate dead space. A passive drain that can be removed prior to 5 days is probably unnecessary. Active drains pull tissues together, causing early obliteration of dead space and permitting early drain removal (typically 2–3 days after surgery). Further, active suction and the closed nature of the drain help protect against ascending infection. The major disadvantage of active drains is that they are more expensive than passive drains; however, their effectiveness may offset the expense.

Antibiotic Therapy in Wound Management

There is a tendency to prescribe antibiotic therapy for animals with wounds to provide a “cover” for infection, even when there is no evidence that infection is present or likely (see Chapter 200). However, indiscriminate use of antibiotics is potentially harmful. And, as a profession, if we do not curtail inappropriate use of antibiotics, governmental restrictions could limit, or prevent altogether, access to certain antimicrobial drugs for veterinary use.

When managing a wound, certain questions should come to mind regarding antibiotic therapy. Answering these questions is much preferred to the simpler “knee jerk” response of prescribing an antibiotic or applying an antimicrobial ointment. The reader is encouraged to carefully consider the following questions before prescribing systemic or topical antibiotics in the treatment of wounds.

Acute Wounds

The mere presence of a laceration is not an indication for emergency administration of antibiotic therapy. However, the acutely traumatized patient may require antibiotic therapy for other reasons. List some potential indications for antibiotic therapy in acutely traumatized patients. How might antibiotic administration affect the wound?

Infected Wounds

Most clinicians feel that antibiotic therapy is indicated for infected wounds. If that is the case, what antibiotic should be used? By what route should the antibiotic be given? How long should the duration of antibiotic therapy be? What factors guide the choice of antibiotic? Should antibiotic therapy be guided by culture and susceptibility? If so, when and how should the bacteriology sample be obtained? What would be some disadvantages of antibiotic administration in the management of open wounds?

Here are some answers: Patients with traumatic wounds often have concurrent injuries or co-morbidities, and some of the co-existing problems may warrant antibiotic therapy. If the patient is at risk for sepsis, systemic antibiotic therapy is unquestionably warranted. In most cases, such therapy will not adversely affect the wound; however, one must consider that wound infections have been shown to be more common in wounds of patients treated inappropriately with antibiotics than when no antibiotics were used at all [7], and the wrong choice for the wound could exacerbate a resistant infection. In human beings, antibiotic therapy for non-bite wounds treated in the emergency room has been shown to offer no protection against development of wound infection [8]. Furthermore, a lack of advantage has been demonstrated with antibiotic usage in human beings with gunshot wounds [9–12].

In acute wound patients where there is no other reason for antibiotic therapy, a rational approach would be to not use antibiotic therapy unless signs of infection ensue, or to employ perioperative intravenous antibiotics if primary or delayed primary closure is employed, similar to what is done with planned surgical procedures that

warrant antibiotic prophylaxis. If the urge to administer antibiotics as part of wound management is strong, then secondary wound closure would be more appropriate than primary closure.

Choice of empirical antibiotic for the wound itself should be based on the most likely contaminant given the situation. Culture and susceptibility is the ideal method for antibiotic choice; however, the bacteria in the wound at the time of wounding are not always the bacteria responsible for the ultimate infection [13,14], and not all culture-positive wounds result in clinical infection [15]. Therefore, it is most prudent to wait for gross evidence of infection before performing culture and

susceptibility. To optimize accuracy of the culture, tissue from the wound should be obtained rather than merely swabbing the wound. The wrong antibiotic choice can lead to a wound with a resistant infection that is difficult to treat; therefore, wise empirical choices and choices based on appropriately timed cultures of wound tissue are important for optimal results. Intravenous antibiotics are recommended when initiating antibiotic therapy, but a switch to oral medications can often be done to finish a proper course of antibiotics (5–7 days after the last gross evidence of infection). In wounds with established infection, reculturing before secondary wound closure is often warranted.

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Section 5

Fluid and Blood Product Therapy

Crystalloid Fluid Therapy

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Introduction

Crystalloid fluid therapy is one of the most common treatments administered to veterinary patients. Descriptions of intravenous fluid resuscitation date back nearly 200 years, when Dr Thomas Latta used intravenous saline for patients with hypovolemic shock from cholera in Scotland in the early 1800s [1]. Despite great medical advances since that time, controversy regarding fluid dosing and choice continues. Crystalloids are water-based solutions containing electrolyte and non-electrolyte solutes, and are capable of entering all body fluid compartments [2]. The decision to use a crystalloid, and the choice of which crystalloid to administer, should be based on an individualized assessment of the patient.

Physiology of Fluid Distribution

Total body water content in healthy, adult dogs and cats is approximately 60% of body weight. Neonatal animals have a higher total body water content compared to adult dogs and cats (approximately 80% of body weight) [2]. It is important to recognize that these estimates are based on lean body weight, and as such adjustments in fluid therapy may be considered in overweight or cachectic animals.

Total body water is distributed between two major compartments: the intracellular (ICF) and extracellular (ECF) fluid compartments (Figure 167.1). The ICF compartment comprises approximately 66% of total body water (approximately 40% of body weight). It is separated from the ECF compartment by a semi-permeable membrane. The ECF contains the remaining 33% of total body water (approximately 20% of body weight), and is further divided into the interstitial (75% of ECF) and plasma (25% of ECF) compartments. An easy way to remember the division of body water is the 60:40:20 rule; 60% of

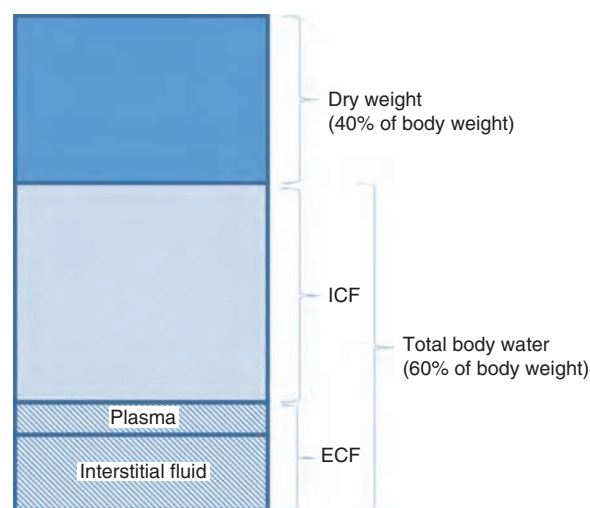


Figure 167.1 Distribution of total body water in small animals.

body weight is water, 40% of body weight is ICF, and 20% of body weight is ECF [2]. These major compartments are separated by semi-permeable membranes which are permeable to water and some other molecules.

Patient Assessment

Crystalloid fluid therapy should be tailored to an individual patient based on the patient's history, physical examination, clinical pathology (e.g. acid–base status, electrolyte abnormalities), and the presence of co-morbidities.

The need for fluid therapy may be divided into three categories: resuscitation (correction of hypovolemia by restoration of intravascular volume), rehydration (replacement of extravascular fluid), and maintenance (maintaining normal hydration status) [2]. It is important

Table 167.1 Physical examination parameters and clinical pathology variables that can be used in the evaluation of dehydration and/or intravascular volume depletion in dogs and cats.

Physical examination	Clinical pathology
Heart rate	Packed cell volume/total solids
Pulse quality/character	Lactate
Mucous membrane color	Urine specific gravity
Capillary refill time	Acid–base status
Mentation	Electrolytes
Skin turgor	Creatinine
Temperature of extremities	
Urine output	
Blood pressure	
Body weight change over time	

to determine if a patient is hypovolemic, dehydrated, or both, as this will direct the rate and volume of fluid administration. Not all patients that are dehydrated are in shock, and not all patients that are in hypovolemic shock are dehydrated. Parameters that are useful to assess a patient’s volume and hydration status may be divided into physical examination and clinical pathology variables (Table 167.1). Based on patient assessment, the clinician should determine whether or not a fluid bolus is indicated (see Chapter 153). The estimated shock volume for dogs is 80–90 mL/kg, and for cats is 50–60 mL/kg. Approximately one-quarter to one-third of this shock volume should be administered as a bolus rapidly over a period of less than 20 minutes. Following administration of a fluid bolus, the patient should be reassessed to determine whether or not additional fluid boluses are necessary.

Following correction of intravascular deficits, consideration should be given to whether or not the patient will benefit from rehydration over a longer period of time, such as the subsequent 6–24 hours (Table 167.2) (see Chapter 171). Maintenance fluid therapy is indicated in patients that are not eating or drinking, but do not have ongoing fluid losses (see Chapter 172).

Types of Crystalloids

Crystalloid fluids consist primarily of water with a sodium or glucose base and the addition of other electrolytes and buffers. They are the fluids most widely used for treating clinical patients suffering from dehydration, cardiovascular shock, free water deficits, and electrolyte imbalances. Crystalloids exert their effects primarily on

Table 167.2 Physical examination parameters associated with varying degrees of dehydration in small animals.

Percent dehydration (%)	Clinical signs
<5	None
5–7	Decreased skin turgor, dry mucous membranes, eyes may be recessed in orbits
8–10	Progressively decreased skin turgor, dry mucous membranes, slightly prolonged CRT
10–12	Tented skin stays up, prolonged capillary refill time, dry mucous membranes, may show signs of shock
>12	Above clinical signs, definite signs of shock, risk of death

the interstitial and intracellular compartments [2]. They may be categorized as replacement or maintenance, and hypotonic, isotonic, or hypertonic.

The main difference between replacement and maintenance crystalloids is in their electrolyte concentrations. Replacement fluids are relatively isotonic to the ECF and are intended to replace lost body fluids and electrolytes. Isotonic crystalloids are either balanced electrolyte solutions or 0.9% saline. Crystalloids with a chemical composition that approximates that of the extracellular fluid have been termed balanced or physiological solutions (see Table 167.3 for further details of composition). Normal plasma osmolality is 290–310 mOsm/L in dogs, and 311–322 mOsm/L in cats, and isotonic replacement crystalloids typically have an osmolality in the range of 270–310 mOsm/L [3].

Isotonic crystalloids are the least expensive resuscitation fluid available, and are commonly used as the first fluid in patients requiring intravenous fluid resuscitation. These solutions are indicated for the rapid replacement of intravascular volume and electrolytes, and are used in clinical conditions such as hypovolemic shock associated with acute hemorrhage or volume loss associated with vomiting or diarrhea. They rapidly redistribute into the interstitial compartment following administration, with approximately 75% of the delivered volume leaving the vascular space within 30 minutes following administration [2].

Isotonic, polyionic crystalloid fluids such as lactated Ringer’s solution (LRS) or Plasma-Lyte 148 may be used as either replacement or maintenance fluids. However, longer term administration of these fluids may predispose patients to hypernatremia and hypokalemia because they contain more sodium and less potassium

Table 167.3 Composition of commonly used replacement fluids.

Fluid type	Sodium mmol/L	Chloride mmol/L	Potassium mmol/L	Magnesium	Calcium	Organic anion (mEq/L)	Glucose (g/L)	Osmolarity (mOsm/L)	<i>In vivo</i> SID	pH
Lactated Ringer's solution	130	109	4	0	3	28 (L)	0	272	29	6.5
Normosol-R	140	98	5	3	0	23 (G) 27 (A)	0	296	42	6.4
Plasma-Lyte 148	140	98	5	3	0	23 (G) 27 (A)	0	294	50	5.5
Plasma-Lyte A	140	98	5	3	0	23 (G) 27 (A)	0	294	50	7.4
0.9% NaCl	154	154	0	0	0	0	0	308	0	5.0
0.45% NaCl	77	77	0	0	0	0	0	154	0	5.0
D5W	0	0	0	0	0	0	50	252	0	4.0
7.5% NaCl	1282	1282	0	0	0	0	0	2564	0	5.0

A, acetate; G, gluconate; L, lactate; SID, strong ion difference.

than a patient will typically excrete [4]. Patients with normal kidney function will not typically become hypernatremic but patients with decreased intake or ongoing losses may become hypokalemic because the kidneys are not able to effectively conserve potassium.

Maintenance crystalloids (such as Normosol-M) contain approximately half the sodium and chloride concentrations of replacement crystalloids, and are therefore hypotonic to the normal patient. These fluids are appropriate to use in patients that do not have any ongoing losses except for expected insensible and sensible losses [5], but are unable to maintain normal fluid and electrolyte intake.

The crystalloid 5% dextrose in water (D5W) is also considered hypotonic, as there is no sodium in this fluid to produce osmolality. Dextrose is added to this solution to prevent hemolysis or vascular endothelial damage but once administered, the dextrose is metabolized to carbon dioxide and water. Administering D5W is therefore effectively delivering intravenous free water, which is then distributed equally according to the distribution of total body water. Thus, D5W is only used to correct free water deficits [5].

Hypotonic fluids distribute throughout both intracellular and extracellular fluid compartments; the larger volume of distribution relative to isotonic fluids and the free water content make these fluids a safer choice for treating patients that have decreased ability to excrete excess sodium or tolerate an increased intravascular volume (such as those with chronic kidney disease or heart disease). Hypotonic fluids should never be given as a

bolus, as they may cause rapid and dangerous changes in the serum sodium concentration and serum osmolality.

Hypertonic saline is a sodium chloride solution with an osmolality greater than that of the patient. It is typically administered as either a 3% solution (osmolality 1026 mOsm/L) or 7.5% solution (2565 mOsm/L). Stock solution of 23.4% hypertonic saline solution may be combined with 6% hetastarch, pentastarch, or 0.9% saline in a 1:2 ratio (resulting in a 7.8% hypertonic saline solution), which is given as a bolus of 3–5 mL/kg [3] over at least 20 minutes. It is important not to administer hypertonic saline at a rate greater than 1 mL/kg/min, as this can result in hypotension associated with effects on the central vasomotor center or via peripheral vasomotor effects [6].

Administration of relatively small volumes of these solutions results in rapid movement of water from the interstitial and intracellular spaces into the intravascular space [5]. This causes volume expansion by 3–5 times the volume administered. However, this volume expansion is relatively short-lived (<30 min) because of redistribution of electrolytes throughout the extracellular space [7].

Additionally, hypertonic saline appears to have minimal effect on overall blood volume post administration, most likely due to the relatively small doses typically used to avoid hypernatremia [7]. Because of the transient effects within the circulation due to fluid redistribution and ensuing osmotic diuresis associated with the high sodium load, additional volumes of isotonic crystalloids or colloids are required to stabilize a patient that is hypovolemic.

Hypertonic saline has additional benefits for the cardiovascular system beyond the volume expanding effects, as well as immunomodulatory effects, and improved cerebral perfusion in patients with head trauma (see Chapter 19).

Crystalloid Fluids in Resuscitation

The identification of patients that require immediate fluid resuscitation is important in order to direct appropriate fluid therapy. Isotonic replacement crystalloids are adequate for initially treating most hypovolemic patients. An important aspect of fluid resuscitation is the individual assessment of the patient's fluid requirements, understanding that these requirements are dynamic and can change frequently.

Fluids are often prescribed in a "one dose fits all" manner for reasons of convenience or when following preset guidelines. Importantly, especially in critically ill patients, one dose does *not* fit all. Considering where in the spectrum of fluid resuscitation and responsiveness a given patient is can significantly affect our approach to how that patient is managed. The volume-expanding effects of crystalloids appear to be context sensitive [8]. This means that hypovolemic patients respond much better to crystalloid fluid boluses than normovolemic patients. As such, patient monitoring, including repeat physical examinations, reassessment of acid–base status and lactate concentrations, and urine output, should be performed frequently.

Based on the large amount of data available, it appears that crystalloids are favorable as the first choice for fluid resuscitation in most patients with non-cardiogenic forms of shock [9]. Because rapid loss of any bodily fluid typically results in extracellular fluid depletion and fluid shifts, crystalloids are a viable initial fluid choice for intravascular volume resuscitation in patients showing signs consistent with hypovolemia.

Several retrospective studies have shown improved outcome in dogs receiving crystalloids compared to those receiving synthetic colloids. One study showed that approximately 74% of hypotensive dogs that received crystalloids alone showed normalization of blood pressure [10]. This was compared to 45.5% of dogs that received both crystalloids and colloids. A second study showed significantly better outcome in critically ill dogs receiving crystalloids (89%) compared to dogs receiving tetrastarch (74%) [11]. In a recent experimental study, it was shown that dogs receiving lipopolysaccharide (LPS) to induce a systemic inflammatory response syndrome (such as may be seen in clinical patients that are septic) had similar hemodynamic responses to a bolus of 0.9% saline versus a bolus of tetrastarch [12].

Due to concerns regarding the potential adverse effects associated with synthetic colloid administration, the most recent edition of the Surviving Sepsis Campaign recommends against the use of hydroxyethyl starches for fluid resuscitation of human patients with severe sepsis or septic shock [13]. Further research examining the adverse effects of synthetic colloids will provide insight as to whether the human guidelines should be applied to small animals.

Which Crystalloid Should We Use?

Both animal and human experimental models have shown that infusions of moderate to large volumes of 0.9% saline can cause a hyperchloremic metabolic acidosis; result in greater extravascular expansion and increased risk of interstitial edema; and result in renal vasoconstriction and reduced GFR, leading to salt and water retention, compared to balanced electrolyte solutions [14,15]. Additionally, the use of 0.9% saline compared to a balanced electrolyte solution has been shown to result in significantly increased in-hospital mortality in critically ill people [16]. The use of saline for fluid resuscitation in dogs with GDV has been shown to result in significant worsening of metabolic acidosis, compared to LRS. The worsening metabolic acidosis was associated with a hyperchloremic metabolic acidosis as the lactate decreased significantly in all dogs [17]. However, in healthy dogs undergoing orthopedic surgery, a comparison of 0.9% saline to Hartmann's solution and a maintenance solution revealed that a hyperchloremic metabolic acidosis did not develop in dogs receiving 0.9% saline [18].

In cats with urethral obstruction, the use of a balanced electrolyte solution during resuscitation compared to the use of 0.9% saline resulted in significantly greater increase in blood pH and bicarbonate [19]. Importantly, there was no effect on blood potassium concentrations (which has been a purported benefit of using 0.9% saline in these cases compared to a balanced electrolyte solution).

These veterinary studies support the use of a balanced electrolyte solution as the fluid of choice in most small animal patients.

How Much Fluid?

As important as the discussion about what type of fluid to use is determining how much fluid to administer. Importantly, optimizing fluid use does not necessarily mean maximizing fluid amounts in our patients. In order to minimize organ injury secondary to hypotension, Rivers et al. [20] introduced the concept of early goal-directed therapy to guide resuscitation in people. Recently, the use of early goal-directed therapy in patients has been

shown to result in the development of fluid overload in up to 67% of patients at 24 hours [21]. Fluid overload and a positive fluid balance following the initial resuscitation period have been shown to result in significantly increased mortality in sick dogs [22]. Positive fluid balance can result in impaired microcirculation and organ dysfunction (of primary concern in critically ill small animal patients are kidney, lung, and GI dysfunction).

Consideration should be given to resuscitating patients according to an individualized physiology-based approach. A conservative fluid therapy approach, aiming to achieve negative fluid balance or at least avoid a positive fluid balance, may be warranted. Additionally, based on recent evidence showing that earlier use of norepinephrine is associated with improved outcome and lower cumulative fluid balance in critically ill people, small animals may benefit from earlier vasopressor support rather than continued fluid boluses to patients that are not responding [23].

Crystalloid Fluids for Rehydration and Maintenance

Following treatment of hypovolemia, continued crystalloid fluid therapy may be indicated to address dehydration and any ongoing losses or maintenance requirements.

To determine the volume of fluid required for rehydration, the typical formula used is body weight (kg) $\times$ % dehydration $\times$ 1000 (see Table 167.2). For example, if a 20 kg dog is assessed as 10% dehydrated, the overall fluid requirement to rehydrate that patient would be 2 liters of fluid.

Maintenance fluid requirements vary according to the age, size, and body condition of a given animal, but estimates of 2–4 mL/kg/h are commonly used initially. Very

small (<2 kg) or giant breeds (>50 kg) may benefit from a body surface area calculation of daily fluid requirements using: body weight (kg)^{0.75} $\times$ 70. Any calculated fluid deficit is typically added to maintenance fluid requirements and corrected over 6–24 hours in stable patients. Ongoing losses may be quantified (for example, weighing vomitus or diarrhea), but this is a rough calculation. As such, ongoing losses are often estimated at 2–4 mL/kg per episode of vomiting or diarrhea. Any estimate of ongoing losses is added to the calculated deficit and maintenance fluid requirements.

Continued monitoring and reassessment of a patient is of the utmost importance during the replacement phase of fluid therapy. Monitoring of physical examination parameters, clinical pathology, and body weight should be performed frequently in all patients receiving intravenous fluid therapy. Body weight monitoring can be particularly useful, as any rapid change in body weight is likely to reflect changes in water weight in the patient. Other physical examination variables and clinical pathology parameters that should be serially monitored are presented in Table 167.1.

Complications of Crystalloid Fluid Therapy

While fluid therapy is often considered relatively benign, it is not without risk. The benefits versus risks associated with the use of crystalloid fluids should always be considered, as with use of any other drug administered to a patient. Complications that can develop associated with the use of crystalloids include volume overload and associated complications; heart failure; development of pulmonary edema; rapid changes in serum sodium concentrations which may result in immediate or delayed neurological signs; and/or development of other electrolyte or acid–base derangements.

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Colloid Fluid Therapy

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Introduction

Colloids are large molecular weight (MW) particles that remain dispersed in liquid due to their size and electron charge. Colloids are too big to pass through the vascular endothelial membrane and exert an oncotic pressure that pulls additional fluid into the vascular space from the interstitial fluid compartment [1]. These properties make colloid solutions desirable during fluid resuscitation because of their rapid and efficient intravascular volume expansion and relatively long-lasting effects. However, colloid solutions are not without side-effects, which tend to occur in a dose-dependent manner.

Colloid Osmotic Pressure

Colloid osmotic pressure (COP) is the oncotic pressure exerted by proteins or protein-like substances. In the context of the intravascular compartment, plasma COP tends to pull fluid into the vasculature in opposition to hydrostatic pressure, thus limiting extravasation of fluid into the interstitium [2].

Starling's equation has been used to describe fluid movement across the vascular wall:

$$J_v = K[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

where J_v is the difference between hydrostatic ($P_c - P_i$) and oncotic ($\pi_c - \pi_i$) gradients, P_c is the intravascular (capillary) hydrostatic pressure, P_i is the interstitial hydrostatic pressure, π_c is the intravascular oncotic pressure, and π_i is the interstitial oncotic pressure. K is the filtration coefficient that represents the ease with which fluids move across the membrane, whereas σ is the reflection coefficient that represents the pore size or permeability of the membrane [2].

In healthy animals, albumin accounts for 80% of plasma COP, while other proteins such as immunoglobulins and

fibrinogen contribute a lesser amount [3]. COP is also enhanced by the Gibbs–Donnan effect, which occurs due to the negative charge of these proteins. Cations such as sodium become non-covalently bound to the negatively charged proteins, which further increases their water-retaining effects [2].

In recent years, a modified Starling equation has taken into account the role of the endothelial glycocalyx, the small pore system responsible for maintenance of the semi-permeable vascular membrane. This glycocalyx covers the intercellular clefts and separates plasma from the space below the glycocalyx that is essentially protein free. The subglycocalyx COP is believed to replace π_i as the primary determinant of flow across a capillary membrane. The low protein concentration in the subglycocalyx of the intercellular spaces accounts for the low J_v , and lymphatic flow from the tissues appears to return a majority of filtered fluid to the circulation as lymph [4].

Colloid Osmometry

Commercially available colloid osmometers are machines used to measure the COP in blood samples (serum, plasma, whole blood) or other solutions. This is achieved by placing the sample into a chamber, which is allowed to equilibrate across a selectively permeable synthetic membrane with a reference chamber that contains 0.9% NaCl. The COP of the sample will cause water and small solutes to move into its chamber from the reference chamber, thereby creating a negative pressure that is measured by a transducer and produces the sample COP measurement [3].

The COP in healthy animals is approximately 21–25 mmHg [3], with plasma COP measuring approximately 0.5 mmHg less than whole blood in healthy dogs [5]. The difference between plasma and whole-blood COP in healthy cats is not significant, but due to slight differences, sample types should remain consistent when serial measurements are performed [6].

Types of Colloid Solutions

Colloid solutions can be classified as natural or synthetic. Natural colloids are blood products that contain albumin, which is largely responsible for COP. Examples include whole blood, plasma components, or concentrated albumin. Synthetic colloids contain high MW particles manufactured from other substances that are suspended in crystalloid solutions. Examples include dextrans, gelatin, and hydroxyethyl starch (HES) solutions. Use of natural versus synthetic colloids, as well as the type of synthetic colloid solution, varies geographically based on what is available or approved by the country’s drug administration program [7].

Natural Colloids

The characteristics of commonly administered natural colloids are summarized in Table 168.1. Because natural colloids are blood products, they often have the inconvenience of a shorter shelf-life, need for specialized storage equipment (e.g. temperature-controlled refrigerator) and administration sets (e.g. filters), as well as requirements for pretransfusion recipient screening (e.g. blood typing and/or cross-matching) [8]. Likewise, blood products are sometimes in short supply or unavailable at the time of need. More information regarding the administration of blood products can be found in Chapter 176.

Whole Blood

Whole blood contains all components of circulating blood, including red and white blood cells, platelets, clotting factors, globulins, and albumin, which exerts the majority of COP. Whole blood is considered *fresh* if stored briefly (<8h) at room temperature prior to

transfusion, whereas *stored* whole blood can be refrigerated for up to 30 days depending on the anticoagulant preservative solution used [8]. Whole blood is typically used as a colloid in patients experiencing life-threatening hemorrhage.

Plasma

Plasma components are prepared from whole blood by centrifugation and are available from most commercial blood banks or in-hospital blood donor programs. Plasma is available as fresh frozen plasma (stored in a -18°C freezer within 6–8 hours of collection), frozen plasma (fresh frozen plasma stored for longer than 1 year or plasma frozen more than 24 hours after collection), or liquid plasma (never frozen and refrigerated for up to 5 days) [9]. While these components vary in terms of their clotting factor activity, they all contain equal amounts of albumin and thus have a similar ability to increase COP and be used as a colloid. However, this is not generally an efficient use of blood products since a large volume of plasma is necessary to increase the albumin by a significant amount.

Plasma components are typically used to correct clotting factor deficiencies in patients with congenital or acquired bleeding disorders, as well as for support of hemostasis in patients with severe hemorrhagic shock and/or undergoing massive transfusion [10]. Plasma can be administered as a colloid in hypoproteinemic patients, but large volumes (20–25 mL/kg) are required to raise the albumin by 0.5 g/dL, assuming no major ongoing losses [8].

Albumin

Concentrated albumin solutions are of a uniform molecular size according to the species of origin and are

Table 168.1 Composition, colloid osmotic pressure, and storage recommendations for natural colloids (blood products) used in veterinary patients [8,34].

Blood product	Composition	COP (mmHg)	Storage
Whole blood	RBCs, WBCs, platelets, albumin, globulin, all clotting factors	21–25	Refrigerated for <30 days
Fresh frozen plasma	Albumin, globulin, all clotting factors	17	< –18°C for 1 year
Frozen plasma	Albumin, globulin, clotting factors II, VII, IX, X, XI, XII	17	< –18°C for 5 years
Cryopoor plasma	Albumin, globulin, clotting factors II, VII, IX, X, XI, XII	17	< –18°C for 5 years
Liquid plasma (<5 days old)	Albumin, globulin, all clotting factors	17	Refrigerated for <5 days
Human serum albumin	Albumin	>200 (25%) 23 (5%)	Room temperature
Canine-specific albumin	Albumin	Unpublished	Room temperature or refrigeration

COP, colloid osmotic pressure; RBC, red blood cell; WBC, white blood cell.

therefore monodisperse colloid solutions. Colloid support in the form of concentrated albumin solutions can be considered for critically ill, hypoalbuminemic patients (i.e. serum albumin < 1.5–2.0 g/dL). Examples include patients with vasculitis, systemic inflammatory response syndrome (SIRS), or sepsis [11]. Unfortunately, patients with ongoing or refractory protein loss (e.g. protein-losing enteropathy or nephropathy) are ultimately going to lose any albumin that is administered and are less likely to benefit.

Human Serum Albumin

Human serum albumin (HSA) is available as 5% or 25% solutions. Dosing regimens are extrapolated from human studies and generally recommended as 2 mL/kg over 2 hours, followed by 0.1–0.3 mL/kg/h. A total daily dose of 2 g/kg should not be exceeded (typically 2.5–5 mL/kg of the 25% HSA solution) [12–14]. Alternatively, some advocate the use of 5% HSA given to dogs at a rate of 2 mL/kg/h over 10 hours, repeated daily as needed to maintain serum albumin concentrations [15].

The possibility of severe and potentially fatal type III hypersensitivity reactions after initial or repeated exposure to HSA has been reported [16–18] even though many hospitalized patients have been given HSA without significant adverse effects. Delayed hypersensitivity reactions have also been reported so repeated administration after 48–72 hours is not recommended.

Canine-Specific Albumin

Canine-specific albumin (CSA) is a lyophilized product that is available in a 5 g vial that can be reconstituted with 0.9% NaCl or 5% dextrose in water (D5W) to a 5% (considered iso-oncotic), 10%, or 16% concentration. A dose of 450 mg/kg is expected to raise the serum albumin concentration by 0.5 g/dL but a maximum daily dosage has not been determined [19]. CSA administration has been

reported in hospitalized dogs recovering from septic peritonitis with minimal adverse effects [20]. Theoretically, CSA is non-antigenic in dogs, so repeat transfusions should not elicit reactions.

Synthetic Colloids

The characteristics of commonly administered synthetic colloids are summarized in Table 168.2. Synthetic colloids are readily available fluid solutions that can be stored at room temperature for extended periods of time. They do not require specialized equipment for administration, nor do they require any form of recipient screening. They are simply administered as an IV fluid, with adjustments in dosing compared with crystalloid solutions, in order to ameliorate the side-effects.

Dextrans

Dextrans are composed of glucose polymers suspended in D5W or 0.9% NaCl. They are polydisperse colloid solutions, meaning they have a broad range of molecules with different MWs, for example, dextran-40 (average MW 40 kDa) and dextran-70 (average MW 70 kDa) [2]. Because a large percentage of the molecules are below the renal threshold for clearance, these colloid solutions have a short half-life and have been associated with acute kidney injury (AKI). They also impair platelet adhesion and factor VIII/von Willebrand factor complex formation [2]. As such, their use and availability have markedly decreased.

Gelatins

Gelatins are colloid solutions derived from bovine gelatin, a derivative of collagen. The forms most commonly used include urea-linked gelatins (polygeline) or succinylated gelatin (modified fluid gelatin). Gelatins are polydisperse colloid solutions and more than 75% of the

Table 168.2 Properties and maximum recommended daily dose of synthetic colloid solutions [24,33,34].

Product	Conc.	Carrier fluid	MW (kDa)	Molar substitution	C2:C6 ratio	COP (mmHg)	Maximum daily dose (mL/kg/day)
Dextran-70	6%	0.9% NaCl	70	NA	NA	62	20
Succinylated fluid gelatin	4%	0.9% NaCl	30	NA	NA	34	Unspecified
Urea cross-linked gelatin	3.5%	0.9% NaCl	35	NA	NA	15	Unspecified
Hespan	6%	0.9% NaCl	600	0.75	4-5:1	26	20
Hextend	6%	LRS	670	0.75	4:1	31	20
Pentaspan	10%	0.9% NaCl	200	0.4–0.5	4–5:1	66	30
Voluven	10%	0.9% NaCl	130	0.38–0.45	9:1	70–80	50
Voluven/ VetStarch	6%	0.9% NaCl	130	0.38–0.45	9:1	36	50

Conc., concentration; COP, colloid osmotic pressure; LRS, lactated Ringer's solution; MW, weight-average molecular weight; NA, not applicable.

molecules are <30 kDa [2]. Therefore, while the small molecules exert a powerful initial COP, the effect is relatively short-lived as the molecules are rapidly cleared. Anaphylactoid reactions have been reported following administration of gelatins. They are manufactured and used mostly in Europe.

Hydroxyethyl Starch Solutions

Hydroxyethyl starch solutions are the most commonly used synthetic colloid in veterinary practice and are the focus of this chapter. First-generation HES solutions were introduced to the United States market in the 1970s. Concerns regarding AKI, hemostatic impairment, tissue deposition, and persistent pruritus in people led to the development of newer generation HES solutions that were initially considered safer. However, these products, which are simply modifications of former HES solutions, have the same side-effects as the older HES solutions [21].

Physiology and Classification

Hydroxyethyl starch solutions contain a polymer of glucose units derived from amylopectin and modified by substituting hydroxyethyl for hydroxyl groups at C2, C3, and C6 positions on the glucose units [22]. HES solutions are polydisperse and classified according to the concentration, MW, molar substitution, carrier fluid, and type of starch molecule. The concentration (e.g. 6% HES) refers to the concentration of HES in solution (i.e. 6 g HES/100 mL).

Hydroxyethyl starch solutions are categorized as first-, second-, or third-generation products relative to their average MW [1]. First-generation HES solutions include high MW products (HES 450/0.7, HES 550/0.7, and HES 670/0.75), second-generation HES solutions include medium MW products (HES 200/0.5), and third-generation HES solutions include low MW products (HES 130/0.4 and HES 130/0.42).

Hydroxyethyl starch solutions are also classified according to their molar substitution or the average number of hydroxyethyl residues per glucose unit, from which the terminology of hetastarch (0.7), hexastarch (0.6), pentastarch (0.5), and tetrastarch (0.4) is derived [22]. HES solutions exist in a variety of carrier solutions, including 0.9% NaCl and balanced/buffered crystalloids (e.g. lactated Ringer's solution).

The starch molecule is either waxy maize (e.g. 6% HES 130/0.4) or potato (e.g. 6% HES 130/0.42), which have small differences in the molar substitution. Potato starch HES solutions have a slightly larger negative charge, which is theorized to contribute to the formation of complexes between HES molecules and endogenous lipid molecules, but with unclear clinical effects [23].

Metabolism and Excretion

Most HES molecules are metabolized by alpha-amylase in the plasma and then cleared by renal excretion or tissue uptake. Small HES (<45–60 kDa) are not metabolized, but simply filtered by the glomerulus and excreted [22]. The rate of metabolism by alpha-amylase is slower with high MW and high molar substitution HES molecules. Likewise, HES molecules with a higher ratio of constituent glucose units hydroxylated at C2 to C6 (i.e. larger C2:C6 ratio) also have a slower rate of metabolic breakdown in the plasma [22].

If not metabolized or excreted, HES molecules are recognized by the reticuloendothelial system as foreign and taken up by monocytes, macrophages, endothelial cells, proximal tubule (renal epithelial) cells, liver parenchymal cells, Schwann cells, and keratinocytes and incorporated into lysosomes where they are resistant to degradation [22]. Smaller HES molecules are hypothesized to be more likely to undergo pinocytosis into cells leading to tissue accumulation, which might explain why recent clinical trials have failed to demonstrate a safety benefit of the low MW and lower molar substitution HES solutions. HES molecules have been detected in the skin, muscle, intestines, and kidneys more than 12–50 months after intravenous infusion in people [22].

Side-Effects

Large randomized controlled trials in the human medical field demonstrate safety concerns with all generations of HES solutions, namely an increased risk of AKI requiring dialysis, coagulopathies, volume overload, and allergic reactions [24]. However, serious adverse effects are largely unreported in small animals.

Suggested mechanisms causing AKI include osmotic nephrosis (i.e. proximal renal tubular vacuolization and swelling), tubular plugging due to hyperviscous urine, attenuation or cessation of glomerular filtration rate, and inflammation of the kidney interstitium [1,24]. A retrospective cohort study investigated the association between HES 250/0.5 administration and AKI or mortality in dogs admitted to a tertiary referral hospital intensive care unit. AKI was defined as a ≥ 2 -fold increase in baseline creatinine or new onset of oliguria or anuria lasting ≥ 12 hours. After adjusting for illness severity, admission type, and concurrent administration of blood products, HES administration was found to be an independent risk factor for AKI and in-hospital mortality, with a number needed to harm of 6 [25]. A prospective investigation of HES administration in canine patients is warranted to confirm these findings.

Coagulopathies are thought to occur secondary to a dilutional coagulopathy, platelet dysfunction, and increased fibrinolysis, as well as decreased concentrations of von Willebrand factor (vWF) and factor VIII

(FVIII) [23]. Veterinary studies investigating the *in vitro* effect of HES solutions on coagulation in canine blood suggest that HES solutions decrease platelet function and fibrinogen in a dose-dependent manner, but there is controversy as to whether these findings are clinically relevant [26–29]. *In vivo* canine studies also demonstrate alterations in coagulation after HES boluses (10–40 mL/kg) and constant-rate infusions (1–2 mL/kg/h), but with no documentation of clinical bleeding [30–32].

Indications

Hydroxyethyl starch solutions can be administered to patients requiring volume resuscitation (i.e. hypovolemic shock) or colloid support, especially those with concurrent hypoproteinemia or hypoalbuminemia (e.g. SIRS or sepsis) that are unresponsive to conventional fluid resuscitation with crystalloids [11,24,33]. HES solutions have also been advocated for hypercoagulable human patients at risk of venous thrombosis [24].

Dose Recommendations

Hydroxyethyl starch solutions should be given in combination with isotonic balanced/buffered crystalloids

and dosed to effect based on goal-directed cardiovascular parameters. Typical IV bolus doses are 5–20 mL/kg (dogs) or 2–10 mL/kg (cats), administered over 15–20 minutes. Alternatively, HES solution administration has been used for COP support at a constant-rate infusion of 20–30 mL/kg/day [24].

Contraindications – Human Medicine

In 2013, marketing authorizations for HES solutions were suspended in Europe. Since then, the United States Food and Drug Administration has stated that HES solutions are contraindicated in critically ill patients, patients with sepsis, severe liver disease, AKI or kidney dysfunction, as well as oliguria or anuria not related to hypovolemia [24].

Conclusion

Hydroxyethyl starch solutions are relatively widely used colloids in veterinary practice with possible side-effects in canine patients that are similar to those in humans. As such, caution should be exercised when using HES solutions in veterinary patients until further prospective studies can be performed.

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Crystalloids Versus Colloids

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Introduction

Intravenous fluid therapy is ubiquitous and often essential for successful patient outcomes in the emergency room. Fluids are drugs and, like all others, vary with respect to indication, composition, dose, and adverse effects [1]. Appropriate fluid selection and generation of a fluid prescription tailored for the individual sick patient will optimize therapy and avoid untoward effects. Recognition of the ebb and flow phases of shock and the need to “de-resuscitate” once shock reversal and/or rehydration have been achieved are also important in ensuring a positive **outcome**.

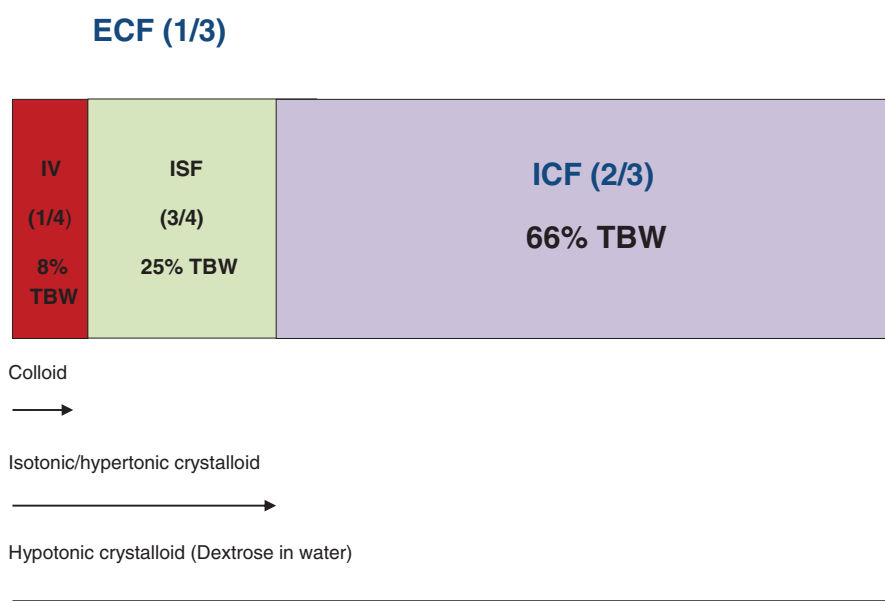
Suitability

Total body water is approximately 60% of body weight. Two-thirds of this water (66%) is intracellular, while the

remaining 33% is extracellular (~25% interstitial; ~8% intravascular) (Figure 169.1). When selecting a particular fluid type, consideration must be given to which body fluid compartment is being targeted. Patients with intravascular dehydration (hypovolemia) will exhibit signs of hypoperfusion, including altered mentation, prolonged capillary refill time, tachycardia, poor pulse quality/low blood pressure (BP), and hypothermia. Alternatively, interstitial fluid deficits are estimated by physical examination findings consistent with dehydration (e.g. dry mucous membranes, decreased skin turgor, retracted eye and/or acute weight loss).

Crystalloids and colloids are the mainstays of fluid therapy in emergent patients. Both fluid types will correct hypovolemia and have historically played integral roles as resuscitation fluids in both human and veterinary patients. However, redistribution of crystalloids across the vascular endothelial barrier to the interstitium

Figure 169.1 Total body water (TBW) is 60% of the body weight. Two-thirds of TBW is intracellular, while one-third is extracellular. Extracellular water is distributed to the interstitium (75%) and the blood (25%). The expected distribution of various fluid types across body fluid compartments is also illustrated below. ECF, extracellular fluid; ICF, intracellular fluid; ISF, interstitial fluid; IV, intravenous.



requires a larger volume infusion and may result in tissue edema (approximately 80% of the volume infused leaves the intravascular space (IVS) within 1 hour of administration). Due to this large volume of distribution, the predominant effect of crystalloids is expansion of the interstitial space. On the other hand, in the face of healthy endothelium, colloids are primarily confined to the blood, and have historically been recommended for selective rehydration of the IVS.

Fluid Prescription: Crystalloids (see Chapter 167)

Indications

Crystalloids are indicated for restoration of intravascular volume in shock states, correction of interstitial and/or intracellular dehydration and concomitant acid–base and electrolyte derangements, and maintenance of total body water (TBW) in the face of ongoing losses.

Composition and Selection

Crystalloids are the most commonly prescribed fluids in human and veterinary patients, and isotonic crystalloids remain the fluid of choice for resuscitation from traumatic shock in people (see Chapter 167) [2]. These fluids are electrolyte solutions dissociated in water that pass through the vascular endothelial membrane barrier and equilibrate throughout the body according to their tonicity. Crystalloids can be further described as replacement versus maintenance, unbalanced or balanced, and hypotonic, isotonic or hypertonic compared with plasma.

Replacement fluids are relatively isotonic to plasma (290–310 mOsm/L). Balanced crystalloids are composed of salt (sodium concentrations, 130–154 mEq/L) and other electrolytes (calcium, magnesium, potassium), in concentrations that make them similar in composition to plasma, and organic buffers (e.g. lactate, acetate) which are metabolized to bicarbonate to help maintain a normal blood pH of 7.4. Examples of isotonic balanced crystalloids include lactated Ringer's solution (LRS), Normosol-R, and Plasma-Lyte-A. LRS is supplemented with potassium and has lactate as a buffer. Normosol and Plasma-Lyte contain potassium and magnesium, and are buffered by acetate and/or gluconate (Table 169.1). These solutions are appropriate for extracellular volume (ECV) repletion.

The prototype crystalloid is 0.9% sodium chloride (isotonic saline). This has historically been considered the fluid of choice as a calciuretic in patients with hypercalcemia, for correction of hypochloremic metabolic alkalosis, and for co-administration with citrated blood products to avoid clot formation. While relatively isotonic to plasma, 0.9% sodium chloride is unbalanced and contains a supraphysiological concentration of chloride (see Table 169.1) [3].

Chloride-rich fluids have also been associated with detrimental renal effects [4,5] and possibly worse outcomes in sick humans [6,7]. Saline infusion compared to balanced solution decreased renal artery flow velocity and renal cortical perfusion in healthy people [4] and increased incidence of acute kidney injury (AKI) and need for renal replacement therapy (RRT) in sick people [5]. Administration of saline versus balanced crystalloids has also been associated with increased postoperative infections, blood transfusion requirements [6], and mortality [7]. One postulated mechanism for this observation

Table 169.1 Composition of commonly prescribed isotonic, hypotonic, and hypertonic crystalloids.

Crystalloid	Osmolality	Organic	Sodium (mEq/L)	Chloride (mEq/L)	Potassium (mEq/L)	Calcium (mEq/L)	Magnesium (mEq/L)	Glucose (g/L)
	mOsm/L	Anion						
Normosol-R	296	Acetate, Gluconate	140	98	5	0	3	0
Plasma-Lyte-A	294	Acetate	140	98	5	0	3	0
0.9% NaCl	308	0	154	154	0	0	0	0
Lactated Ringer's solution	272	Lactate	130	109	4	3	0	0
0.45% NaCl+2.5% dextrose	280	0	77	77	0	0	0	50
Normosol-M+5% dextrose	364	Acetate	40	40	13	0	3	25
Plasma-Lyte-M	363	Acetate	40	40	13	0	3	110
D5W	252	0	0	0	0	0	0	50
3% NaCl	1026	0	513	513	0	0	0	0
7.2% NaCl	2566	0	1283	1283	0	0	0	0

is that enhanced chloride delivery to the macula densa activates tubuloglomerular feedback, triggering afferent arteriolar vasoconstriction and decreasing GFR [8]. Given the evolving data suggesting that 0.9% saline infusion is deleterious, current human recommendations are for preferential selection of balanced crystalloids in most patient cohorts [9,10].

In healthy dogs, saline solutions were more likely to cause metabolic acidosis and lead to increased chloride and decreased potassium concentrations when compared to multielectrolyte solutions [11]. Two studies compared administration of 0.9% sodium chloride with balanced electrolyte solutions to cats with urethral obstruction [12,13]. Both investigations concluded that while these solutions were equally safe and effective, balanced electrolyte solutions (Normosol-R, LRS) led to more rapid normalization of acid–base status. In the prospective clinical investigation, chloride was significantly higher at 2, 6, and 12 hours from baseline in cats receiving 0.9% saline versus Normosol-R [12]. The true clinical relevance of complications attributed to isotonic saline is a matter of ongoing debate [14,15], and large prospective randomized trials (RCT) are needed to further elucidate the role of isotonic saline in dogs and cats.

Maintenance crystalloids (e.g. Normosol-M + 5% dextrose, Plasma-Lyte-M) contain less sodium and more potassium than replacement fluids (with the exception of 0.45% saline + 2.5% dextrose which contains no potassium) (see Table 169.1). Such fluids are typically utilized in hospitalized patients requiring prolonged fluid administration (due to ongoing sensible and insensible fluid losses) and for replacement of interstitial and/or intracellular fluid deficits.

Hypotonic crystalloids primarily add water to the extravascular fluid compartment. These fluids (e.g. 5% dextrose in water) are appropriate for replacement of extravascular free water deficits and maintenance of TBW in hospitalized patients (see Table 169.1). Maintenance and hypotonic fluids are not appropriate for resuscitative purposes, as rapid or large-volume administration can result in acute hyponatremia and/or cell swelling and lysis that can be fatal [16–18].

Hypertonic saline (HTS) (e.g. 7.5% and 23.4% NaCl) contains high concentrations of sodium and chloride, which draw water by osmosis from cells and the interstitium and expand the intravascular fluid compartment in excess of the volume infused. These fluids are best reserved for patients who are hypovolemic but euhydrated. The ability of HTS to rapidly increase plasma volume (PV) after a small-volume infusion makes it an attractive fluid for incorporation into limited fluid volume resuscitation (LFVR) strategies. The goal of LFVR is to reach resuscitation endpoints with the smallest volume of fluid possible, and this strategy may benefit

patients suffering from traumatic brain injury (TBI) or severe burn injury (SBI) (or following polytrauma), where interstitial fluid accumulation following aggressive initial resuscitation can increase patient morbidity and mortality [19]. As with other crystalloids, the PV-expanding effect is short-lived (20–30 min) due to sodium and fluid equilibration across the endothelium. Concurrent administration with a non-protein colloid (HTS with hetastarch or dextran HTS-D) can help retain fluid in the intravascular space, prolonging the effects for 2–3 hours [19].

In addition to its PV-expanding effects, HTS results in vascular smooth muscle relaxation and arteriolar vasodilation, lower blood viscosity, reduced endothelial cell swelling, and improved regional blood flow. Beneficial cardiac effects include increased cardiac output and improved coronary perfusion. Increased PV results in reflex cerebral vessel vasoconstriction and subsequent reduced intracranial volume. This effect, along with improved blood rheology, leads to reduction of intracranial pressure (ICP) and improved cerebral perfusion. Additionally, HTS has favorable immunological effects, including blocked expression of neutrophil adhesion molecules, inhibition of proinflammatory cytokines (e.g. IL-1-beta, IL-6, TNF-alpha), promotion of T-cell function, and augmentation of neutrophil phagocytic activity [17–23].

To date, the evidence suggests that while HTS boluses (alone or combined with a colloid) are effective at transiently increasing BP in shock patients and reducing ICP in patients with neurological disease, they do not appear to consistently reduce mortality or improve neurological outcomes in these patient groups [22,24–26]. Additionally, meta-analyses have failed to identify an advantage associated with their preferential administration (with or without a colloid) over isotonic crystalloids [25,26].

Adverse Effects

Crystalloids are readily available, cheap, and believed to have a favorable safety profile compared to colloids (see below). However, there are fluid-related complications which can be either specific for individual solutions or general across all fluids of this type. The specific complications associated with normal saline have already been discussed. LRS is hypotonic (and may result in hyponatremia with prolonged infusion) and contains calcium (which can bind to citrate anticoagulant and cause clot formation if administered concurrently with blood products). Additionally, the D-isomer of LRS is proinflammatory (the current veterinary LRS formulation is a racemic mixture of L- and D-isomers) [24]. Buffers found in IV fluids can also result in untoward effects. Lactate in LRS can accumulate in patients with liver dysfunction,

and may complicate interpretation of hyperlactatemia as a global index of cellular hypoxia. Acetate, metabolized predominantly by the muscle (versus the liver for lactate), may be preferable in patients with hepatic disease, but can cause vasodilation and hypotension following rapid infusion. Dextrose-containing solutions (maintenance and hypotonic fluids) can lead to hyperglycemia, which is associated with immunosuppression, increased infection risk, and increased mortality in critically ill human patients [27]. And complications associated with HTS administration include cellular and interstitial dehydration, hypernatremia and increased serum osmolality, hyperchloremic metabolic acidosis, hypokalemia, coagulopathy, and vagally mediated bradycardia, hypotension and bronchoconstriction following rapid infusion [22,23].

Most commonly utilized isotonic crystalloids (with the exception of the L-isomer of LRS and 0.9% saline) can contribute to “resuscitation injury” (see Chapter 158), which is characterized by upregulation of proinflammatory cytokines, augmentation of neutrophil adhesion to the vascular endothelium, stimulation of the neutrophil oxidative burst, and increased cellular apoptosis in various organs [24]. These alterations may lead to increased risk of infection.

The most deleterious effect of isotonic crystalloid administration is likely fluid overload (FO). Historically, the recommended dose of isotonic crystalloids for traumatic shock patients was 3 volumes infused for every volume of blood lost (3:1 rule) [28]. It has become apparent, however, that redistribution of these large volumes to the extravascular space results in interstitial and organ edema, organ dysfunction, and increased patient morbidity/mortality [29–39]. Pulmonary edema from FO impairs gas exchange, reduces compliance, and increases work of breathing. Diastolic dysfunction and arrhythmias may result from myocardial edema. Splanchnic edema and/or hepatic congestion can lead to ileus and increased gut wall permeability and cholestasis, respectively. Renal impairment can occur subsequent to increased interstitial pressures or as a consequence of abdominal compartment syndrome (as this occurs in association with tissue edema). Hemodilution, coagulopathy, and hypothermia are other possible consequences of FO. Soft tissue edema with a concurrent heightened proinflammatory response can result in decreased wound healing. Hypervolemia results in atrial stretch and subsequent release of atrial natriuretic peptide (ANP), which serves to increase renal salt and water excretion and reduce plasma volume. However, ANP has also been shown to directly damage the endothelial glycocalyx (EG), a crucial component of the endothelial surface layer (ESL) that controls vascular permeability and regulates extravascular fluid flux [30–32].

The adverse effects of FO are well-documented in human emergency critical care (ECC) patients [29]. In 1990, Lowell et al. demonstrated that acute postoperative weight gain (an indication of water and sodium retention) was correlated with mortality [29]. More recently, human patients with acute lung injury or acute respiratory distress syndrome randomized to a conservative versus liberal fluid strategy showed improved oxygenation, decreased ventilator days, and fewer days in ICU in the conservative group [35]. Trials evaluating patients at risk for or with AKI have found that FO is associated with worse outcomes if present at diagnosis of AKI or at peak serum [creatinine], and that achieving a negative mean daily fluid balance decreases risk of death in this patient group [36–39].

Fluid Prescription: Colloids (see Chapter 168)

Colloid solutions contain macromolecules that are impermeable to the endothelial barrier and generate an intravascular oncotic pressure. The pharmacodynamic profile of colloidal solutions differs from that of crystalloid solutions, with a volume of distribution theoretically limited to the intravascular space. Data from healthy people and experimental animals historically demonstrated that 3–4 times as much crystalloid as colloid infusion volume is needed to achieve an equivalent increase in intravascular volume [1]. The volume-sparing potential of colloids makes them an attractive alternative to crystalloids in both shock resuscitation (LFVR) and treatment of hypo-oncotic states. However, recent clinical data have challenged these purported advantages, particularly in severely ill patients [26,27,40,41]. In addition, documented adverse effects associated with the use of synthetic colloid solutions have raised serious concerns regarding their safety [42,43].

Composition and Selection

Colloid solutions can be broadly categorized as natural or synthetic. Natural colloids include plasma products, purified albumin products, and concentrates. Synthetic colloids include hydroxyethyl starches (HES), dextrans, and gelatins. Hydroxyethyl starches are currently the most commonly used synthetic colloid in veterinary medicine.

Natural Colloids

Plasma products are primarily indicated for patients with acute hemorrhage or coagulopathy [24]. Large volumes of plasma are required to increase serum albumin

concentrations and plasma colloid osmotic pressure (COP), with approximately 40 mL/kg of plasma required to increase serum albumin concentration by 1 g/dL [44]. Administration of blood products carries the risk of both immediate and delayed reactions, ranging from self-limiting febrile reactions to more severe or even fatal reactions such as anaphylaxis or transfusion-associated acute lung injury (TRALI). Other possible transfusion-related adverse events include immunomodulation, citrate toxicity, and blood-borne pathogen transmission [45]. In veterinary patients, limited availability and expense must also be considered. Given the risks associated with plasma products, their role in the treatment of shock (in the absence of significant bleeding) or general oncotic support is limited.

Human serum albumin (HSA) solutions are commonly used in critically ill human patients and are commercially available in concentrations ranging from 4% to 25%. These solutions can be used to treat hypoalbuminemia, as an adjunct in shock resuscitation, and for maintenance of oncotic support. Advantages of albumin over non-protein colloids include drug and hormone binding, maintenance of ESL integrity, and antioxidant properties [44]. Even so, the general utility or advantage of albumin therapy in human ECC patients remains controversial. The landmark SAFE trial, published in 2004, evaluated resuscitation with 4% HSA compared with normal saline in ICU patients. Although albumin administration was found to have an acceptable safety profile, an outcome advantage was not found with this therapy over saline alone. In subgroup analysis, patients with TBI randomized to albumin resuscitation had an increased rate of death at 2 years, suggesting a detrimental effect in some cohorts [46].

More recently, the ALBIOS trial evaluated the use of albumin in human patients with severe sepsis or septic shock. Patients treated with albumin had a higher MAP and lower net fluid balance, but neither a mortality difference nor a difference in total administered fluid volume was found between groups [47]. Although albumin administration may improve hypoalbuminemia and ameliorate certain parameters of shock, the failure to demonstrate an improvement in outcome challenges the preferential selection of this more expensive product.

Despite incomplete albumin homology between species, HSA has been successfully utilized in veterinary patients. Initial studies demonstrated that administration of HSA in critically ill dogs and cats was safe and significantly increased serum albumin concentration, COP, BP, and total protein concentrations [48–50]. Severe, even fatal, type III hypersensitivity reactions in dogs treated with HSA have been reported, but this risk was postulated to be limited to HSA administration to healthy dogs [51,52]. However, type III hypersensi-

tivity reactions in two ill dogs treated with HSA were recently reported, confirming that critical illness does not preclude the risk of antigenic reactions to this solution [53]. Risk also exists with repeat administration, as anti-HSA antibodies are produced in dogs within weeks of administration [54]. While routine administration of HSA solutions to veterinary patients is controversial, this fluid type may have a role in treatment of specific populations of severely hypoalbuminemic patients provided there is recognition of the associated risks. To date, outcome data with the use of albumin products in veterinary patients are absent.

A lyophilized canine-specific albumin (CSA) is sporadically available and was evaluated in seven dogs with septic peritonitis. Dogs treated with CSA had increased albumin concentrations, COP, and systemic BP 2 hours post transfusion, compared with a matched, clinician-directed, control group. In this small trial, the product appeared to have an acceptable safety profile, but sample size was insufficient for outcome analyses [55]. Future studies and product availability will dictate the role of CSA as a fluid therapy adjunct.

Synthetic Colloids: Hydroxyethyl Starches

Hydroxyethyl starches are natural polysaccharides dissolved in isotonic saline or a balanced crystalloid solution. Modification of HES molecules alters their metabolism, with half-life directly proportional to the average molecular weight (MW), molar substitution, and C2/C6 substitution ratio [56]. The isotonic, hyperoncotic HES formulation (6%) is most commonly used in both veterinary and human medicine. Commercially available HES solutions are outlined in Table 169.2 and further details can be found in Chapter 168.

Hydroxyethyl starch is metabolized in the blood by serum amylase and subsequently excreted in the urine or taken up into tissues. In the presence of an intact, healthy ESL, the volume of distribution of HES solutions is theoretically limited to the intravascular space. The large osmotically active particles in these solutions retain water within the plasma compartment and impede tissue edema. Absorption of HES molecules into the glycocalyx layer of the ESL has been proposed to further augment resistance to ultrafiltration of fluid across the capillary barrier [57].

In an effort to minimize the risk of FO, colloid solutions have been implemented in the treatment of diverse populations of sick patients. However, studies in severely ill human patients have revealed a less than predicted volume-sparing effect of colloidal solutions compared to crystalloids, with intravascular volume expansion efficacy close to a ratio of 1.2–1.4:1 for crystalloid:colloid [40,41].

Table 169.2 Nomenclature and classification of various available hydroxyethyl starch solutions.

Generation	MW/MS	Concentration	Classification	C2/C6 ratio	Carrier solution	Trade name
First	670/0.75	6%	Hetastarch	4.5:1	Balanced	Hextend®
	600/.07	6%	Hetastarch	5:1	Saline	Hespan®
	480/0.7	6%	Hetastarch	5:1	Saline	Plasmasteril®
Second	200/0.62	6%	Hexastarch	9:1	Saline	Elohes®
	200/0.5	6% or 10%	Pentastarch	5:1	Saline	Pentaspán®
	70/0.5	6%	Pentastarch	3:1	Balanced	Hemohes®
Third	130/0.42	6% or 10%	Tetrastarch	9:1	Saline	Tetraspán®
						Vetstarch®
						Voluven®
	130/0.42	6% or 10%	Tetrastarch	9:1	Balanced	Volulyte®

MS, molar substitution; MW, molecular weight.

The integrity of the ESL is thought to play a critical role in the fluid flux between the IVS and the interstitium. In healthy euvoletic patients with an intact ESL, colloids are retained in the IVS and maintain intravascular volume better than crystalloids [1]. A veterinary study evaluated blood volume (BV) expansion by different solution infusions in healthy dogs, and synthetic colloidal solutions (Dextran-70 and 6% HES) generated the largest cumulative effects, with BVs that continued to increase beyond the administration interval [21]. However, damage to the ESL is common in critical illness and can occur secondary to systemic inflammation, FO and hypoalbuminemia itself [32]. When the EG becomes degraded and capillary hydrostatic pressures are low, increased vascular permeability and capillary leak ensue and allow for extravasation of both proteins and synthetic colloids [1]. Under these conditions, crystalloids may be as effective as colloids in volume-expanding capacity. A comparative veterinary research study evaluated the effect of tetrastarch administration on hemodynamic and laboratory variables in healthy dogs and dogs with lipopolysaccharide (LPS)-induced systemic inflammation, compared with an equal volume of saline. Despite the provision of oncotic support, no significant beneficial effect on hemodynamic stabilization (HDS) in the LPS-treated dogs was demonstrated with tetrastarch over normal saline [58].

Under ongoing debate is the utility of colloids for the treatment of hypovolemia and anesthetic-induced hypotension. Clinical data have supported a hemodynamic advantage of colloid administration over crystalloids in the acute phase of hypovolemic resuscitation. Data from large RCTs in human intensive care have shown that resuscitation with HES solutions, compared to crystalloids alone, provided more rapid HDS, reduced vasopressor doses, and significantly higher central venous

pressures [40,41,59,60]. There are smaller human trials which have favored the use of colloids over crystalloids in the treatment of trauma and hypovolemic shock [60,61]. These studies have shown trends towards improved outcome, with insufficient study populations to demonstrate an outcome advantage. Similar to other larger clinical trials, although time to HDS was expedited and initially more efficient with the use of HES, a sustainable volume-sparing effect was not documented. Meta-analyses have failed to show an outcome advantage with the use of HES in any patient cohort [42,43].

Experimental veterinary trials have shown an advantage with HES resuscitation over crystalloids for anesthetic-induced hypotension. In one of these trials, hypovolemia was induced via blood draw in isoflurane-anesthetized dogs, and resuscitation with HES was more effective than LRS at achieving HDS [62]. A second trial evaluating isoflurane-induced hypotension in normovolemic dogs also found HES to be superior to LRS at restoration of HDS. These authors recommended colloid administration in lieu of crystalloid for anesthetic hypotension, particularly in the face of ongoing surgical blood loss [63]. Given the short duration and low volume of HES administered in the perioperative setting, it is possible that some of the described adverse effects of HES use may be avoided in this patient population. However, robust safety data in veterinary patients are lacking, and vigilance is warranted.

Adverse Effects of HES

Safety concerns with HES products have made their continued use controversial. The most significant adverse effects are coagulopathies, AKI, tissue accumulation, and trends towards increased mortality [1]. Increased postoperative bleeding tendencies and transfusion requirements have been documented in people treated with HES.

The etiology of HES-associated coagulopathy is multifactorial. Administration of HES leads to platelet dysfunction, reduced von Willebrand factor (vWF) and factor VIII (FVIII) activity, and an acquired fibrinogen deficiency or dysfunction in both animals and people [64]. Hypotheses that more modern HES solutions (tetrastarches) would be devoid of hemostatic impairment remain unsubstantiated. Recent data evaluating these solutions in both people and animals have shown reduced, but not absent, HES-associated coagulation abnormalities and clinical bleeding tendencies. The hemostatic effects and clinical bleeding associated with 6% HES (600/.75), compared with LRS, in healthy dogs anesthetized for orthopedic surgery were evaluated. Although there was a significant prolongation of prothrombin time and buccal mucosal bleeding time at 1 hour post infusion in both groups, there was no significant difference between groups in vWF antigen concentration, FVIII activity, platelet aggregation or clinical bleeding [65]. Numerous other experimental and *in vitro* veterinary studies have confirmed the coagulopathic effects of HES, with hypocoagulable changes demonstrated via platelet function tests and thromboelastographic analyses [66–70]. It has yet to be determined whether these hemostatic changes translate into an increased risk of clinical bleeding in veterinary patients.

Several RCTs in critically ill human patients have demonstrated an association between HES administration and AKI and increased need for RRT. Proposed pathophysiologies are hyperviscosity-mediated ischemic injury, HES uptake by the renal interstitial reticuloendothelial system (a property unique to HES over other synthetic colloids), and osmotic nephrosis [71–74]. The CHEST and S6 trials were two highly influential RCTs that showed an increased incidence of AKI and need for RRT in patients randomized to receive HES solutions [40,41]. Similarly, a recent Cochrane review specifically evaluated the effect of HES on kidney function, compared with any other fluid therapy. This meta-analysis concluded that all HES products increase the risk of AKI and RRT across patient populations and that a safe volume of any HES solution has yet to be determined [43]. The use of HES solutions is currently banned in Europe and Surviving Sepsis Campaign guidelines recommend against the use of HES for fluid resuscitation of patients with severe sepsis and septic shock (grade 1B) [75].

The incidence or risk of HES-induced AKI in the veterinary population has been less well investigated. A recent retrospective study evaluated the incidence of AKI in dogs treated with 10% HES 250/0.5 and found that dogs treated with this HES solution had an overall increased risk of in-hospital death and AKI [76]. This risk persisted after adjustment for confounding variables, and appeared to be dose dependent. A small prospective study investigated the presence of neutrophil gelatinase-associated

lipocalin (NGAL), an early biomarker of AKI, in 15 dogs with sepsis requiring laparotomy. Dogs that were treated with HES had significantly higher NGAL levels than dogs that did not receive HES across all time points in the study, suggesting a contribution to kidney injury [77]. Conversely, a second retrospective study evaluated creatinine levels in dogs admitted to a university ICU and found no increase in creatinine in dogs treated with HES compared with those treated with crystalloids alone [78]. Large RCTs are needed to better assess the risk of these products in veterinary patients.

Summary

The only clearly defined role for (natural) colloids in ECC patients is for treatment of coagulopathy. Preferential selection of colloids for treatment of shock and/or maintenance of plasma COP in sick animals cannot be recommended based on current literature. The incorporation of artificial colloids into LFVR strategies for short-duration use in low doses (e.g. for traumatic shock or anesthesia-associated hypotension) may prove to be safe and of therapeutic value. However, at this time their role remains unclearly defined.

Fluids: Strategies, Dosages, and Endpoints

Undeniably, fluids play a fundamental role in shock reversal. However, overzealous or indiscriminate fluid administration can result in patient harm. When designing a fluid strategy individualized for a sick patient, consideration must be given to injury type, severity, and stage.

For shock patients, fluid resuscitation can be divided into four stages: Rescue (or salvage); Optimization; Stabilization; and De-escalation (ROS-D) [79,80]. During the Rescue stage, patients typically require aggressive early IV fluid therapy to restore effective circulating volume and prevent multiple organ failure (the ebb phase of shock) [80]. In both human and veterinary patients, early goal-directed therapy (EGDT) has been shown to improve patient outcomes [81,82]. Fluid accumulation and a positive fluid balance may be anticipated and are accepted during this early resuscitative stage.

Fluid resuscitation from shock can be accomplished utilizing isotonic and/or hypertonic crystalloids, with consideration being given to incorporation of non-protein colloids to achieve prolonged expansion of the intravascular space with less total volume infused (as part of LFVR). Fluids are administered as boluses (typically one-fourth of the total shock volume, or 1 blood volume), and these are repeated as needed to meet desired endpoints (Table 169.3). Asanguinous fluids are not substitutes for blood products, which may be incorporated into a

patient's resuscitation protocol for treatment of anemia, coagulopathy or massive blood loss. Vasopressor therapy is indicated in shock patients that fail to respond to fluid challenges and demonstrate clinical and laboratory parameters consistent with ongoing tissue hypoperfusion.

Implementation of EGDT may not be suitable for all shock patients, however. Aggressive fluid therapy may exacerbate bleeding in trauma patients with

uncontrolled hemorrhage, and fluid restriction in the forms of delayed and hypotensive resuscitation strategies has been investigated in both experimental animal and human trials evaluating this patient subset (exclusive of TBI patients) [18,24,83–86]. The former strategy was found to be beneficial in selected human patients, but these positive effects do not appear generalizable across human patient cohorts or to clinical veterinary

Table 169.3 Initial fluid strategy for shock resuscitation: choices and dosages.

Dosages		
Isotonic crystalloid (lactated Ringer's, Plasma-Lyte)	10–20 mL/kg over 10–15 min	
<ul style="list-style-type: none">Assess for clinical response; repeat boluses with same fluid type as needed to achieve desired endpoints.Shock dose (avoid fluid overload by titrating as above): 90 mL/kg (dog); 50–60 mL/kg (cat).Consider the addition of synthetic colloids and/or hypertonic crystalloids in selected cases as part of limited fluid volume resuscitation (e.g. large-breed dog; traumatic brain injury; severe burn injury).		
Hydroxyethyl starch solutions (HES)	5–10 mL/kg over 15–30 min: maximum daily dose, 20–50 mL/kg	
7–7.5% Hypertonic saline (HTS)	4–6 mL/kg over ~ 15 min	
HTS+synthetic colloid (HES) (Turbostarch)	4 mL/kg IV over 4–5 min	
Turbostarch “cheat sheet”:		
Weight in kg (lb)	23.4% HT (mL)	6% HES (mL)
1 (2)	1.3	2.7
2 (5)	2.6	5.5
4.5 (10)	6	12
7 (15)	9	18
9 (20)	12	24
11 (25)	15	30
14 (30)	19	38
16 (35)	21	42
18 (40)	24	48
20.5 (45)	27	54
23 (50)	31	62
25 (55)	33	66
27 (60)	36	72
29.5 (65)	39	78
32 (70)	43	86
34 (75)	45	90
36 (80)	48	96
38.5(85)	51	102
41 (90)	55	110
43 (95)	57	114
45.5 (100)	61	122
Blood component therapy as indicated:		
15 mL/kg will increase packed cell volume (PCV) by 10%; over 4–6h		
Packed red blood cells	20–30 mL/kg will increase PCV by 10%; <6h	
Fresh whole blood	10–20 mL/kg over 4–6h for clinically significant coagulopathy	
Fresh frozen plasma		

patients [24,83]. Hypotensive resuscitation involves targeting lower than normal BP (mean arterial BP and systolic BP of 50–60 mmHg and 80–90 mmHg, respectively) that support vital organ perfusion but are less likely to exacerbate bleeding from dilution or clot dislodgement. While sustained hypotension (>120 min) can increase tissue hypoxia and organ damage, experimental animal models have found that shorter periods of permissive hypotension result in improved patient survival [84,85].

The effect of fluids on patient outcome may be influenced by hemorrhage severity [85]. In animal trials, fluid resuscitation following severe hemorrhage reduced risk of death. Alternatively, withholding resuscitation fluids from patients with less severe hemorrhage conferred a survival advantage, possibly by prevention of hemodilution and blood clot disruption [85]. While there are several RCTs and observational studies which have shown that permissive hypotension reduces morbidity and mortality in bleeding human trauma patients, other investigators and meta-analyses have failed to replicate this findings. Larger prospective RCTs are necessary [86–89].

During the Optimization stage of resuscitation, the patient is in compensated shock, and responses to fluid challenges are assessed to guide continued fluid resuscitation and avoid excessive fluid accumulation. Patients are categorized as “responders” or “non-responders” based on increased (10–15%) or unchanged stroke volume following fluid infusion, respectively. Giving fluids to non-responders (reportedly >50% hemodynamically unstable patients) will not improve perfusion but only exacerbate tissue edema [90,91].

Patients overcoming severe injury will experience restoration of homeostatic mechanisms and hemodynamic stability, and re-establishment of adequate tissue perfusion (the flow phase of shock). These patients are in the Stabilization stage, and require fluid only for ongoing fluid losses and maintenance of hydration.

In severely ill human patients hospitalized for several days, conservative late fluid management (CLFM) and fluid De-escalation (de-resuscitation) have been shown

to confer a survival advantage [90,92–94]. Conservative late fluid management is defined as achievement of an even-to-negative fluid balance at least two consecutive ICU days during the first week in the hospital (accomplished via fluid restriction, diuretic administration, and/or hemodialysis) [90]. Achievement of CLFM has been shown to be an independent predictor of survival in patients with septic shock and in critically ill, mechanically ventilated patients. Patients with global increased permeability syndrome (GIPS) demonstrate continued positive fluid balance, progressive capillary leak and organ dysfunction, and increased mortality [90,92].

The concept of “the best fluid may be the one that has not been given to the patient” was most dramatically demonstrated in the FEAST trial, which found that boluses of either albumin or saline (versus no bolus) to severely ill and hypotensive African children increased 48-hour mortality [95]. The investigators postulated that reversal of blood shunting to vital organs and/or reperfusion injury could, in part, explain these findings in this very specific patient population. These results, while absolutely not generalizable to other ECC patient cohorts, do demonstrate that fluid plans should be patient and disease specific. Optimal individualized fluid plans target replenishment of body fluid compartments while minimizing unnecessary fluid loading. For shock patients, early goal-directed fluid therapy endpoints include normalization of perfusion parameters, blood lactate, base excess, central venous oxygenation saturation, and/or shock index (heart rate/BP), among other parameters [96–100]. For patients with interstitial and/or intravascular dehydration, fluids are discontinued when hydration is restored and ongoing losses have ceased. A single ideal fluid likely does not exist. Judicious and attentive use of any selected fluid is advocated with incorporation of CLFM to mitigate detrimental effects. Due to the concerns for toxicity associated with HES solutions and isotonic saline, their role in critically ill human and veterinary patients requires further investigation and definition [101,102].

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Management of Hemorrhagic Shock

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Signalment/History

The signalment and history may present information regarding the etiology of hemorrhage to help direct immediate care and obtain a definitive diagnosis. Young patients are at risk for trauma, congenital coagulopathies, infectious disease, and toxin ingestion (anticoagulant rodenticides), while older patients are at risk for spontaneous hemorrhage associated with neoplasia. Any age patient undergoing emergency or elective surgery or invasive procedures is at risk for significant hemorrhage and critically ill patients are at risk for development of secondary coagulopathies (e.g. DIC). Collection of a complete history may have to be delayed while urgent care is initiated; an attempt may be made to quantify external blood loss if evident. Dogs are far more frequently affected by hemorrhagic shock than cats.

Physical Examination

The physical examination of a patient with hemorrhage varies substantially depending upon the location and severity of blood loss. External hemorrhage is immediately apparent, but internal hemorrhage may not be as obvious.

Patients will demonstrate signs of shock when as little as 15–20% of their blood volume is lost [1]: approximately 15–20 mL/kg in the dog or 10–15 mL/kg in the cat. Quantifying blood loss is challenging unless a patient has a bandage that can be weighed, a drain tube in place, or is in surgery with available suction; a 4×4 inch gauze can hold approximately 10 mL of blood when fully saturated [2,3].

Hemorrhage leads to decreased cardiac output, intravascular volume and blood hemoglobin concentration, resulting in decreased delivery of oxygen (DO₂). With a

significant enough decrease, the DO₂ is unable to meet the body's oxygen consumption demands (VO₂), resulting in signs of cardiovascular shock. Patients that present with signs of poor perfusion (shock) warrant immediate resuscitation (see Chapter 152). Physical signs of shock can be rapidly assessed and include alterations of heart rate, blood pressure, mucous membrane color, capillary refill time, respiratory rate, pulse quality, and level of consciousness. Patients under general anesthesia may not have the same physiological compensatory mechanisms due to cardiovascular effects of anesthetic drugs; these patients should be monitored closely with ECG, blood pressure, pulse oximetry, end-tidal CO₂, and an experienced veterinary technician (e.g. VTS-anesthesia) or ideally an anesthesiologist. Temperature assessment is important as both severe hyper- and hypothermia can affect normal coagulation.

Abnormal heart sounds may indicate anemia, arrhythmias or location-specific hemorrhage. Increased respiratory rate, effort or altered breathing pattern along with abnormal lung sounds may indicate pulmonary or pleural hemorrhage. Patients with abdominal hemorrhage may have a fluid wave or positive ballotment, but this may not be apparent until hemorrhage is significant (40 mL/kg) [4].

Soft tissue swelling or bruising may be present with soft tissue bleeding. Measuring a swollen area with a tape measure may help monitor progression. The mucous membranes, skin, retina, and rectum should be closely examined for evidence of petechia, ecchymoses or frank blood. Hemorrhage into specific locations, such as the retroperitoneal space, pharyngeal area or airways, or around neurological tissues has specific localizing signs and presents additional therapeutic and diagnostic challenges. Evidence of hemorrhage at more than one location without a history of trauma is supportive of coagulopathy [5] (see Chapters 69 and 70).

Point-of-Care Diagnostics

Point of care (POC) diagnostics support evidence of hemorrhage and poor perfusion, identify coagulopathy, and help identify hemorrhage location(s).

Laboratory Testing

Consideration should be given to the location, method, and frequency of blood collection. Patients with a potential coagulopathy should have blood collected from peripheral sites where hemorrhage can be controlled with a bandage; frequency of blood collection should be minimized to avoid repeated phlebotomy; and only the smallest sample necessary should be collected to minimize iatrogenic blood loss. Resuscitation should begin before results are obtained.

Emergency Database

An emergency database, including PCV/TS, electrolytes, glucose, blood gases, lactate, and BUN, is important for immediate diagnostics. A normal or even elevated PCV with a disproportionate decrease in total solids may reflect acute hemorrhage in the dog, as the PCV is preserved through sympathoadrenal splenic contraction [6,7]. The PCV and TS will both decrease with ongoing fluid resuscitation and continued blood loss.

Any bloody fluid collected from a cavity should also have a PCV/TS performed. Active hemorrhage is supported by PCV from cavity fluid within 5% of peripheral blood. In more long-standing hemorrhage, the PCV of the fluid may be higher than the periphery (see Chapter 84).

Gastrointestinal tract hemorrhage (see Chapter 77), poor renal perfusion, renal failure or urinary obstruction can elevate the BUN; a low BUN suggests hepatic dysfunction, prior PU/PD or IV fluid therapy.

Lactate provides a monitor of restoration of DO_2 (see Chapter 156). Canine studies of hemorrhagic shock and critically ill and injured dogs have demonstrated that an increase in lactate is correlated with a worse prognosis after blood loss and a lack of lactate normalization is associated with an increase in morbidity and mortality. Normalization of lactate is an indicator of adequate resuscitative efforts [8–14] (see Chapter 156).

Blood gas data and central venous oxygenation (ScvO_2) may help identify metabolic acidosis from hypoperfusion and oxygen extraction status. Acidemia can have detrimental effects on coagulation; if pH is <7.200 , bicarbonate therapy should be considered (see Chapter 174). A study of dogs suffering blunt force trauma found that an admission base excess cut-off of -6.6 was 88% sensitive and 73% specific for later transfusion requirement and

a cut-off of -7.3 was 81% sensitive and 80% specific for survival with no difference in admission PCV between survivors and non-survivors [15].

Coagulation Assessment (see Chapters 69 and 70)

Assessment of coagulation should occur in patients with concern for coagulopathy or prior to invasive procedures. The results of coagulation testing should always be interpreted with the clinical picture of the patient (signs of blood loss, PCV/TS, etc.). If an intervention is deemed necessary (transfusions, etc.), it is appropriate to recheck these values to ensure the therapeutic benefit has been achieved.

The prothrombin time (PT) reflects both the function and quantity of the coagulation factors in the extrinsic (factor VII, tissue factor) and common (factors I, II, V, and X) coagulation pathways. The activated partial thromboplastin time (aPTT) reflects the function and quantity of coagulation factors in the intrinsic (factors VIII, IX, XI, XII) and common pathways. A decrease of $>70\%$ of one or more of these clotting factors is necessary for the PT or aPTT to be prolonged. Prolonged aPTT in dogs that have sustained trauma has been correlated with non-survival [16]. PT and aPTT testing does require specific equipment that is widely available and affordable [17].

A machine count and manual platelet estimate should be performed in patients with signs of thrombocytopenia. The feathered edge of the blood smear is examined for platelet clumping and morphology [18]. Patients are typically at risk for spontaneous hemorrhage when platelet counts are less than 30 000–50 000/uL. Buccal mucosal bleeding time is an uncommon method of evaluating *in vivo* platelet function. It may be run in patients with concern for a primary platelet disorder and normal platelet numbers, such as Dobermans with unknown vWF status.

Other coagulation testing may include thromboelastography (TEG) or thromboelastometry (also called rotational thromboelastography, ROTEM); these viscoelastic methods assess many aspects of coagulation.

Radiography and Ultrasound

Radiographs and ultrasound are both useful to identify free fluid, hemorrhage into tissues or other disease processes. Although radiographs are less sensitive for detection of free fluid in the abdomen, they are useful for assessment of pulmonary patterns, mineralized tissues, and free air. Animals can be quickly evaluated for abdominal, thoracic (or pulmonary), and pericardial fluid with the focused assessment with sonography technique (FAST) (see Chapter 182) [19]. The abdominal and thoracic FAST

(aFAST and tFAST) are simple, inexpensive POC diagnostic tests which most emergency clinicians can perform and are recommended as an assessment and monitoring tool [20]. The presence of free fluid warrants centesis as a diagnostic measure (PCV/TS, etc.), and potentially a therapeutic measure, relieving respiratory distress and collecting fluid for potential autologous blood transfusion (ABT) (see Chapters 183 and 186).

Ultrasound can also be used to evaluate ventricular chamber and vessel size to assess intravesicular volume. An experience operator can detect changes in volume status and contractility [21–23]. Small inferior vena cava diameter during inspiration (<2 cm) has been shown to be an indicator of poor prognosis in human trauma patients and acute surgical patients [24]. A collapse index has also been investigated and is associated with shock and increased CO when fluids are administered, but this has yet to be investigated in veterinary patients [25].

Other diagnostics such as CBC, blood smear evaluation, serum biochemistry, and urinalysis are simple, widely available tests that may give insight into underlying disease processes. Other tests such as platelet assays, antithrombin levels, D-dimers, activated protein C, toxin quantification, individual clotting factors tests, and others may be important for definitive diagnosis and long-term therapy but are not often immediately available.

Treatment

Rapid identification and correction of hemorrhage are critical to prevent systemic consequences and death. Initial stabilization requires rapid, appropriate, and potentially aggressive intervention. Therapy may need to be initiated prior to collection and interpretation of any diagnostics due to the life-threatening nature of hemorrhage.

Providing supplemental oxygen during resuscitation can increase oxygen transport by ensuring that the blood hemoglobin is fully saturated and by raising the quantity of oxygen carried in solution in the plasma [26] (see Chapter 181). Most patients will require rapid placement of an IV or IO catheter for administration of fluids, blood products, and medications or to facilitate sedation or anesthesia.

Patients with location-specific hemorrhage (such as airway or pharynx) may require rapid-sequence induction of anesthesia with intubation or tracheostomy (see Chapter 191). If hemorrhage into the pleural or pericardial space is identified, a therapeutic centesis may be required (see Chapter 183). Blood collected from a patient via centesis should be collected in a sterile fashion and preserved for analysis (PCV/TS, lactate, glucose, cytology if indicated) and for potential ABT [27,28].

Patients with signs of hypoperfusion require fluid resuscitation and internal hemorrhage often requires more invasive diagnostics and therapeutics as outlined below (see Chapter 153).

Limiting External Blood Loss

External sources of hemorrhage should immediately have a compression bandage or digital pressure applied with a gloved hand to limit further blood loss while the patient is prepared for definitive care.

External coaptation with pressure can be placed easily on some body parts to minimize blood loss temporarily. Tourniquets are generally not recommended as they limit blood flow, which may delay healing and can exacerbate blood loss from the venous system; tourniquets should be removed within 10 minutes.

Many external sources of hemorrhage (such as arterial bleeding, or bleeding from the tongue or nasal cavity) may not be amenable to direct compression, in which case, the patient will require rapid-sequence induction of anesthesia with an injectable agent, and maintenance of anesthesia as deemed appropriate to allow hemostasis; this may include application of hemostatic agents, surgical correction (tissue or vessel ligation), local packing or local or distant source control (arterial ligation).

There are a variety of external and internal hemostatic agents available to assist in arresting hemorrhage (Table 170.1); these work through obstructing blood flow, providing a framework for clotting, absorbing water to increase effectiveness of natural clotting, or stimulating the coagulation cascade. Many are absorbable and do not need to be removed, but should be used with care in surgical wounds as they may inhibit healing [29]. These are commonly used in surgery in conjunction with thermal coagulation units. Administration of epinephrine into a nasal cavity is often ineffective as it is rapidly diluted by ongoing hemorrhage.

Fluid Resuscitation

The concept of damage control resuscitation (DCR) involves a combination of techniques to minimize derangements that commonly occur in the actively hemorrhaging patient (acidosis, coagulopathy, and hypothermia). DCR involves a combination of permissive hypotension, early use of blood products, limitation of crystalloid therapy, and minimizing surgical time to avoid these systemic complications and this has led to improved mortality [32–35].

Permissive hypotension uses small-volume fluid infusion techniques (discussed below) with low-normal resuscitation endpoints; this avoids potentially dislodging a fragile clot, hypothermia and dilution of

Table 170.1 Examples of hemostatic agents by category [30,31]. Reproduced with permission of John Wiley & Sons.

Category/ mechanism	Examples	Manufacturer	Notes
Caustic agents: coagulate proteins, tissue necrosis, eschar formation			
	Aluminum Cl, ferric sulfate, silver nitrate, Zn Cl	Many manufacturers including Vet One (GF Health Products, Atlanta, GA), Kwik-Stop (ARC Laboratories, Atlanta, GA)	Silver nitrate will cause pigmentation, Zn Cl is uncommonly used; often applied with an applicator stick or powder; external use only
Non-caustic agents: primarily create a physical mesh facilitating platelet aggregation and amplification and propagation of coagulation			
	Gelatins; provide a matrix for clot formation, activated thrombin	Gelfoam (Pfizer, Memphis, TN) Vetspon (Ethicon, Somerville, NJ)	Requires blood in field, not a sealing agent
	Microporous polysaccharide hemospheres (MPH) from potato starch; hydrophilic and concentrate blood	Hemablock (Abbott, Abbott Park, IL)	Increase in volume of the spheres
	Oxidized regenerated (methyl) cellulose (plant cellulose) – physical barrier for clotting, provides a matrix for clotting	Surgicell (Ethicon, Somerville, NJ)	Acidic and therefore bacteriocidal
	Microfiber collagen (bovine collagen) – aggregation and degranulation of platelets	Instat (Ethicon, Somerville, NJ), Helistate (Integra, Plainsboro, NJ)	Wound should be dried and product applied with pressure using gauze
	Physiological hemostatics (fibrin, thrombin, platelet gels, antifibrinolytics)	Aminocaproic acid (Hospira, Lake Forest, IL), others	Topical use may not be effective; few reported data
	Fibrin glue – activates conversion of fibrinogen to fibrin	Tisseel/Tissucol (Baxter), Hemaseel (Haemacure), Evisel (Ethicon)	Dry field preferred, spray delivery
	Glutaraldehyde adhesives – cross-linking cell to cell proteins	Bioglue (Cryolite)	Dry field preferred
	Waxes; malleable and form physical block as well as clotting surface	Bone wax (Aesculap, Center Valley, PA)	Difficult to apply to flat surface, may delay healing
Hemostatic dressings: used as wound dressings to prevent bleeding			
	Alginate dressing – seaweed protein, absorbs fluids through ion exchange reaction, releases calcium	Sorbosan (UDL Laboratories, Rockford, IL)	Not effective in high-pressure bleeding nor for intracavitary use
	Mineral zeolite – kaolin impregnated polyester gauze, kaolin immediately activates XII, XI; absorbs water	Quickclot (Z-Medica, Wallingford, CT)	Foreign body reaction; early products were exothermic
	Chitin (chitosan) dressing, from crab exoskeletons, adheres to and seals wounds	Celox gauze and powder (Medtrade, Crewe, UK)	May also be antimicrobial

clotting factors [32]. Low normal endpoints of resuscitation include a patient with normal physical perfusion parameters (BAR, HR 80–140bpm dog and >160bpm cat, pale or pale pink mucous membrane color, with a capillary refill time <2sec, strong synchronous pulses, a normal body temperature, and an adequate, but conservative blood pressure (systolic >90mmHg and mean 60–80mmHg)) [33]. Other parameters include normalization of ScvO₂ and lactate (see Chapter 153).

Fluid resuscitation is most often initiated with a combination of crystalloids and colloids, while the need for blood products is assessed (see Chapters 167–169).

Balanced isotonic crystalloids such as Plasma-Lyte-A, Normosol-R or lactated Ringer's are the most common initial choice. Small-volume resuscitation utilizes 10–20mL/kg of a crystalloid with or without 2–5 mL/kg of a colloid, administered over 10–15 minutes, at which point the patient is reassessed (see Chapter 167).

Colloids (see Chapter 168) such as hydroxyethyl starch solutions have been known to exacerbate coagulopathies through dilution of coagulation proteins, coating platelets and interference with normal clotting factor activity [36]; some solutions have been associated with acute kidney injury and increased mortality, although further research is indicated [37]. Hypertonic solutions may be considered in patients that are not dehydrated; benefits of decreased neutrophil function, increased inotropy, and other effects have been reported [38–43], but these solutions may also worsen normal coagulation [44].

Transfusion of Blood Products

Patients experiencing a significant amount of hemorrhage will require blood products; early administration in clinical and hemorrhagic models has demonstrated improved outcome in some studies [32–35]. The type of blood product required depends on the underlying disease process and availability of blood products. A guide

for selection of products along with dose is provided in Table 170.2 and in Chapter 176.

Massive transfusion (see Chapters 177 and 190) predisposes patients to electrolyte (K, Ca, Mg) abnormalities, coagulopathies, thrombocytopenia, hypothermia, metabolic acidosis, delayed wound healing, and increased infection rates [45–52].

Alternatives to Blood Products

If species-specific stored or fresh blood is not available, alternatives may be considered and include autologous blood and xenotransfusions. Hemoglobin-based oxygen-carrying solutions (HBOCs) are not currently available, but may be useful in the future (see Table 170.2).

Autologous Blood Transfusion (ABT)

Patients with surgical or cavitory losses of blood that can be collected in a sterile fashion can be given ABTs. Advantages of ABT include immediate availability and

Table 170.2 Choice of product, indications, and dose for small animal transfusions [4]. Reproduced with permission of John Wiley & Sons.

Product	Indication	Suggested dose
Fresh whole blood (FWB)	Acute hemorrhage, anemia with hypoproteinemia, coagulopathy	2 mL/kg to raise PCV 1% (often 10–20 mL/kg) titrated to effect until stable
Stored whole blood	Same as FWB; NOT factor V or VIII deficiency	Same as FWB
Autologous blood	Volume resuscitation or RBC administration	Entire salvaged volume can be infused, avoid volume overload if given with concurrent additional blood products
Frozen plasma	Hypoproteinemia, coagulation factor deficiency (NOT V, VIII), augment COP	Coagulopathy: 6–20 mL/kg PRN to stop hemorrhage Hypoalbuminemia: 45 mL/kg to raise albumin 1 g/dL
Fresh frozen plasma	Coagulopathy of many etiologies without anemia, augment COP	Same as frozen plasma
Packed red blood cells	Anemia, without coagulopathy	1 mL/kg to raise PCV 1% or until PCV supports sufficient DO ₂
Platelet concentrate	Thrombocytopenia with life-threatening hemorrhage	1 unit/10 kg PRN to arrest bleeding or until platelet count ≥ 30–50 000 platelets/mL
Platelet-rich plasma	Thrombocytopenia with life-threatening hemorrhage	1 unit/3 kg
Cryopreserved or lyophilized platelets	Thrombocytopenia	Limited data; estimated that 2–3 times as many units needed as platelet-rich plasma to achieve same effect
Cryoprecipitate	Von Willebrand's disease, hemophilia A, hypofibrinogen	1 unit/10 kg
Hemoglobin-based oxygen carriers	Anemia when allogenic blood is not available, may help with concurrent hypotension	Dog 1–5 mL/kg, titrated to effect Cat 0.5–1 mL/kg, titrated to effect Constant-rate infusion 0.8 mL/kg/h

COP, colloid oncotic pressure; PCV, packed cell volume; PRN, as needed (*pro re nata*); RBC, red blood cell.



Figure 170.1 A patient that developed life-threatening pleural hemorrhage after lung lobectomy. This patient is being given an autologous blood transfusion (ABT) while being transferred back to the surgical suite. Note the syringe on the left removing blood from the thoracostomy tube and the syringe on the right administering the same blood IV through a filter. Reproduced with permission of John Wiley & Sons.

compatibility, normothermic blood products, lack of infectious agents, higher levels of RBC 2,3-DPG than stored blood and decreased overall cost [53]. Studies in humans undergoing oncological surgery have demonstrated no worse outcome in patients with ABT compared to banked blood [54,55]. If the ABT has GI contamination, culture, susceptibility, and antibiotic therapy are warranted. Blood that has been in a peritoneal cavity for prolonged periods may contain inflammatory mediators that could contribute to systemic inflammation, warranting careful monitoring for SIRS. ABT has been reported in veterinary patients with vascular injury (from trauma and GDV and after ovariohysterectomy), neoplasia, and anticoagulant rodenticide intoxication [28] (Figure 170.1).

Xenotransfusion

A xenotransfusion is the transfusion of blood from one species to another. In veterinary medicine, this specifically refers to canine blood administered to a cat. There is some evidence to support the use of xenotransfusion and it may be considered as a one-time option if type-specific (allogenic or autologous) feline blood is not available and the cat is suffering life-threatening anemia or hemorrhage [56].

Limiting Internal Hemorrhage

Internal hemorrhage may be severe enough that additional measures may be necessary prior to and during definitive (surgical) intervention.

External abdominal counterpressure may be used to help increase abdominal pressure and minimize blood loss from organs in trauma patients or patients with normal coagulation for which surgery is not an option. It is described in Box 170.1 and pictured in Figure 170.2 [4].

Many cases of internal abdominal (and occasionally thoracic) hemorrhage require surgical intervention; most commonly this occurs from blunt or penetrating trauma, bleeding tumor, organ torsions or recent surgical cases with uncontrolled hemorrhage (such as recent gonadectomy or other surgery; see Figure 170.1). In these cases, it is best to try to stabilize the animal as discussed above

Box 170.1 Application of external abdominal and hindlimb counterpressure* [4]. Reproduced with permission of John Wiley & Sons.

1. Provide sedation and analgesia.
2. Place urinary catheter if time allows.
3. Place patient in lateral recumbency.
4. Place rolled towel between the hindlegs for padding.
5. Place a rolled towel along ventral midline from xiphoid to pubis.
6. Wrap towels, cotton roll or disposable pads tightly around the circumference of the feet in a spiral pattern, ascending the limbs, over the pelvis and around the abdomen to the xiphoid.
7. Assess degree of tamponade – should be snug but allow a hand to slide between abdomen and bandage. Adequate ventilation should be allowed.
8. Place duct tape or stretch bandage in a spiral pattern from toes to xiphoid to secure position of bandage.
9. Monitor physical perfusion parameters, ventilation efforts, urine output, blood pressure, PCV and TS for evidence of ongoing hemorrhage.
10. Allow bandage to remain in place until patient has stabilized for >4 hours or until aseptic preparation needed for surgical intervention begins.
11. Release the tape first, section by section, in the direction from xiphoid to toes and monitor for decompensation for at least 5 minutes per section. This may be performed more rapidly if the patient is going to surgery.
12. Loosen and remove the towels or cotton slowly in the direction of xiphoid to toes, but leave in place in case counterpressure needs to be reapplied. Monitor for decompensation.

*Patients with hindlimb or pelvic fractures may not be able to tolerate this procedure without general anesthesia or epidural analgesia.



Figure 170.2 Abdominal and hindlimb counterpressure in a patient with a traumatic hemoabdomen. Reproduced with permission of John Wiley & Sons.

prior to anesthesia and surgical intervention (this may not be possible in all patients). For patients that require surgery, it is important to be as prepared as possible prior to anesthetic induction (Table 170.3) (see Chapter 191). Penetrating foreign objects should not be removed until the patient is stable enough to receive definitive surgical care. An experienced surgeon with rapid technique is essential; multiple challenging procedures may be necessary to control hemorrhage. Steps for emergency surgery are discussed in Box 170.2.

Internal Abdominal Pressure and Damage Control

With blunt force trauma, it may not be possible to arrest or remove all the sources of hemorrhage (such as diffuse crush injury to the liver). Damage control techniques (see Chapter 189) are necessary: blood may be collected for ABT, then further hemorrhage is limited by internally packing the abdomen with sterile towels or laparotomy sponges in a brief surgical procedure [4], with definitive surgical care delayed until the patient can tolerate prolonged anesthesia.

Additional Therapy for Specific Conditions

Patients with liver failure (see Chapter 90), DIC, acute traumatic coagulopathy (see Chapter 163), anticoagulant rodenticide intoxication (see Chapter 130), and other disease may also benefit from additional medical therapy (Table 170.4). The liver is responsible for making factors I, II, V, VII, IX, X, and XI. Vitamin K1 is an important co-factor for the carboxylation of factors II, VII, IX, and X, making administration of plasma products and vitamin K1 necessary for patients suffering from hemorrhage from these conditions.

Table 170.3 Preparation checklist for patients with significant hemorrhage which require surgical hemostasis.

To be set up prior to emergency surgery	Notes
Anesthesia machine	Ensure tubes connected, oxygen connected, appropriate size reservoir bag, sufficient volatile agent, leak test, appropriate ventilator settings
Anesthesia	Preoxygenate patient if time allows. Premedications calculated and administered; balanced/multimodal anesthesia/analgesia used; induction agents should allow rapid-sequence induction and intubation
Monitors to set up	Ensure adequate monitors in area and ready to go: CVT, ECG, ET CO_2 , blood pressure, SpO_2 , etc.
Monitoring patient	Prepared anesthetic monitor record is printed, with anesthetic and emergency drugs precalculated based on patient weight. Drugs drawn up and/or nearby
Surgical preparation area	Monitors and anesthetic machine as above, endotracheal tube size, check cuffs for leaks, laryngoscope, ET tubes, cuff syringe, pressure monitor and tie-in, eye lube, warming units, clippers, vacuum, scrub
Surgical area	Monitors and anesthetic machine as above, warming unit, ventilator, second scrub ready, suction unit, thermal or cautery units ready
Surgical equipment ready	Gloves, gowns, caps, masks, instruments, suture, lavage, blades, cautery, retractors, sterile suction, laparotomy pads, light handles, warmed lavage fluids, etc.
Patient preparation	IV catheter(s), analgesia, presurgical bloodwork, shave prior to induction (may need to shave both abdominal and thoracic cavity)
Blood administration	Type and cross-match if possible, allogenic blood or materials for ABT, blood filters, correction of coagulopathy (see below)
Additional staff	To assist with anesthetic or surgical challenges
Coagulation status	Check coagulation parameters if indicated and time allows. Administer blood products or medications to treat coagulopathy if present

ABT, autologous blood transfusion; CVT, certified veterinary technician; ECG, electrocardiogram; ET, endotracheal; ET CO_2 , end-tidal carbon dioxide; IV, intravenous; SpO_2 , peripheral capillary oxygen saturation.

Box 170.2 Steps for emergency surgery for abdominal hemorrhage. Reproduced with permission of John Wiley & Sons.

1. Have personnel, equipment, and medications (doses calculated) ready at time of induction (see also Table 170.3).
2. Clip and aseptically prepare patient prior to anesthetic induction.
3. Use multimodal analgesia and anesthesia that supports blood pressure.
4. Make 10–15 cm incision on midline below xiphoid to allow digital compression of anterior aspect of aorta for immediate hemostasis (compression for 10 minutes maximum).
5. Collect free peritoneal blood aseptically in sterile suction container for ABT if necessary.
6. Extend midline incision caudally to pubis.
7. Pack abdomen with sterile laparotomy pads to provide hemostasis by tamponade.
8. Explore each quadrant and control hemorrhage as indicated using local or source vessel compression or ligation, use of surgical instruments, organ removal or other hemostatic equipment, supplies or techniques.
9. Control bleeding from massive crush injuries by placing large surgical towels or laparotomy pads to pack off organs, limit hemorrhage and contamination and apply internal abdominal pressure (called damage control technique).
10. Close the abdomen with towels or pads in place, applying internal tamponade to oozing organs.
11. Re-explore in 12–36 hours for definitive therapy.

Acute traumatic coagulopathy (ATC) (also called trauma-induced coagulopathy and acute coagulopathy of trauma shock) is a severe coagulopathy described in human and veterinary trauma patients (see Chapter 163). A combination of key factors is the driving force in the initiation and propagation of ATC: tissue damage, inflammation, hypoperfusion, hemodilution, hypothermia, and acidosis [57,58]. Animals experiencing ATC may benefit from antifibrinolytic therapy (tranexamic acid or epsilon-aminocaproic acid), but further investigation is warranted (see Chapter 68) [57,58]. The use of tranexamic acid has been investigated in human medicine and has demonstrated positive effects in human patients [59]. One study evaluated 68 dogs with bleeding disorders treated with blood products and tranexamic acid (Hexakapron; mean dosage of 8.6 ± 2.2 mg/kg q6–8h) [60]. The dogs given tranexamic acid received fewer blood transfusions and a lower blood component dose with minimal adverse effects. Patients with acidosis or hypothermia should have those abnormalities corrected.

Patients predisposed to specific coagulopathies may benefit from administration of additional drugs (see Table 170.4). Greyhounds may suffer from hyperfibrinolysis and benefit from administration of aminocaproic acid in the perioperative period [61]. Patients with von Willebrand's or hemophilia will benefit from the administration of plasma products (see Table 170.1) and/or desmopressin. Desmopressin may also alleviate clinical signs of bleeding secondary to aspirin administration [62] (i.e. prior to emergency therapy).

Table 170.4 Medications that may be administered for patients with hemorrhage. Reproduced with permission of John Wiley & Sons.

Medication	Indication	Dose
Vincristine	Thrombocytopenia	0.5 mg/m ² IV through new IV catheter as delivery outside the vein causes tissue sloughing
Antivenom/antivenin	Snake bites	1–10 vials as directed and indicated based on coagulopathy, pain and clinical judgment
DDAVP (desmopressin)	Von Willebrand's disease, platelet inhibitory drugs, FVIII deficiency	Intranasal product 1–4 mg/kg SC to control bleeding or preoperatively; parenteral product should be given slowly and at lower doses, 0.3–1 mg/kg SC or IV
hrVIIa	Bleeding from coagulopathies, sepsis, DIC	90 ug/kg bolus q2h until hemostasis; little information to support use
Epsilon-aminocaproic acid	Hyperfibrinolysis, greyhounds	50–100 mg/kg IV loading then 15 mg/kg/h CRI q8h or 15–40 mg/kg IV followed by 500–1000 mg PO q8h
Ca-gluconate	Hypocalcemia (may be secondary to multiple or massive transfusion)	50–150 mg/kg (0.5–1.5 mL/kg of 10% solution) slow IV, monitor ECG, stop infusion with bradyarrhythmia
Vitamin K1	Liver disease, anticoagulant drugs or toxicity	2.5–5 mg/kg SC or PO q12–24h
Protamine sulfate	Heparin toxicity	1 mg for every 100 U heparin slow IV
Tranexamic acid	Hyperfibrinolysis	10–15 mg/kg SC IM, slow IV q6–8h
Human IV immunoglobulin	Immune thrombocytopenia	0.5–1 g/kg IV over 6–12h once
Yunnan Baiyao	Neutraceutical but may be helpful with prolonged bleeding	Dog: <15 kg, 1 capsule PO q12h; 15–30 kg, 2 capsules PO q12h; >30 kg, 2 capsules PO q8h Cats: ½ capsule PO q12h

Anecdotal reports support the use of Yunnan Baiyao for veterinary bleeding disorders; some reports support topical and oral use in humans [63,64]. Other products such as recombinant human (or canine) factor VII (hrFVII) and activated protein C have yet to demonstrate substantial benefit; cost and availability and immune reactions will likely limit the role of these medications as well.

Investigation and treatment of the concurrent injuries and/or underlying disease leading to patient hemorrhage is essential, but beyond the scope of this chapter. The author recommends that any critically ill patient should have the Patient's Rule of 20 assessed twice daily (see Supplemental Reading).

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Management of Dehydration

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Introduction

Water is vital to homeostasis in the body. It forms the body’s blood supply, carries substrates across cellular membranes, evaporates to assist with thermoregulation, and functions as the universal solvent of the body. The healthy animal maintains an essential balance between fluid loss into the gastrointestinal tract, urine, and insensible losses and fluid gain through oral hydration [1].

Changes in the volume and distribution of water in the body can affect patient outcome. Significant water loss can lead to life-threatening alterations of blood pressure, temperature regulation, neurological function, and electrolyte abnormalities. However, excess body water can also cause fluid accumulation inside organs and body cavities, leading to impaired organ function and potentially fatal complications [2,3].

Definition of Dehydration

Dehydration is a state of reduced body water content resulting from either decreased intake or increased loss. Bodily fluid losses can occur through the gastrointestinal tract, urinary system, respiratory system, wounds, sweat, or a combination thereof, resulting in dehydration. Clinically, dehydration is specific to the interstitial and intracellular compartments, but if severe enough can affect the intravascular compartment [4].

The type of fluid lost from the body and the tonicity or effective osmolality of the remaining body fluid can further classify dehydration as hypertonic dehydration, isotonic dehydration, or hypotonic dehydration. Tonicity or effective osmolality can be estimated by the following formula: $2(\text{Na}) + \text{glucose}/18$ [5]. Note that effective osmolality is simply the calculated plasma osmolality $[2(\text{Na}) + \text{BUN}/2.8 + \text{glucose}/18]$ minus the effect of blood urea nitrogen (BUN) because BUN freely distributes in

total body water, whereas sodium and glucose are impermeant solutes and do not readily distribute across cell membranes. Pure water loss and hypotonic fluid loss (e.g. uncontrolled diabetes insipidus, fever, small intestinal obstruction, etc.) cause hypertonic dehydration. Isotonic fluid loss (e.g. some types of diarrhea, vomiting, hemorrhage) results in isotonic dehydration because sodium and water are lost in equivalent ratios from the body. Hypertonic fluid loss or isotonic fluid loss with free water replacement (e.g. water deprivation, iatrogenic) results in hypotonic dehydration [5].

Estimating Dehydration

On physical examination, the minimal degree of dehydration detectable is 5% of body weight; see Table 171.1 for more details [5,6]. At approximately 5–6% dehydrated, a very subtle loss of skin elasticity is detected. After 6–8% dehydration, a prolonged capillary refill

Table 171.1 Physical examination and approximate percent interstitial dehydration [4].

Approximate percent dehydration	Physical exam findings
<5	Undetectable, history of fluid loss
5–6	Tacky mucous membranes
6–8	Decreased skin turgor
	Dry mucous membranes
8–10	Retracted globes within orbits
10–12	Persistent loss of skin tent
	Evidence of hypovolemia
>12	Hypovolemic shock
	Death

time, sunken eyes, dry mucous membranes, and tented skin become apparent. At approximately 10–12% dehydrated, the intravascular compartment is affected and the above clinical signs are present with the addition of signs associated with hypovolemic shock such as tachycardia, weak pulses, tachypnea, and dull mentation. A poor prognosis is associated with greater than 12% dehydration [5,6].

A decrease in body weight may be the most practical and even most accurate method to determine loss of total body water over a short period of time. Discrepancies in variable scales, patient positioning, and accuracy of scales may limit the ability to use weights reliably when patients present to the emergency room. In order to use weights appropriately, the scale should be calibrated and zeroed prior to placing the patient on the scale. If done properly, weights over the duration of hospitalization can be used as an indication of fluid loss or gain, which can then be converted to an estimation of dehydration because 1 kg is equivalent to 1 L of fluid.

Unfortunately, often we do not have the known prior accurate weights of dogs and cats presenting for emergency treatment unless medical records are presented with the owner and the scale discrepancies are minimal. In addition, one must consider a change in weight with the disease process of the patient. For example, weight gain in a postoperative septic abdomen patient could be due to interstitial, intracellular, or intravascular volume changes or third-spacing of fluid into the abdominal compartment (see Chapter 159). Often, on initial assessment, we rely on physical examination findings and clinicopathological values [6]. Clinicopathological parameters such as packed cell volume (PCV), total solids (TS), and urine specific gravity (USG) may help to clarify hydration status. The PCV and TS increase with all fluid losses excluding situations when splenic contraction occurs (e.g. acute hemorrhage, acute stress). The USG should be high in a dehydrated animal with normal renal function. Other diseases that also alter the USG and make its use

as a measure of hydration status inappropriate include liver disease, pyelonephritis, diabetes mellitus, pyometra, central or peripheral diabetes insipidus, hyper- or hypoadrenocorticism, and hypercalcemia [7].

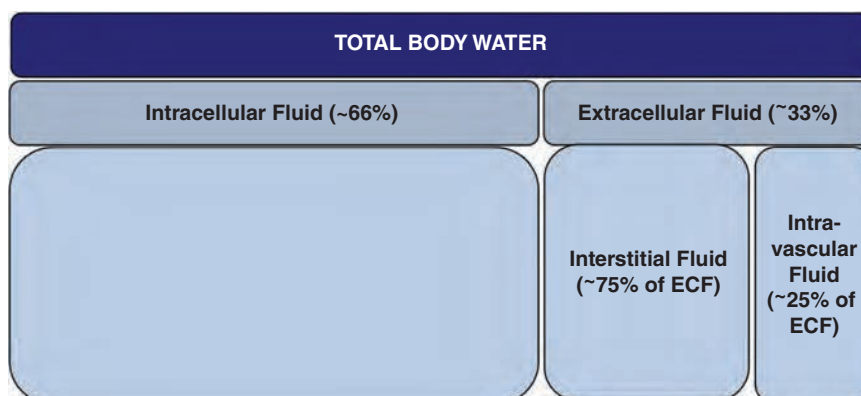
Additionally, it is important to note that serum sodium concentration may or may not be helpful in evaluating dehydrated patients. Hypernatremia develops with excess sodium intake, retention, or administration (such as through salt poisoning, hyperaldosteronism, hyperadrenocorticism, or hypertonic saline therapy), inadequate water intake, and hypotonic fluid loss such as gastrointestinal losses (vomiting, diarrhea), third space losses (peritonitis, pancreatitis), and cutaneous losses (burns) [5].

Total Body Water

The total body water in the intracellular and extracellular compartments is 0.6 L/kg or 60% of body mass in adult animals. In neonatal or pediatric patients, total body water is increased at 80% of body weight [8,9]. Total body water has been estimated as approximately 534–660 mL/kg in healthy adult dogs and cats [10]. In addition, total body water is typically decreased in perioperative patients and those with systemic inflammatory conditions (i.e. sepsis, major trauma, burns) due to changes in vascular permeability [11,12] (see Chapter 159).

The intracellular compartment is approximately 0.4 L/kg or 66% of total body water and represents the largest water compartment [8]. The extracellular component is 0.2 L/kg or 33% of the total body water. The extracellular compartment is further broken down into interstitial (75% of the extracellular fluid) and intravascular (25% of the extracellular fluid) [11] (Figure 171.1). The majority of the intravascular volume is plasma which is about 42–58 mL/kg in adult dogs and 37–49 mL/kg in adult cats [8]. Dehydration is typically referred to as a loss of fluid in the extracellular fluid compartment and, more specifically, in the interstitial space [4,5,12].

Figure 171.1 Division of total body water.



Body water is distributed across two compartmentalizing membranes: endothelium (intravascular from interstitial space) and the cell membranes separating the intracellular from extracellular space. Osmosis regulates the movement of water in the direction of higher solute concentration as shown in Starling's law [13]. A modified Starling's equation takes into account the role of the endothelial glycocalyx in the control of transvascular fluid movement [14].

Fluctuations in total body water vary depending on hormonal mechanisms to control water and sodium balance through the renin-angiotensin-aldosterone system, thirst mechanisms, and ADH hormone secretion from the pituitary [8].

Interstitial changes can be evaluated by monitoring the moistness of mucous membranes, skin tent response, eye position, and corneal position. All of these changes equilibrate within the intravascular space such that dogs and cats with evidence of interstitial dehydration will also have some degree of hypovolemia. Interstitial overhydration leads to increased turgor of the skin and tissue, gelatinous appearance, peripheral or ventral pitting edema, chemosis, and/or clear nasal discharge. Frequent monitoring of a patient's respiratory status is important as tachypnea and cough often occur before clinical signs of chemosis and nasal discharge [13]. With severe fluid overload, organ edema can occur and impair oxygenation of the tissues [13].

Intravascular changes are assessed by perfusion parameters such as mucous membrane color, capillary refill time, heart rate, pulse quality, temperature, and mentation. Rapid intravascular losses, such as occur with acute hemorrhage, result in hypovolemia without causing clinical changes in interstitial dehydration. Acute, severe intravascular fluid loss will progress to hypovolemic shock [12]. In contrast, hypervolemia leads to jugular venous distension, increased central venous pressure, and eventually the most obvious clinical sequelae of tachypnea or cough due to pulmonary edema. This is particularly true in the lungs when pulmonary capillary pressures exceed 25 mmHg [13].

Intracellular changes cannot be readily identified on physical exam. However, the clinician must rely on changes in effective osmolality $[2(\text{Na}) + \text{glucose}/18]$ of the extracellular fluid to determine changes in cell volume [4,5]. With decreases in effective blood osmolality, movement of water into the intracellular compartment increases the volume in the cell. This is evident in cases of hyponatremia in which overzealous correction of the hyponatremia results in central pontine myelinolysis characterized by progressive neurological abnormalities [15]. Alternatively, with increases in extracellular effective osmolality, there will be decreased intracellular volume. This can result in tissue shrinkage and vascular trauma [15,16].

Mechanism of Thirst

Thirst is regulated by an area in the anterior wall in the third ventricle of the hypothalamus, known as the thirst center [17,18]. Fluctuation in osmolality is sensed by osmoreceptors in the circumventricular organs, which lack the blood-brain barrier and can therefore rapidly respond to minute, acute changes in osmolality [18]. This area of the hypothalamus (also known as the Verney receptor) provides the drive for water intake by the dog or cat and also controls excretion of water into the urine [17,19].

Plasma osmolality (primarily sodium concentration) is the most potent driving force for thirst. When plasma osmolality increases around the osmoreceptors, animals will seek out water to return plasma osmolality to normal [17]. In addition, vasopressin (also known as antidiuretic hormone, ADH) is released from the supraoptic nuclei which stimulates reabsorption of water in the renal collecting duct by binding to V2 receptors, ultimately triggering insertion of aquaporin-2 channels in the apical membrane to rapidly increase renal water reabsorption [18,19]. Dogs and cats with an ineffective thirst mechanism or unavailable supply of water are at risk for severe dehydration.

Rehydration

Correction of dehydration involves pre-emptively planning the route of administration and type of fluid to administer, calculating the estimated fluid deficit, determining the time interval to correct the fluid deficit, incorporating maintenance fluid requirements, estimating ongoing losses, and monitoring for progression or resolution of dehydration (Table 171.2) [20,21]. In addition to the initial fluid therapy plan, one must also preconceive how the patient will be monitored for resolution of dehydration, ongoing dehydration, or overhydration. Each clinical situation will vary in the appropriate fluid therapy plan, and ultimately many different plans may be efficacious for each patient.

Fluid can be administered via the following routes of administration: oral, subcutaneous, intravenous, intraosseous, intraperitoneal, or rectal. In the emergency room setting, any route can be appropriate, depending on the clinical scenario. Oral administration of fluid should not be used if the patient is regurgitating, vomiting, or cannot physically drink enough water to account for ongoing losses. Most commonly, the intravenous route is preferred in critically ill patients. Fluid with an osmolality of 600 mOsm/L or less can be safely administered through a peripheral intravenous catheter, whereas a central venous catheter should be used if the osmolality is greater than 600 mOsm/L [21].

Table 171.2 Rehydration fluid therapy plan.

Routes of administration	Intravenous (most common)
	Oral
	Subcutaneous
	Intraosseous
	Intraperitoneal
Type of fluid to administer	Rectal
	Isotonic crystalloids (most common)
	Lactated Ringer's solution (273 mOsm/L)
	Plasma-Lyte 148 (295 mOsm/L)
	Normosol-R (295 mOsm/L)
Estimated fluid deficit	0.9% sodium chloride (308 mOsm/L)
	Weight (kg) × percent dehydration = L fluid to replace
	Length of time to replace deficit
	Typically 6–24 hours
	Maintenance fluid requirements
Estimated ongoing losses	Dog/cat: $[70 \times (\text{body weight}_{\text{kg}})^{0.75}] / 24\text{h}$ [21]
	$[30 \times \text{body weight}_{\text{kg}} + 70] / 24\text{h}$ [21]
	(40–60 mL/kg)/24h [21]
	Dogs: $[132 \times (\text{body weight}_{\text{kg}})^{0.75}] / 24\text{h}$ [14,20]
	2–6 mL/kg/h [14]
Monitoring plan	Cats: $[80 \times (\text{body weight}_{\text{kg}})^{0.75}] / 24\text{h}$ [14,20]
	2–3 mL/kg/h [14]
	Neonate/pediatric: 80–120 mL/kg/day [23]
	Estimate or measure (preferred) vomit, regurgitation, diarrhea, urine, fluid from wounds, fluid from any indwelling tubes
	Body weight, physical examination, urine output, packed cell volume, total solids, blood urea nitrogen, urine specific gravity, and osmolality

Isotonic crystalloids, also known as replacement fluids, are the most commonly used type of fluids to rehydrate a dog or cat. Clinically, most cases of dehydration are due to isotonic fluid loss resulting in interstitial dehydration [4]. Therefore, isotonic crystalloids such as lactated Ringer's solution, Plasma-Lyte 148, Normosol-R, or isotonic saline are the most commonly used fluids (see Chapter 167). Normal osmolality in the dog is 290–310 mOsm/L and in the cat is 311–322 mOsm/L, whereas the commonly used isotonic crystalloids have an osmolality of 270–310 mOsm/L [5,22]. Clinical situations in which dehydration is treated with hypotonic or hypertonic fluids, with or without addition of isotonic fluids, typically involve those with chronic sodium disorders in which plasma osmolality needs to be slowly adjusted to minimize central nervous system consequences (cerebral edema or central pontine myelinolysis). A thorough

discussion of the treatment of sodium disorders is beyond the scope of this chapter, but further details can be found in Chapter 108.

Approach to the fluid plan for rehydration is, at best, an estimation of the animal's fluid deficit and maintenance fluid requirements. Clinical signs of dehydration, discussed above, are subjective evaluations. In general, the fluid deficit is calculated by multiplying the estimated percent dehydration by the animal's body weight in kilograms which will yield a number in kilograms. One kilogram of water is equivalent to 1 L of water so the number obtained is converted to liters and multiplied by 1000 to obtain milliliters [9,20]. For example, if a 20 kg dog is estimated to be 7% dehydrated, then the deficit will be 1.4 L or 1400 mL. After calculating the fluid deficit, one must then decide how fast to replace the deficit. Many advocate replacing the deficit over 6–24 hours in cardiovascularly stable patients, depending on how quickly dehydration developed [9].

In any fluid plan, beyond simply replacing a deficit, provision of maintenance fluid requirements is needed. Insensible (fecal, cutaneous, respiratory; 13–20 mL/kg/day) and sensible (urine output; 27–40 mL/kg/day) losses are incorporated into the maintenance fluid requirements and do not need to be calculated separately [20]. Daily fluid requirements parallel daily resting caloric requirements so calculation of an animal's resting energy requirement (RER) will provide an estimate of daily fluid requirements because 1 kcal of energy is equivalent to 1 mL water [29,21]. Neonatal (0–21 days) and pediatric (<6 months) patients have higher maintenance fluid requirements (80–120 mL/kg/day) and are highly susceptible to dehydration [23].

Many different formulae exist for calculating daily maintenance fluid requirements (see Table 171.2). One must keep in mind that the formulae for maintenance fluid requirements pertain to healthy animals with normal renal function. If the animal is polyuric and/or polydipsic (e.g. uncontrolled diabetes, hyperadrenocorticism, chronic kidney disease), then the formulae are inherently inaccurate and so clinical judgment and history must be used when creating a fluid plan.

Replacement isotonic crystalloids have little or no added potassium, so maintenance potassium supplementation should be incorporated into the overall fluid plan and the animal's measured serum potassium will guide supplementation (see Chapter 173). It is important to remember that when adding potassium to any fluid, the bag should be thoroughly agitated to prevent iatrogenic hyperkalemia and the total rate of potassium administration should not exceed 0.5 mEq/kg/h without ECG monitoring [24]. Some advocate administering two types of fluids, an isotonic replacement fluid and a maintenance fluid, simultaneously, with a goal of

replacing the dehydration deficit with an isotonic crystalloid while providing a lower sodium, higher potassium maintenance fluid to prevent excessive sodium administration. More commonly, many replace the deficit and provide maintenance with an isotonic replacement solution appropriately supplemented with potassium.

Ongoing losses (also known as contemporary losses) can be estimated subjectively or objectively [20]. When the rehydration plan is initiated, ongoing losses are always a subjective estimate based on the animal's history. With inpatient monitoring, more objective estimates of ongoing losses can be obtained. Fluid losses which can be measured include vomitus, diarrhea, urine output, wound drainage, fluid collected from indwelling drains, and blood loss [9]. Many hospitals use diaper pads to absorb fluid in kennels; thus, weighing the pad after a patient has vomited, regurgitated, or had diarrhea can enable conversion to a quantitative fluid amount (diaper pad with bodily fluids – diaper pad dry weight = $\text{kg} \times 1000 = \text{mL}$ contemporary loss). Alternatively, if an indwelling tube (urinary catheter, nasogastric tube, chest tube, abdominal drain, wound drain, etc.) is in place, the fluid collected is easily measured in milliliters and can be added to the ongoing losses estimate. Ongoing losses are likely to change during the course of hospitalization and the daily fluid plan should account for these changes.

Complications of rehydrating an animal can be associated with the route of administration, iatrogenic fluid overload, persistent dehydration, and acid–base or electrolyte abnormalities. Most commonly, emergency patients are rehydrated with intravascular fluids, so phlebitis, hemorrhage, thrombosis, catheter embolism, or infection (catheter-related bloodstream infection, endocarditis) are possible [13,20]. Intravenous catheters should be placed aseptically and maintained properly. Patients should be evaluated several times per day for fever, new-onset cardiac murmurs, or swelling, heat, or pain around the catheter. If the aforementioned signs occur, the catheter should be promptly removed with subsequent cultures taken from the tip of the catheter or serial blood cultures from the patient [20].

Animals should be monitored daily for signs of fluid overload or persistent dehydration. Weighing the animal can be quite helpful, keeping in mind the considerations

discussed above. Iatrogenic fluid overload manifests clinically as tachypnea, cough, pulmonary crackles, clear nasal discharge, serous nasal discharge, chemosis, edema (especially around the hock), diarrhea, gelatinous subcutaneous tissues, and shivering [13,20]. Decrease in PCV, TS, BUN, urine osmolality, and urine specific gravity can also be associated with fluid overload; however, this must be evaluated in context with the animal's condition and concurrent diseases [4].

Fluid overload has been associated with increased morbidity and mortality in humans and clinically associated with impaired cognition, impaired pulmonary gas exchange, decreased lung compliance, increased work of breathing, ileus, gastrointestinal bacterial translocation, malabsorption, impaired cardiac contractility, cardiac conduction abnormalities, poor wound healing, wound infection, acute kidney injury, salt and water retention, cholestasis, and impaired hepatic synthetic function [25].

Frequent, diligent daily monitoring of the animal is essential and once dehydration is corrected, fluid should be adjusted or discontinued, accordingly. If fluid overload occurs, exogenous fluid administration should be discontinued and diuretics considered [25].

Conclusion

Management of dehydration in the emergency room setting starts with the history of the patient and assessment of the clinical level of dehydration. Once these factors are known, a fluid plan can be designed to replace the fluid deficit while supplying maintenance fluids and correcting ongoing losses. Isotonic replacement fluids are the most commonly used fluid type to correct interstitial dehydration. As with any therapeutic intervention, complications must be considered and monitored for regularly. In veterinary medicine, frequent physical examinations, assessment of urine output, trends in clinicopathological variables, trends in patient weight, and evaluation of ongoing losses are recommended to monitor the rehydration plan. Iatrogenic fluid overload is not without potentially serious clinical consequences and rehydration must be monitored vigilantly.

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Maintenance Fluid Therapy

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Introduction

In veterinary medicine, the term *maintenance fluid(s)* has several different meanings. Maintenance fluid(s) may refer to the daily fluid requirement of a patient to maintain normal physiological processes or a type of fluid resembling the usual fluid and electrolyte losses of a given patient throughout the day [1]. It is important to distinguish between calculation of a patient's "maintenance" fluid requirements versus using a crystalloid with a composition classified as a maintenance fluid (or both). These concepts will be explained in more detail throughout this chapter.

Estimation of a Patient's "Maintenance" Fluid Requirement

Fluid requirements in health and disease may vary substantially between patients and may even have significant variability in the same patient over a period of time. There are several methods of estimating the patient's daily maintenance fluid requirements. Regardless of the method chosen, the most important part of any fluid plan is frequent reassessment of the patient's fluid balance.

Disease states such as kidney disease/injury, diabetes insipidus, diabetes mellitus, hyperadrenocorticism, endotoxemia, trauma, and many others may greatly increase the daily fluid requirement of a patient. Within these disease states, common etiologies of increased fluid loss include hemorrhage, panting, inability to concentrate urine, exudative wounds or burns, and increased fecal fluid excretion (e.g. diarrhea). Adding another level of complexity is the composition of the fluid that is being lost. For example, panting and certain causes of polyuria may lead to excessive water loss without a significant loss of electrolytes such as sodium, whereas other disease processes, such as wounds and diarrhea, may cause fluid

losses with a composition closer to that of normal serum or plasma.

Calculating the estimated daily fluid requirement of a patient will help the clinician determine the starting rate of fluids for a given patient, but often requires alterations during treatment based on serial evaluations of the patient.

The following are common methodologies employed to estimate daily fluid requirements in dogs and cats.

- Use of a resting energy requirement calculation and substituting milliliters of water per day for calculated kilocalories per day [2–4].
- Cats: $80 \times \text{body weight (kg)}^{0.75}$ [5].
- Dogs: $132 \times \text{body weight (kg)}^{0.75}$ [5].
- General estimates based on species and size of the patient.

Adult cats generally have lower fluid requirements than dogs due to their lower blood volume, slower metabolic rate, and greater ability to concentrate urine and conserve water. As a generalization, young animals or dogs with a larger surface area to body weight ratio, as well as smaller or lean animals, will tend to require greater fluid supplementation to maintain adequate hydration states than obese or large animals with decreased surface area to body weight ratios [2–4].

Commonly suggested estimations include the following.

- Cats: 40–50 mL/kg/day
- Giant-breed dogs: 30–40 mL/kg/day
- Large-breed dogs: 50 mL/kg/day
- Medium/small-breed dogs: 60 mL/kg/day
- Puppies and kittens: 80–90 mL/kg/day
- Neonates: 100–140 mL/kg/day

Estimation of maintenance fluid requirements does not take into account the hydration status of the patient or potential additional ongoing losses such as vomiting and diarrhea. It is important to develop a more

comprehensive fluid plan for patients with pre-existing or ongoing losses.

Having decided upon an estimation and initiated maintenance fluid therapy, reassessment of the patient is critical. Serial physical examinations may be used to assess hydration status. In addition, once hydration is deemed corrected, monitoring the patient's body weight is another simple method of assessing fluid loss or gain. A patient should be weighed every 4–6 hours to monitor for weight gain or weight loss. For example, if the patient loses 0.2 kg over a 4-hour period, remembering that 1 kilogram is equal to 1000 mL of fluid, then the patient has lost a total of 200 mL of fluid or an average of 50 mL of fluid per hour. When using this method, it is important to use the same scale and methodology such as taking measurement of weight after a short walk to allow the animal to urinate and defecate.

Composition of a Maintenance Fluid

Crystalloids are often classified as maintenance or replacement fluids based on their sodium and potassium content. Maintenance fluids are indicated in patients that are not eating or drinking, but also do not suffer from hypovolemia, hypotension or excessive ongoing fluid losses. Maintenance fluids typically resemble fluid loss during normal processes such as sweating, panting, normal urination, and defecation. Often, these fluid losses are lower in sodium (hypotonic) and higher in potassium relative to patient serum composition. Most maintenance fluids will have a sodium content in the 50–70 mEq/L range and a potassium content in the 10–20 mEq/L range [6].

Many maintenance fluids also contain dextrose in order to supplement basal energy requirements and increase the osmolality of the fluid. When administered at conservative rates, the amount of dextrose added to common commercial fluid preparations supplies only a small percentage of the daily caloric requirements and is of little clinical utility in maintaining a patient's daily

energy requirements [6]. However, if dextrose was not added to maintenance fluids, most of the preparations would have a dangerously low tonicity and osmolality compared with plasma. It is important to note that water distributes freely across all body compartments and dextrose is metabolized to water and carbon dioxide. Therefore, the dextrose in maintenance fluids does not affect the patient's plasma osmolality unless the patient becomes hyperglycemic.

The major differences between the various maintenance fluids available are addition of other electrolytes (such as calcium and magnesium) and type of buffer contained within the fluid (see Table 172.1).

The major buffers encountered in commercially prepared fluids include lactate, gluconate, and acetate. These commonly used buffers form salts of a weak acid when combined with sodium ions found in fluid preparations. The pKa of many of these buffers is near the pH of the patient and when administered intravenously, the salt will disassociate, resulting in a sodium ion and an acid anion (lactate, acetate, gluconate). The resulting acid anion will act as a weak base by binding hydrogen ions, producing bicarbonate during metabolism. Buffers help to offset the acidifying effect of sodium chloride-containing fluids. Generally, patients will not develop a significant metabolic alkalosis as excess bicarbonate is excreted by the kidneys [6].

Use of Maintenance Fluids

Maintenance fluids are primarily intended for use at conservative fluid rates and not for bolus therapy or aggressive fluid resuscitation in patients with a normal sodium concentration. Major electrolyte imbalances such as hyponatremia and hyperkalemia may occur with rapid or chronic administration due to the lower sodium content and higher potassium content of maintenance fluids. In addition, red blood cell lysis may occur with rapid intravenous administration of a hypotonic fluid as water moves into the red blood cells according to the sodium gradient.

Table 172.1 Composition of maintenance fluids.

Fluid	Na ⁺ (mEq/L)	K ⁺ (mEq/L)	Glucose (g/L)	Cl ⁻ (mEq/L)	Ca ²⁺ (mEq/L)	Mg ²⁺ (mEq/L)	Buffer	Osmolarity (mOsmol/L)
0.45% NaCl	77	0	0	77	0	0	0	154
2.5% dextrose in 0.45% NaCl	77	0	25	77	0	0	0	280
Normosol-M in 5% dextrose*	40	13	50	40	0	3	Acetate 16 mEq/L	363
Plasma-Lyte 56 in 5% dextrose†	40	13	50	40	0	3	Acetate 16 mEq/L	363

* Hospira, Inc., Lake Forest, IL.

† Baxter Healthcare Pty Ltd., Toongabbie, NSW.

The major advantage of using a maintenance fluid to supplement daily fluid requirement is that the composition is closer to the actual typical daily fluid losses of patients. Use of replacement fluids, which are higher in sodium, may lead to natriuresis or sodium overload in some animals. Sodium is a major determinant of water balance within the body and excess body sodium may lead to hypervolemic states. Other potential uses of maintenance fluids include correction of electrolyte disturbances and rehydration or maintenance of hydration in patients with disease processes that predispose them to sodium overload (e.g. congestive heart failure, liver cirrhosis, and nephrotic syndrome). For example, management of a dehydrated patient with a history of significant heart disease and congestive heart failure can be challenging. Patients with congestive heart failure retain sodium due to decreased cardiac output, arterial underfilling, and poor renal perfusion leading to excessive activation of the renin-angiotensin-aldosterone system [7–9]. Hypovolemia and increased angiotensin II levels result in vasopressin release from the pituitary gland which leads to water retention via aquaporin-2 channels in the kidney [10–15]. Due to excess water retention, in addition to sodium retention, the patient plasma sodium level is often low due to a dilutional effect; however, there is still a total body excess of sodium.

While fluids are not typically administered to patients with congestive heart failure, occasionally, a patient with significant heart disease may become dehydrated and require fluid therapy. A maintenance fluid with lower sodium content is often the preferred fluid choice for use in these patients, although alternative fluid plans such as lower rates of isotonic crystalloids and free access to water may be more logical in hypovolemic or dehydrated patients. Typically, the patient is administered a conservative rate of maintenance fluids, the hydration status is frequently reassessed, and the fluids discontinued when the patient is rehydrated. During fluid administration, the patient must be closely monitored for signs of congestive heart failure such as an increased respiratory rate or effort, coughing, crackles on lung auscultation, or development of a gallop rhythm (predominantly in cats).

Lower sodium fluids are also indicated for resuscitation of patients suffering from chronic hyponatremia (>48h) in order to prevent a rapid increase in the sodium concentration (see Chapter 108). Rapid correction of a chronic hyponatremia may lead to permanent paralysis or death due to osmotic demyelination or central pontine myelinolysis [16–19]. Often, the duration of hyponatremia is difficult to ascertain and a reasonable precaution would be to manage all patients with an unknown duration of hyponatremia as if they were chronically affected. It is important to realize that even with a fluid containing a lower or similar sodium concentration to that of a patient's serum, the patient's sodium concentration may rise rapidly and frequent monitoring is necessary. If the patient's sodium concentration rises too quickly, it is recommended that the sodium rapidly be lowered down to a safer range using 5% dextrose in water solution.

Management of hypernatremia will also often require the use of lower sodium-containing fluids. Animals with mild elevations in sodium may benefit from treatment with hypotonic maintenance fluids rather than isotonic replacement fluids, but high fluid rates may lead to a rapid decline in blood sodium concentrations. During states of hypernatremia, the brain will form idiogenic osmoles to maintain normal cellular volume and prevent cell shrinkage and dehydration (see Chapter 108). If hypernatremia is corrected too quickly, the low serum sodium concentration will lead to a net movement of water into the cells of the brain, causing cerebral edema and potentially brain herniation. It is recommended to not exceed a change in the patient's serum sodium of greater than 0.5 mEq/L/h or 12 mEq/L in 24 hours [20,21].

Conclusion

In conclusion, it is important to develop a fluid plan that is tailored to the individual patient based on hydration, electrolyte status, and concurrent disease processes. The developed plan should be reassessed on a regular and consistent basis to ensure that hydration is maintained and that no acute dramatic shifts in fluid and electrolyte concentrations are experienced.

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Potassium Supplementation

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Introduction

Hypokalemia is a common electrolyte disorder. Extrapolation from the human literature would support a relatively high incidence, with 20% of hospitalized patients affected by this derangement [1]. As the major intracellular cation, potassium is essential for the maintenance of a normal resting cell membrane potential. Hypokalemia results in a more negative resting membrane potential, thereby hyperpolarizing the cell, and contributes to muscle weakness, electrocardiographic changes, and arrhythmias [2]. Therefore, potassium supplementation is a crucial aspect of fluid therapy for the hospitalized, and particularly critically ill, patient.

Potassium Physiology

Knowledge of the role of potassium in generating the resting membrane potential is essential in understanding the importance of supplementation in hypokalemic states. The majority of body potassium (roughly 98%) is located intracellularly with concentrations of approximately 140 mEq/L intracellularly and 4 mEq/L extracellularly. This normal relationship is maintained by cellular membrane Na/K-ATPase that pumps sodium ions out of and potassium ions into a cell in a 3:2 ratio. This results in a concentration gradient for potassium to flow extracellularly.

Because the cell membrane is impermeable to most intracellular anions, a net electrical difference is generated across the cell membrane with potassium outward flow. This electrical difference or resting cell membrane potential is crucial in the generation of action potentials in excitable tissues (i.e. cardiac muscle, skeletal muscle, nerves). Hypokalemia, by increasing the concentration difference across the cell membrane, results in a more negative resting membrane potential and hyperpolarization

of the cell. It is therefore readily apparent that while the absolute amount of potassium is important, the ratio of the potassium concentration intracellularly relative to the concentration extracellularly is perhaps more important when considering the clinical implications of hypokalemia. Generally, extracellular (and therefore plasma) concentrations of potassium are reflective of total body potassium stores. In certain conditions, as will be discussed below, this is not always the case [2,3].

Normal potassium levels are maintained by intake (namely the diet) and output (approximately 90–95% via the kidneys, the remainder via the gastrointestinal tract). An additional aspect of potassium balance is the normal distribution of potassium between the cells and the extracellular fluid. At the cellular level, potassium balance is mainly affected by the upregulation of Na/K-ATPase by insulin and beta-2 adrenergic stimulation. Additionally, acid–base status has an impact on potassium distribution with acidosis, typically resulting in the movement of potassium extracellularly and alkalosis leading to intracellular movement [2,3].

Causes of Hypokalemia

When considering causes of hypokalemia, it is important to distinguish total body potassium depletion and extracellular (or plasma) measured hypokalemia. Total body potassium depletion is typically a consequence of excessive loss from the kidneys and gastrointestinal tract. Excessive renal loss occurs with chronic kidney disease, postobstructive diureses, dialysis, mineralocorticoid excess, and treatment with drugs (namely loop diuretics). Other processes that result in a primary or secondary polyuria also can result in hypokalemia, due to increased tubular flow and decreased renal reabsorption. Excessive gastrointestinal loss occurs primarily as a consequence of vomiting [2].

Anorexic patients that are not experiencing excessive gastrointestinal or renal loss of potassium are usually normokalemic. However, when treated with intravenous fluid therapy not containing potassium supplementation, these patients can frequently develop an iatrogenic dilutional hypokalemia [2].

A measured plasma hypokalemia in spite of normal total body potassium levels occurs in conditions that cause increased translocation of potassium from extracellular to intracellular fluid. Conditions include alkalemia, administration of insulin, glucose-containing fluids or other insulin-inducing products, medications or states (i.e. xylitol, oral hypoglycemic medications, refeeding syndrome), catecholamines (as a result of beta-2 agonist stimulation), hypothermia, albuterol overdose, thyrotoxicosis, barium toxicosis, and hypokalemic periodic paralysis of Burmese cats [4–7].

Potassium supplementation is an important consideration in all patients, but in patients with excessive loss or those with conditions predisposing to increased intracellular translocation of potassium, supplementation becomes critical.

Clinical Signs of Hypokalemia

Many patients with hypokalemia do not have any clinical signs. Muscle weakness, polyuria, and polydipsia are the most common clinical signs reported. It is important to remember that there is individual variation in the potassium level at which clinical signs of hypokalemia develop. This occurs for two primary reasons. As discussed previously, the effect of hypokalemia is dependent predominantly upon the degree to which there is a similar change in intracellular potassium concentration. The measured plasma potassium is not always an accurate reflection of alterations in the intracellular:extracellular potassium ratio. Additionally, membrane excitability is determined by factors other than potassium, including calcium concentration and blood pH, that may result in clinical signs independent of potassium derangements [3].

Muscle weakness typically develops when serum potassium is less than 3 mEq/L, increases in creatine kinase occur when potassium decreases to less than 2.5 mEq/L, and rhabdomyolysis may occur when potassium decreases to less than 2 mEq/L. Hindend weakness and plantigrade stance may be seen in dogs and cats with hypokalemia. Cervical ventroflexion is commonly observed in hypokalemic cats. Hypokalemia also can result in respiratory muscle weakness, potentially necessitating ventilatory support [2].

Hypokalemia also can result in cardiac arrhythmias (see Chapter 53), by delaying ventricular repolarization and increasing the duration of the action potential and

automaticity. Generally, this does not occur until potassium levels are less than or equal to 2.5 mmol/L [1]. ECG changes are inconsistently seen in veterinary patients, but can occur. Supraventricular and ventricular arrhythmias occur more frequently than ECG changes. ECG alterations associated with hypokalemia include blunted T-waves, ST segment depression, and U-waves. Additionally, hypokalemia can decrease the clinical response to class I antiarrhythmic medications [2].

Hypokalemia also can result in hypokalemic nephropathy, characterized by renal vasoconstriction leading to a decrease in renal blood flow and glomerular filtration rate. Polyuria and polydipsia occur because of impaired responsiveness to antidiuretic hormone [2].

Potassium Supplementation

It is important to remember that the clinical guidelines for potassium supplementation are merely guidelines. Due to the inconsistent relationship of measured plasma potassium levels with total body potassium levels and intracellular:extracellular ratio and independent factors that impact translocation, serial monitoring is imperative. This monitoring is particularly important in patients with severe hypokalemia, those that are demonstrating clinical signs of hypokalemia and those that have factors affecting translocation (i.e. treatment with insulin, significant acid–base derangements, treatment with beta-blockers or beta-agonist toxicity). Please see Table 173.1 for commonly used guidelines for potassium supplementation.

Maintenance potassium supplementation to account for dilutional effects of intravenous fluid therapy (particularly in the anorexic animal) is roughly 0.05 mEq/kg/h. Frequently, it is recommended to limit potassium supplementation to <0.5 mEq/kg/h. However, there are also reports of supplementation with 0.5–0.9 mEq/kg/h in cases of life-threatening hypokalemia [8,9]. Due to concerns for life-threatening complications that can occur with supplementation greater than 0.5 mEq/kg/h,

Table 173.1 Guidelines for intravenous potassium supplementation in dogs and cats [2].

Serum potassium concentration (mEq/L)	mEq KCl to add to 1 L	Maximal fluid infusion rate* (mL/kg/h)
<2.0	80	6
2.1–2.5	60	8
2.6–3.0	40	12
3.1–3.5	28	18
3.6–5	20	25

*So as to not exceed 0.5 mEq/kg/h.

continuous electrocardiographic assessment should be performed to ensure that these do not occur. ECG changes that may be seen with too rapid infusion of potassium include tented T-waves, shortening of the QT interval, prolongation of the PR interval, widening of the QRS complex, shortening or absence of P-waves, development of pronounced bradycardia with sinoventricular rhythm, merging of the QRS complex with the T-wave creating a sine wave appearance, ventricular fibrillation, and finally ventricular asystole [10]. It is also important to remember that higher concentrations of potassium supplementation (i.e. greater than 60 mEq/L) should be infused via a central line due to higher concentrations potentially resulting in phlebitis when administered peripherally [3].

For patients that remain refractory hypokalemic despite high-level supplementation, it is important to consider supplementation of magnesium. Hypomagnesemia can result in secondary potassium depletion. This occurs because potassium secretion from the cells of the thick ascending limb of the loop of Henle and the cortical collecting tubule is mediated by ATP-inhibitable luminal potassium channels. Hypomagnesemia leads to a decrease in intracellular magnesium which can result in decreased ATP levels. Decreased ATP causes loss of inhibition of potassium secretion. Supplementation of magnesium in these cases is necessary to correct hypokalemia. Magnesium can be supplemented as magnesium sulfate in D5W, administered at 0.75–1 mEq/kg/day as a CRI with gradual taper as dictated by serial measurements [11].

Supplementation of potassium intravenously typically involves the use of KCl (2 mEq K/mL) and potassium phosphate (4.4 mEq K/mL). Potassium chloride is typically used in patients who do not have concurrent hypophosphatemia. Potassium chloride is generally recommended over potassium phosphate because chloride supplementation is also useful in managing the metabolic alkalosis that many patients concurrently demonstrate. Chloride depletion can exacerbate potassium depletion by enhancing urinary loss of potassium [2]. If both potassium chloride and potassium phosphate are being administered to a patient, potassium supplementation rates of both preparations should be calculated to ensure appropriate rates of administration.

Even with supplementation, it is not uncommon to see a decrease prior to increase in serum potassium concentrations as a result of dilution and increased tubular flow rates and/or increased cellular uptake if dextrose or insulin is being administered [12]. This should be kept in mind when considering supplementation rates.

It is also possible to enterally supplement potassium and there have been many recent studies in human medicine comparing parenteral versus enteral supplementation with some evidence to support that enteral supplementation or a combination of the two

may in some cases be preferable [13–15]. Potassium gluconate (Tumil-K) or potassium citrate (not potassium chloride or potassium bicarbonate) is recommended for oral supplementation. Doses for oral potassium supplementation are extremely variable and serial monitoring is recommended to achieve an optimal oral dose [2].

Support for enteral supplementation of potassium is relevant in patients that continue to have clinically relevant electrolyte derangements in spite of improvement/resolution in the underlying disease process, are off intravenous fluid therapy and are otherwise able to be discharged from the hospital successfully. Additionally, there is some risk in potassium supplementation, particularly when considering the inconsistencies of supplementation and the effect inadequate mixing can have on delivered rates of potassium supplementation. A recent study evaluated potassium supplementation in bags of fluids delivered to hospitalized patients (intended versus measured) and the effects of adequate/inadequate mixing on rates of supplementation. The disparities were profound, with measured potassium in hospitalized patients being significantly higher than intended potassium concentrations (mean difference was 9.0 mmol/L with a range of 6.5 to >280 mmol/L, $P < 0.0001$). In 28% of samples the potassium difference between actual measured and intended concentrations was ≥ 5 mmol/L [16].

There is additional evidence to support oral supplementation in patients with hypokalemia secondary to diuretic therapy. A recent study in human medicine evaluated survival benefit in patients empirically supplemented with potassium at the initiation of loop diuretic therapy. This was found to be associated with improved survival, with greater benefit seen with patients supplemented with higher diuretic dosages [17].

Diabetic Ketoacidosis (see Chapter 113)

Diabetic ketoacidosis (DKA) is likely the condition most commonly associated with clinically significant hypokalemia in veterinary medicine. While historically a prevalent issue in human medicine, a recent study documented that hypokalemia was less common than previously reported [18].

Hypokalemia occurs as a result of both the underlying condition (with total body potassium depletion occurring) as a result of osmotic diuresis due to glucosuria and ketonuria, lack of insulin (required for normal reabsorption of potassium at the renal tubules) and gastrointestinal losses), fluid therapy (dilution effect) and the need for insulin supplementation. It is also important to remember that frequently plasma concentrations of potassium are generally increased in the diabetic ketotic/ketoacidotic patient relative to total body concentrations and

that with initiation of treatment, plasma concentrations largely decrease. Extracellular or plasma concentrations are increased as a result of the volume expansion effects of hyperglycemia with associated tendency for potassium shifts from the intracellular to extracellular compartment. Decreased glomerular filtration rates with volume depletion that occurs as a result of osmotic diuresis can result in eventual renal losses. With initiation of fluid therapy and associated volume expansion and insulin supplementation, true total body potassium deficits become reflected in plasma concentrations [11].

The largest study examining clinical findings in canine patients with DKA revealed that intake hypokalemia was documented in 45% of patients and 84% of patients developed a hypokalemia with treatment, resulting in an overall incidence of 92% of cases [19]. Hypokalemia was

also documented to be a common electrolyte derangement in cats with DKA [20]. As a consequence of this, it is generally recommended to delay insulin administration until volume expansion and adequacy of potassium concentrations are achieved. In human medicine, this is considered to be ≥ 3.3 mmol/L [21].

There is some evidence advocating earlier initiation of insulin therapy in veterinary patients [22]. Therefore, higher supplementation rates than standard would be administered for rapidity of correction. With higher rates of supplementation, more frequent serial evaluations should be performed. After starting fluid or insulin therapy, serum electrolyte concentrations ideally should be re-evaluated 1–2 hours later and then every 4–6 hours until normal hydration and adequate glycemic control are achieved [11].

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Administration of Sodium Bicarbonate

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Introduction

Sodium bicarbonate (SB) has been studied extensively in multiple disease states including cardiopulmonary resuscitation, renal disease, intoxications, and acidosis. Despite a large body of research, the therapeutic role of SB and its efficacy are still in doubt [1–6]. Still, some evidence for SB use persists and will be discussed here. Other injectable buffers do exist, including carbicarb (not commercially available at this time) and THAM (significant concern for side-effects) [7,8]. SB is considered CO₂ generating, whereas these other buffers are considered CO₂ consuming and may have some advantages that have not been clearly validated [9]. This chapter will focus only on IV SB; oral SB therapy and SB use in dialysis will not be covered.

Bicarbonate is an important buffer in the body, combining with protons to form CO₂ and water via carbonic anhydrase in two steps. Ventilation and renal compensation then waste excess acid. The role of the lungs and kidneys in acid–base homeostasis cannot be overemphasized since the pK for the bicarbonate buffering system is well below normal pH of the extracellular fluid (pH 5.1–7.1) although the pH in cells is usually lower than serum (7.1–7.3). Bicarbonate is also an important blood transport molecule for CO₂ as it returns from cells [10]. The complexity of the physiological role of bicarbonate and CO₂ likely explains the variable experimental results seen so often.

Sodium bicarbonate is a convenient buffer as it has no requirement for metabolism to alkalinize. Therefore, unlike buffers such as lactate and acetate used in balanced electrolyte solutions, SB is able to have immediate effect. For example, in normal, non-acidotic dogs, infusion of 6.6 mEq/kg SB over 30 minutes produced transient alkalemia, hypercapnia, and reduction in H⁺ ions as predicted. These changes were sustained for greater than 180 minutes after starting the infusion [11]. Cats

administered variable doses (0.5–4 mEq/kg) over 1 minute had dose- and time-dependent increases in pH, PCO₂, and HCO₃[−] but to a smaller magnitude than dogs [12]. The ability of SB to raise the pH of the intracellular fluid (pHi) has been harder to consistently document. This may be due to separate compartments with differing permeabilities throughout the body and the fact that bicarbonate is “not an independent determinant of blood pH” [9]. SB has varying effects on pHi of the myocardium, CSF, liver, and skeletal muscle from study to study but the majority of studies document no change or a fall in pHi [9].

Sodium bicarbonate is a hypertonic solution with a sodium concentration similar to common hypertonic saline solutions (Table 174.1). SB also contains dissolved CO₂ and may have a PCO₂ as high as 200 mmHg [5]. After IV administration of SB, 10–15% is immediately metabolized to CO₂; therefore, hypoventilation and an impaired ability to change ventilation (e.g. sedation or obtundation) are both contraindications for SB use [13]. Hyponatremia, hypokalemia, and hypocalcemia (ionized and total) may also result from bolus injections but not always in a clinically significant amount [14,15]. Other possible but variably evident complications of SB include impairment of tissue oxygenation, diffusion of PCO₂ across cell membranes more quickly than the charged HCO₃[−] ion, causing intracellular acidosis, paradoxical cerebrospinal fluid acidosis, and lowering of blood pressure, presumably from the vasoactive properties of a hypertonic solution [13,16]. Excessive use

Table 174.1 Comparison of hypertonic saline (HS) and sodium bicarbonate (SB).

	7.2% HS [69,70]	SB 8.4% [13,17]
[Na] mEq/L	1232	1000
Osmolarity mOsm/L	2464	2000
Dose (bolus)	4 mL/kg over 2–10 min	1–4 mL/kg over 5–10 min

of SB, as with other hypertonic solutions, can cause a hyperosmolar state and possible fluid overload so SB is contraindicated with hypernatremia and heart failure [17,18].

Major uses of SB in clinical medicine are to buffer acidic blood, treat significant bicarbonate-rich fluid loss, elevate urinary pH to increase solubility of certain weak acids and toxins and possibly in hyperkalemic conditions (see Chapter 109).

Metabolic Acidosis (see Chapter 107)

It is generally agreed that SB is indicated in the treatment of metabolic acidosis from bicarbonate loss, including severe diarrhea or renal tubular acidosis [8,13,16] (see Chapter 107 for an extensive discussion of acid–base disorders). Common clinical disorders causing acidosis in small animal practice include lactic, uremic, and diabetic ketoacidosis.

Is Acidosis Harmful?

Both beneficial and harmful side-effects of acidosis have been found in clinical and experimental models. Severe acidemia (pH <7.20) may decrease CO, MAP, myocardial contractility, and hepatic and renal blood flow. Acidemia may shift potassium out of cells in exchange for protons but this effect is variable and mild hyperkalemia could occur [13]. Metabolic effects include a decreased response to catecholamines, insulin resistance, and reduced lactate clearance by the liver [8]. Acidemia causes arterial vasodilation, venoconstriction and shifts the oxyhemoglobin curve to the right, increasing tissue off-loading of oxygen (Bohr effect) [19]. Initially, the right shift can be of benefit, offloading more oxygen to the tissues, but over 6–8 hours the body normalizes with a decrease in 2,3-DPG to shift the oxyhemoglobin curve back to the left. There is some evidence that an increase in ionized calcium occurs due to a shift of albumin, calcium's carrier in blood; this effect may increase myocardial contractility, countering the direct effects of acidosis to a degree [19]. While in some studies, acidosis had other protective effects including delayed apoptosis and limiting myocardial infarct size, other studies noted increased apoptosis [9,19].

Part of the problem in assessing the detrimental effects of low arterial pH (pHa) is a lack of correlation with the pH of the venous or pulmonary circulation, especially in low- or no-flow states [20]. This discrepancy extends to pHi in which both the mitochondrial and cytoplasmic pH may differ and vary in resulting pathology [9,19]. For many patients, it is difficult to isolate the effect of acidemia from the detrimental effect of their underlying

disease (e.g. sepsis, renal failure). Severe acidemia is generally well tolerated in mechanically ventilated patients with permissive hypercapnia [9]. Persistent hyperlactatemia is a known risk for mortality independent of pH.

Uremic Acidosis

Acute or acute-on-chronic renal failure presents commonly in the ER and is usually accompanied by a moderate-to-severe acidosis. Treatment with buffered IV fluids (lactated Ringer's, Normosol) is generally sufficient to steadily correct uremic metabolic acidosis. No veterinary studies have been performed on the use of SB in uremic patients, to the author's knowledge. Contraindications to SB treatment found in uremic patients could include hypernatremia, dehydration, decreased mentation and poor renal excretion of excess alkali. Therapy with dialysis is indicated in humans with continued acidosis in renal failure.

Diabetic Ketoacidosis (see Chapter 113)

The acidosis of DKA may be solely due to ketoacids, beta-hydroxybutyrate, and acetoacetate, which deplete bicarbonate [21]. Commonly, it is a mixed disorder due to volume depletion and impaired tissue perfusion with lactate production and acute kidney injury, combined with the effects of any concurrent disorders (e.g. infection, pancreatitis) [22,23].

According to the medical literature, treatment of DKA with SB has not been successful and has been associated with hypokalemia, intracellular acidosis, and worsened tissue hypoxia. Two studies reported a paradoxical worsening of ketonemia, while others reported no improvement in insulin requirement or resolution of ketosis [22]. Treatments with standard therapy (IV fluids, insulin, electrolytes) will convert ketoacids to bicarbonate without the need for SB. Some clinicians still treat the subset of humans with a pH of <6.9 with SB until pH is greater than 6.9, but it is not clear that SB is useful even in the most severely acidotic patients [21].

In a retrospective study of 127 DKA dogs, Hume et al. noted the use of SB in 34%. Dogs treated with bicarbonate had lower pH and longer hospitalization and were less likely to be discharged. Treatment with SB likely reflected a higher severity of illness [23]. Oster et al. induced ketoacidosis in dogs with injections of beta-hydroxybutyrate. Treatment with SB improved pH and decreased potassium to a small degree [24]. Bureau et al. induced ketosis in diabetic dogs and found that SB worsened CSF PO₂ and pH. Dogs treated with SB progressively deteriorated after the study and demonstrated worsening mentation and vomiting. The authors compared this decline to cerebral edema in DKA humans

observed 4–16 hours after starting treatment [25]. Interestingly, in a study of DKA rats, SB treatment improved arterial pH and pHi of myocardial cells but increased lactate and beta-hydroxybutyrate and worsened blood pressure [26]. Clinical prospective studies are lacking, but the general recommendation for SB in DKA animals is to limit use to patients with pHa < 7.0 or 7.1 despite IV fluids and insulin [13,27,28].

Lactic Acidosis (see Chapter 156)

There are no clinical studies in small animals regarding naturally occurring lactic acidosis (LA) and treatment with SB. Experimental studies have been performed in dogs by injecting compounds to increase lactate without tissue hypoxia (type B) or by reducing inspired oxygen concentration or blood volume to induce hypoxic LA (type A). In two studies of type B LA, SB was ineffective in changing pHa [29] or actually decreased pHa [30], increased arterial lactate, and decreased pHi in liver and RBCs [29]. In other animal models of type B LA, researchers have found similar results and increases in mortality with SB [31].

Hypoxic LA was investigated in four canine models all of which documented an increase in arterial lactate after SB treatment [31–34]. No study documented an improvement in pHa (two unchanged [32,33], two lower [31,34]), cardiovascular parameters, or pHi of liver or myocardial cells. All four studies lacked resuscitation efforts and were performed entirely under hypoxic conditions and therefore are difficult to compare to normal clinical situations. Without oxygen and adequate ventilation, anaerobic metabolism dominates and SB treatment may shunt pyruvate to more lactate by disinhibition of PFK. Intracellular acidosis inhibits PFK to limit production of pyruvate and, in energy-depleted cells, pyruvate shunting to lactate [31,35].

Iberti et al. studied a canine hemorrhagic shock model comparing saline and SB without resuscitation. They observed no change in pHa or HCO₃ but lactate did increase [36]. Benjamin et al. resuscitated dogs with induced hemorrhagic shock for 30 minutes after treatment with SB or hypertonic saline and found that SB did increase pHa and bicarbonate, but severely elevated PCO₂ and increased lactate. Improvements in MAP and cardiac output seen with SB were similar to hypertonic saline controls [37].

The medical literature echoes the findings in animal studies. One study of severely ill and lactic acidotic humans found that SB use was an independent risk factor for mortality [38]. Currently, SB is not recommended for LA regardless of pHa. Treatment of LA should focus on treatment of the underlying disease [8]. Dialysis may be the next treatment option for LA when standard treatments are not successful.

Cardiopulmonary Cerebral Resuscitation

(see Chapter 150)

Quality cardiopulmonary cerebral resuscitation (CPCR) with ventilation with oxygen, support of tissue perfusion and high-quality chest compressions to restore some cardiac output, and rapid return of spontaneous circulation (ROSC) are the mainstays of restoring acid–base balance during cardiac arrest [2]. The current American Heart Association (AHA) guidelines do not recommend SB in CPCR except under special circumstances, including cocaine and antiarrhythmic (Ia and Ic) overdose and hyperkalemia [1,2]. The RECOVER guidelines echo that sentiment; SB is not recommended routinely but can be considered in prolonged CPCR >10–15 minutes without ROSC [39,40].

There is no doubt that cardiopulmonary arrest causes significant mixed acidosis (hypoxic, lactic, hypercapnic) by itself and some patients may have a pre-existing acidosis. In a recent review of acid–base and electrolyte abnormalities in CPCR in dogs and cats, 88% were acidemic (median pH 6.79), hypercapnic (median PCO₂ 64 mmHg), and hyperlactatemic (median 16 mmol/L) [41]. Despite documented acidosis in arrest, when CPCR treatment modalities were compared for impact on ROSC in a large university study of CPCR, SB administration was not significant [42].

The debate over SB in CPCR is understandable when you consider the puzzling results found in similarly devised studies. There are many canine studies examining SB and its impact on ROSC, fibrillation threshold, pHi, mortality, and neurological outcome. Most of these studies are in models of induced ventricular fibrillation (VFIB). In our limited CPCR literature, VFIB is the documented arrest rhythm in 7–20% [42–44].

The appropriate treatment for VFIB is timely defibrillation [2,39]. AHA guidelines recommend vasopressors only after multiple unsuccessful defibrillation attempts. With >4 minutes of arrest, a brief period of CPCR prior to defibrillation is suggested but the benefit of more prolonged CPCR is unclear [2]. After excluding one study that preloaded SB prior to prolonged arrest [45], there are four survival studies with improved outcomes using bolus SB [46–49]. Significant improvements in ROSC (77–90% of dogs) and survival (66–73%) were seen after 10–15 minutes of VFIB arrest. Two studies noted good neurological outcomes in survivors [46,48], one did not comment [47], and one reported poor outcomes for all dogs [49]. All studies employed some CPCR per AHA guidelines, including epinephrine in four studies, atropine in two, and ventilation to maintain normocapnia in all four.

The importance of efficient CPCR is highlighted in a short arrest study by Minuck and Sharma in which both

SB and control animals were defibrillated and resuscitated quickly with open chest CPR and ventilation. Of note, in that study no adverse effects of SB treatment were reported (alkalemia or hypercapnia) [50]. Two studies in canine VFIB arrest could not identify SB-induced paradoxical CSF acidosis [51,52] and in one of those, SB maintained pHi brain over control [51].

Many of the canine VFIB and SB studies cited as “associated with worse outcome” [39] in CPR have designs that hamper the drawing of clear conclusions. For example, three studies by Bleske et al. in short arrest (<5 min) used variable timing of SB and varied protocols (SB bolus versus CRI, $\pm$ epinephrine), treated mildly acidotic and non-acidotic dogs with SB (pH > 7.32 in all studies), and the experiments induced arrest serially in the same dogs for multiple studies [53–55]. Study design complicated interpretation of results in additional VFIB canine research by using arrest dogs multiple times as their own controls [56], treating only moderate acidemia (pHa > 7.2) [15,57,58], short arrest ($\leq$ 4 min) [15,57,58], and late defibrillation (> 18 min post arrest) [59]. One study documenting paradoxical CSF acidosis in short-arrest, non-defibrillated dogs administered SB when they were not acidotic (pHa mean 7.4) and used large, repeated doses of SB, a protocol chosen by the authors because it “frequently culminate[s] in metabolic alkalosis” [58].

There is evidence in the medical literature that SB should be reconsidered in specific arrest conditions: prolonged good CPR without ROSC (> 10–15 min), documented acidemia, and out-of-hospital arrests [60–62]. Empirical use of SB is not advocated for witnessed arrest or short arrests as overshoot alkalemia may occur [63].

Hyperkalemia (see Chapter 109)

Recommendations for treatment of life-threatening hyperkalemia have generally included SB administration

[1,13,27,64,65]. Calcium is administered first to immediately stabilize the myocardial cell membrane, then insulin/glucose to increase an influx of K (in exchange for Na) into cells. The effect of insulin/glucose occurs within 10–20 minutes, lasts 4–6 hours and can be expected to decrease K 0.6–1.0 mEq/L [66]. SB has been thought to act similarly until recently. New evidence in dialysis patients calls into question the ability of SB to cause intracellular influx of K. In multiple studies, SB administration alone has not effectively lowered potassium in dialysis patients [8,66–68]. It is theorized that the modest potassium-lowering effect of SB is instead due to enhanced renal excretion of potassium and is dependent on intact renal function [66]. The current medical recommendation is to avoid SB use for treatment of hyperkalemia unless the patient is also severely acidotic [8,66–68].

In small animal medicine, common causes of hyperkalemia include urinary tract obstruction or rupture, hypoadrenocorticism, and acute kidney injury (AKI). Most will respond to IV fluid therapy and restoration of renal perfusion, treatment of the underlying disorder (e.g. “unblocking,” DOCP), and use of calcium or insulin/glucose as necessary. The hyperkalemia of AKI may necessitate dialysis treatment.

Dosage and Administration

As discussed above, it is difficult to make specific recommendations for SB given the lack of clear efficacy and clinical indications. Clinicians have many choices among recommendations for dose and administration timing as there is no clear consensus in the medical or veterinary literature, other than “not too fast and not too much” (Table 174.2). Many sources recommend dosing based on bicarbonate deficit and titrating to an acceptable pH but this can be difficult given that the

Table 174.2 Administration strategies for intravenous sodium bicarbonate [13,40,53,65].

Disease state	Clinical caveats	Dosage	Time of administration
CPCR	Prolonged CPCR without ROSC (> 10–15 min)	1 mEq/kg	5–10 min or
	Documented metabolic acidosis		0.1 mEq/kg/min
Hyperkalemia	After calcium and insulin/glucose	1–2 mEq/kg	Variable, 10–15 min
	Ensure adequate urine output		
	Documented metabolic acidosis		
Metabolic acidosis	First address underlying disease	Calculate desired $[\text{HCO}_3^-]$	Variable, 1–24 h, recheck bloodwork prior to readministration
	Contraindicated in LA	Titrate	
		Increase pH only to 7.1 or 7.2	

CPCR, cardiopulmonary cerebral resuscitation; LA, lactic acidosis; ROSC, return of spontaneous circulation.

volume of distribution (Vd) of SB is highly variable (0.2–0.5×body weight) and treating to “normal” can lead to alkalemia [27,65]. Another strategy is to calculate to an “acceptable” $[\text{HCO}_3^-]$ of 10 or 12 mEq/L as follows: body

weight (kg)×(Vd)×(desired $[\text{HCO}_3^-]$ – current $[\text{HCO}_3^-]$) [13,19]. For example, a 10 kg dog with a current $[\text{HCO}_3^-]$ of 6 mEq/L could be given 15–30 mEq of SB ($10 \times (0.25 - 0.5) \times (12 - 6)$).

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Continuous-Rate Infusion

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Preparing Drug Solutions for Infusions

There is considerable room for error when making admixtures, and it is vitally important to ensure proper technique is used. Use the following tips to reduce errors.

- Use the closest syringe size for the volume of initial drug concentration (whether full strength or previously diluted) you need for the admixture.
- Choose a compatible carrier fluid; use the product monograph or a drug compatibility chart.
- Instill only the volume measured in the syringe, not the remaining volume in the syringe hub and needle. “Flushing” the hub and needle can lead to considerable error in dosing.
- Ensure adequate mixing of the bag, syringe or buretrol after addition of each drug. Currently, four inversions are recommended for complete mixing of bags or syringes. In burettes, inversion is not recommended, as fluid delivery can be affected if the filter at the top gets wet. Swirl the contents to mix.

Fluid Bag Delivery

Delivery of one or more medications in the fluid bag with maintenance fluids is a very simple method of delivering a CRI. There are some drawbacks that should be mentioned, however.

- *Less flexibility in dosing:* If the CRI is running with the maintenance fluids, there is less flexibility in dosing without changing the amount of fluids the patient is receiving. This method is ideal for CRIs that maintain a standard dose over a long period, for example metoclopramide.
- *More wastage:* The bag method is best for patients that will use the entire bag in a 24-hour period, such as large dogs or patients with higher fluid rates. Using

smaller fluid bags such as 100, 250, or 500 mL may help alleviate wastage, but these bags are typically more expensive/mL than their 1 L counterparts. Light sensitivity and long-term compatibility with the carrier fluid must be investigated.

- *Overfilling of fluid bags leads to inaccuracies:* Fluid bags are overfilled ~10% by the manufacturer. When stored for long periods, bags lose volume due to evaporative losses and may contain less than stated on the label. This will cause the concentration of the bag to be different from that expected. Likely, this will not cause concern but it is important to be aware of this source of error. Because of overfill and evaporative losses, human compounding pharmacies will not provide CRI medication in an IV bag, as the concentration cannot be guaranteed (the exception being if the drug and the fluid in measured quantities are added to an empty, sterile bag). Prefilled IV bags are only used for drug admixtures when they are providing a set number of milligrams, by using the entire contents of the bag in a short period of time (for example, diluting 500 mg of ampicillin in 50 mL of saline and giving over 30 min), where the final concentration is not as important as knowing the number of milligrams being administered. For this reason alone, CRI delivery in a fluid bag should be considered the least desirable method of administering analgesic drugs.
- *The 10% Rule:* This is a rule that hospital pharmacies use to ensure consistency in the final admixture product. If the medication to be added to the bag is 10% or more of the volume in the bag, then the same volume should be removed from the bag prior to addition of the medication. For example, to make a 5% dextrose solution using 50% dextrose, in a 1 L bag of fluid, 100 mL of dextrose must be added to the container. In this case, 100 mL of fluid should be removed from the bag before the addition. In the case of 2.5% dextrose solution, 50 mL must be added to 1 L. As this

is < 10% of the volume in the fluid bag, there is no need to remove 50 mL prior to addition. By ensuring that all parties are following the 10% Rule in your practice, you can be assured that if the solution is made up correctly, the final concentration should be similar from person to person.

- **Mixing:** After addition of an admixture drug, it is important to invert the bag at least four times to ensure adequate mixing.
- **Adjust based on patient response:** Knowing that the final concentration of a drug in a fluid bag can never be guaranteed due to the overfill of the bag, it is important that the veterinarian and veterinary technicians understand that the dose delivered per hour may not be exactly what is expected. This highlights the importance of assessing the patient for response to therapy and adjusting the dosing accordingly.

Drug Infusions Using a Burette

A burette is an inexpensive tool for IV fluid therapy and is an inline, graduated volume cylinder that allows for accurate portioning of IV fluids into a smaller volume. Adjustments to drug dose rate are easily made by adding more fluid (decrease concentration) or more drug (increase concentration), or simply emptying the burette and adding fresh solution. Typically, burettes hold 150 mL and have an IV spike at the top that is attached to the IV fluid bag. A roller clamp allows for fluid entry into the burette, and a standard solution set is either permanently attached or spiked into the bottom of the burette to attach to the patient. Drug infusions in a burette should always be administered using an IV fluid pump for accuracy.

There is an injection port at the top of the burette for medication additions. It is important to note that on some models (usually needleless port types), there is a large amount of deadspace within the injection port. Following addition of small volumes of medication, it is advisable to instill ~1 mL of a sterile fluid (NaCl or fluid drawn aseptically from the fluid bag into a syringe) to flush out the port and ensure that the entire dose has been instilled in the burette. Ensure the mixture is adequately mixed by swirling.

Preparation of Drug Infusions for Bag/Burette

To prepare medications for infusion in a fluid bag or burette, there are several key pieces of information required.

- The dose to be provided per hour
- The initial concentration of the drug
- The weight of the patient
- The volume of the fluid bag OR the actual or desired volume of the buretrol
- The fluid rate/h at which to deliver

Using the provided dose, calculate the number of mL/h of drug that is required.

Example 1: Dexmedetomidine CRI, at 0.5 µg/kg/h for a 20 kg dog, delivered by burette.

$$0.5 \mu\text{g/kg/h} \times 20 \text{ kg} = 10 \mu\text{g/h}$$

Dexmedetomidine is 500 µg/mL (0.5 mg/mL) concentration:

$$10 \mu\text{g/h} / 500 \mu\text{g/mL} = 0.02 \text{ mL/h}$$

Next, determine how many hours of fluid will fit in the burette, if the hourly rate is 30 mL/h and the burette holds 150 mL.

$$150 \text{ mL} / 30 \text{ mL/h} = 5 \text{ h}$$

Finally, how many mL of dexmedetomidine are needed for 5 hours?

$$5 \text{ h} \times 0.02 \text{ mL/h} = 0.1 \text{ mL of dexmedetomidine is needed}$$

Example 2: The exact same calculation is performed for delivery in a fluid bag.

Using a 500 mL 0.9% NaCl bag, calculate how much metoclopramide should be added to deliver 2 mg/kg/day to a 30 kg dog receiving 75 mL/h. Calculate the number of mL/h of metoclopramide required.

$$2 \text{ mg/kg/day} \times 30 \text{ kg} = 60 \text{ mg/day} / 24 \text{ h} = 2.5 \text{ mg/h}$$

Metoclopramide is 5 mg/mL, so:

$$2.5 \text{ mg/h} / 5 \text{ mg/mL} = 0.5 \text{ mL/h}$$

Next, calculate the number of hours, assuming an actual volume of 500 mL.

$$500 \text{ mL} / 75 \text{ mL/h} = 6.7 \text{ h}$$

Finally, how much metoclopramide do we need?

$$6.7 \text{ h} \times 0.5 \text{ mL/h} = 3.3 \text{ mL}$$

Since 3.3 mL is < 10% of the volume of the bag, we simply add it to the bag, and invert to mix.

Labeling the Drug Infusion

It is very important to appropriately label the drug infusion, not only to accurately identify the contents but to

Figure 175.1 Label for drug infusion.

ensure consistency or in some cases, an error in the previous drug calculation may be identified. The admixture should be recalculated as a verification each time a new solution is made.

A simple label can be made for you at the local print shop (Figure 175.1).

Standardized Concentration Infusions

As mentioned above, some veterinarians prefer to use standardized concentrations of analgesics, delivered on a sliding scale based on patient weight. These infusions do have some benefits.

- *Less likely to have calculation errors:* The same amount of drug is added to the same size bag each time it is made up, reducing the chance of an error due to calculations.
- *Less likely to have administration errors:* Likewise, there is less chance of an administration error when the dose is standardized. If prescribed at 1 mL/kg/h, this is simply the body weight of the patient entered into the pump.
- *Recipes can be used to make multidrug bags:* Fairly advanced CRIs can be created using a standard recipe. This delivers each drug at a set rate. Commonly, morphine-lidocaine-ketamine infusions are prepared in this manner.
- *Flexibility in dosing:* While the standard recipe may be delivered at 1 mL/kg/h, increasing or decreasing the hourly rate will allow titration. For multidrug bags, the infusion of each medication is increased or decreased.

Just as there are some benefits, and ease of use for the veterinary staff, there are some drawbacks.

- *Additional fluid line and pump required:* Often the mL/h supplied with the standardized concentration method is not sufficient to meet the individual patient's hourly requirements. Therefore, an additional line and bag with maintenance crystalloid may be required.
- *Wastage:* Wastage can be significant with this method, as the patient may not use the entire bag of medication. Consider recipes for 100/250/500/1000 mL bags to adjust for patient size.

- *Lack of individualization:* Especially with multidrug bags, this method allows increasing or decreasing the dosage of all drugs, but not each drug individually. Often, finding the right level of each drug for the patient is a challenge, and this type of system makes it a little more difficult.

All things considered, the standardized infusion bag is an acceptable method of providing a CRI, and may be preferable in veterinary clinics with a limited number of fluid pumps available.

Preparing a standardized infusion bag is as simple as following a recipe. Several organizations offer recipes and CRI calculators online, which make set-up extremely easy. To produce your own customized recipe, the following information is needed.

- Volume of fluid bag
- Concentration of each drug
- Desired dose for each drug

For example, ketamine has a typical dose range as a CRI of 0.1–1.0 mg/kg/h. Ideally, starting at the middle of the dose for the standardized bag to deliver at 1 mL/kg/h of fluid will allow for some flexibility. The dose can be decreased or increased by changing the fluid rate, so that 0.5 mL/kg/h will reduce the dose to 0.25 mg/kg/h. Doubling the fluid rate to 2 mL/kg/h will deliver ketamine at 1 mg/kg/h. Therefore, calculate based on 0.5 mg/kg/h.

Initial concentration of ketamine is 100 mg/mL. Desired dose of 0.5 mg/kg/h in 1 mL/kg/h of final concentration. Therefore, we want 0.5 mg in every mL of fluid. For a 1 litre bag of fluid:

$$0.5 \text{ mg/mL} \times 1000 \text{ mL} = 500 \text{ mg of ketamine or 5 mL to add to the bag}$$

For alternate bag sizes: 0.5 mL/100 mL, 1.25 mL/250 mL, 2.5 mL/500 mL.

To add fentanyl at 3 µg/kg/h to the same bag at the same 1 mL/kg/h rate:

$$3 \text{ µg delivered in 1 mL/h of fluids} = 3 \text{ µg / mL of final solution}$$

For 1000 mL bag, need 3000 µg. Fentanyl is 50 µg/mL, therefore:

$$3000 \text{ µg} / 50 \text{ µg / mL} = 60 \text{ mL of fentanyl to a 1000 mL bag}$$

For alternate bag sizes: 6.0 mL/100 mL, 15 mL/250 mL, 30 mL/500 mL. Keep in mind that due to overfill/evaporative losses, the actual concentration may vary by ± 10%.

Drug Infusions Using a Syringe Pump

Syringe pumps are becoming much more widely available, and are ideal to administer CRIs. One distinct advantage is the ability to adjust drug dose rate with just a few simple clicks. The drug can be prepared full strength but if very small hourly volumes are required, some syringe pumps may struggle with accuracy, making dilution of the drug a necessity. Many syringe pumps offer onboard programs that allow the manager to create drug libraries and set the concentration, dose range, dosing limits for the drug (min/max), and program boluses. Some basic syringe pumps will be programmed simply with mL/h, and in some cases, pumps are programmed using a chart that converts mL/h for each possible syringe size and manufacturer to mm/h. These latter pumps are very inexpensive but care must be taken to ensure training is sufficient to avoid errors.

An example of a drug that may be administered via syringe pump is midazolam. Midazolam may also be administered via the other methods described above.

Midazolam has a dose rate of 0.25–1 mg/kg/h. To calculate this for a syringe pump, the following information is needed.

- Patient weight
- Desired dose
- Concentration

For a 34 kg dog, to receive 0.5 mg/kg/h of midazolam, the following calculation is used:

$$\begin{aligned}\text{Patient weight (kg)} \times \text{dose} &= 34 \text{ kg} \times 0.5 \text{ mg/kg/h} \\ &= 17 \text{ mg/h}\end{aligned}$$

To calculate mL/h:

$$17 \text{ mg/h} / 5 \text{ mg/mL} = 3.4 \text{ mL/h}$$

The syringe pump will be set to deliver 3.4 mL/h.

Table 175.1 Common continuous-rate infusion (CRI) dosages.

Drug (CRI)	Dose	Units
Butorphanol	0.1–0.4	mg/kg/h
Dexmedetomidine	0.25–1.0	µg/kg/h
Diazepam	0.5–1.0	mg/kg/h
Diltiazem	1–5	µg/kg/min
Dobutamine	5–20	µg/kg/min
Dopamine	5–20	µg/kg/min
Epinephrine	0.025–0.3	µg/kg/min
Fentanyl	2–5	µg/kg/h
Furosemide	0.1–1.0	mg/kg/h
Hydromorphone	0.01–0.03	mg/kg/h
Ketamine	0.1–1.0	mg/kg/h
Lidocaine	25–75	µg/kg/min
Metoclopramide	1–2	mg/kg/day
Midazolam	0.25–1	mg/kg/h
Morphine	0.1–0.5	mg/kg/h
Nitroprusside	1–10	µg/kg/min
Norepinephrine	0.1–1.0	µg/kg/min
Procainamide	25–50	µg/kg/min
Propofol	25–300	µg/kg/min
Vasopressin	1–5	mU/kg/min

Table 175.1 provides CRI doses for commonly used drugs.

Acknowledgment

Some of this work concurrently appears in *Analgesia and Anesthesia for the Critically Ill or Injured Dog and Cat* by Matthews, Sinclair, Steel, and Grub, published by Wiley.

Transfusion of Red Blood Cells and Plasma

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Transfusion Therapy

Transfusion therapy has been a life-saving intervention for many years, with a dog-to-dog blood transfusion being the first known documented transfusion event in medical history [1]. Many advances have been made since the incorporation of small animal transfusion medicine into veterinary practice in the 1950s. Navigating the complex landscape of blood component therapy, pretransfusion screening, and potential complications can become an overwhelming task for the busy emergency room clinician. This chapter summarizes key points in canine and feline transfusion medicine, using an evidence-based yet practical approach when available. Red blood cell and plasma transfusion will be discussed. Expanded component therapy is beyond the scope of this chapter.

Donor and Recipient Screening

Blood products are obtained from donor animals and thus are a limited resource in hospital settings. For the busy emergency practice, it is recommended that commonly used blood component therapy products be stocked. For the canine patient, the most common and practical components include fresh frozen plasma and packed red blood cells. Dependent upon caseload and patient acuity, feline blood products may not be a practical inventory investment. In a very busy setting, it is prudent to keep feline packed red blood cells and fresh frozen plasma available. Many hospitals still manage a feline blood donor program, with the intent of using fresh whole blood on an as-needed basis.

Each hospital must evaluate its practice needs in order to direct which, if any, blood products will be stocked on site.

Blood type of donors and recipients is relevant to unit selection and prevention of hemolytic blood transfusion reactions. Hemolytic transfusion reactions occur when the recipient has existing antibodies that are specific for antigens on the donor erythrocytes. The dog erythrocyte antigen (DEA) system is applied to canine blood types. The canine blood type of most clinical importance is the DEA 1 system (DEA 1.1, DEA 1.2, DEA 1.3), as DEA 1 is highly antigenic. A DEA 1-negative dog that receives a DEA 1-positive transfusion is likely to mount a strong alloantibody response, resulting in sensitization, so that a future DEA 1-positive transfusion may cause a catastrophic hemolytic transfusion reaction. Dogs do not have pre-existing alloantibodies to the DEA 1 system. Although natural antibodies have been demonstrated in some dogs for DEA 3, DEA 5, and DEA 7, these are considered “weak antibodies” and not capable of causing a hemolytic transfusion reaction [2]. The Dal red blood cell antigen is present in most dogs, but lacking in some Dalmatians. As such, a canine patient without the Dal antigen may become sensitized and experience a hemolytic crisis upon future transfusion of Dal-positive red blood cells [3]. The current universal canine blood donor phenotype is DEA 1.1, 1.2, 3, 5, and 7 negative but positive for DEA 4.

A practical approach to stored blood products for most emergency hospitals is to inventory primarily universal donor blood (DEA 1.1 negative). If both DEA 1.1 positive and negative blood is stocked, canine typing systems designed for in-house use are available to screen for DEA 1, for pretransfusion recipient screening. The two most common in-house testing systems available utilize monoclonal anti-DEA 1.1 antibodies. These are the DMS card test (CARD, DMS Laboratories, NJ) and the Quick-test DEA 1.1 (CHROM, Alvedia, France). Autoagglutination will not interfere with the ability to read results with the Alvedia test. Donor screening should be sent to a reference

laboratory for gold standard methodology and if comprehensive typing beyond the DEA 1 system is desired.

The system applied to cats is the AB blood group. Cats are type A, type B or, rarely, type AB. Feline type A is dominant over type B. As such, cats with the type A phenotype are genetically a/a or a/b. In order to demonstrate the type B phenotype, cats must be genetically b/b. The rare cat with type AB phenotype has a genotype with a third allele allowing expression of both A and B substances on the surface of their red blood cells [4]. The geographic distribution of these blood types varies, but the highest reported incidence of type B has been in Australia at 36% [5]. In the north-east region of the United States, the percentage of type B cats has been reported to be between 0.3% and 8% [6]. The United Kingdom reports that 68% of non-pedigree cats are type A, 30% type B, and 2% type AB [7]. All Siamese cats are type A, while type A and B blood has been reported in other exotic cat breeds such as the Devon rex, British short-hair, Cornish rex, exotic short-hair, and Scottish fold. Domestic short-hair cats are also known to have type B blood [8]. The *Mik* red blood cell antigen has been identified in some domestic short-hair cats. Cats that lack the *Mik* antigen may have preformed alloantibodies that can result in transfusion reactions [9].

All donors and recipients should be blood typed. Xenotransfusion of cats with canine blood has been reported, but is not recommended due to a high rate of reaction and the advances made in feline blood transfusion medicine [10]. However, in certain critical circumstances, if feline blood is not available canine blood may be considered [11].

All type A and B cats have preformed natural alloantibodies, and are at risk of hemolytic transfusion reactions if given an incompatible transfusion. Type B cats have strong anti-A antibodies and may experience a fatal transfusion reaction if given as little as 1 mL of type A blood [12]. Type B blood administered to a type A cat is unlikely to cause a fatal reaction, but will result in shortened lifespan of the transfused cells. Type AB cats do not have alloantibodies to either A or B antigens, and should receive either type AB or type A blood if transfusion is needed. The two most common in-house feline blood typing systems available are the CARD Rapid®-VetH Feline (DMS Laboratories, Flemington, NJ) and the Quick-test A+B (Alvedia, France). Type B and AB cats should be confirmed by sending to an outside laboratory [13]. Cats should always receive type-specific plasma.

Cross-Matching

Ideally, all patients should have a cross-match performed prior to transfusion of red blood cells. A major cross-

match tests the recipient's serum for alloantibodies against donor blood cells. The minor cross-match tests the donor's serum for alloantibodies against recipient blood cells. It is reasonable to skip a cross-match in a dog receiving its first blood transfusion, as they do not have pre-existing alloantibodies. Some clinicians recommend that dogs with immune-mediated hemolytic anemia ideally be cross-matched prior to all transfusions. The authors recommend a cross-match in all feline transfusion events, as this is the most reliable bedside method to assess for inaccurate blood typing, incompatibilities due to *Mik* cell antigens, or possibly other unrecognized antigens. A cross-match should also be performed in all patients that have received a blood transfusion greater than 5–7 days prior to the planned transfusion, or have experienced hemolysis with prior transfusion.

Commercial kits are available for in-house cross-matching. In the event that an emergency transfusion is needed prior to the completion of a cross-match, a crude, rapid bedside method for testing AB compatibility in cats is to mix a single drop of donor and recipient blood, then evaluate for agglutination.

Blood Product Administration

Transfusion administration technique will impact recipient safety, efficacy, and efficient use of hospital resources. Red blood cells do not need to be warmed prior to administration but this may be considered when the recipient is a very small patient. Frozen plasma products should be placed in a sealed plastic bag, then warmed in a water bath until thawed. A microwave should not be used to thaw frozen blood products. Use of peristaltic pumps to deliver red blood cell transfusions has been shown to cause damage and decrease survival of transfused red blood cells [14,15]. As such, the authors recommend gravity flow and standard blood filter set (170–260 micron) for canine blood product transfusions. Unfortunately, the priming volume of these sets is too large for cats and small dogs. A human neonatal syringe filter set with a 150 micron filter or a syringe pump with Hemo-Nate (18 micron) filter can be used for these patients. Plasma transfusions should also be administered via a standard blood filter set.

The blood product volume to be transfused is best guided by goal-directed therapy. The most straightforward formula used to calculate volume of pRBCs to transfuse is [16]:

$$\text{pRBC volume to transfuse} = \text{desired \% PCV increase} \times 1.5 \times \text{kg body weight}$$

See Table 176.1 for commonly used doses for blood products.

Table 176.1 Commonly used doses of blood products available at most ER practices. Note that many more blood products and components are available that are beyond the scope of this chapter.

Blood product	Contents	Indications	Common dose (mL/kg)
Packed red blood cells (pRBC)	Red blood cells +/- white blood cells Anticoagulant (CPDA) +/- preservative (Optisol, Nutricel)	Anemia with clinical signs of decreased oxygen delivery (DO ₂) despite optimization of preload and contractility	10–15 mL/kg
Fresh whole blood	Red blood cells White blood cells Plasma (coag. factors) Platelets Anticoagulant (CPDA)	Anemia with clinical signs of decreased DO ₂ despite optimization of preload and contractility if pRBCs not available Need for multiple components – severe hemorrhage	20–22 mL/kg
Stored whole blood	Red blood cells White blood cells Plasma (coag. factors) Anticoagulant (CPDA)	Anemia with clinical signs of decreased DO ₂ despite optimization of preload and contractility if pRBCs not available Need for multiple components (red cells and stable coagulation factors)	20–22 mL/kg
Fresh frozen plasma	Coagulation factors Antithrombin Albumin Globulins	Hypocoagulability with hemorrhage due to coagulation factor deficiency	10–20 mL/kg

The administration rate of the blood product is dependent upon the status of the patient. In patients with acute severe hemorrhage, blood components may need to be administered as quickly as possible. Patients at risk for fluid overload, such as those with congestive heart failure, may need transfusions administered at a conservative rate. For the typically anemic but relatively stable patient, a common method of product transfusion is to begin the transfusion at 0.25 mL/kg/h for 5 minutes and observe for evidence of a transfusion reaction. If no reaction is appreciated based on patient observation and comparing vital signs to baseline vitals, the rate is increased for the transfusion to be delivered over the time desired.

It is generally recommended that blood products are not left at room temperature for more than 4–6 hours to prevent bacterial growth, although one study found no bacterial growth in canine stored whole blood after 24 hours room temperature [17,18]. If fresh frozen plasma is thawed but not used, refreezing within 1 hour is acceptable and does not appear to have deleterious effects on hemostatic protein activity [19]. Additional freeze-thaw cycling has not been evaluated and should be avoided.

Transfusion Reactions

Multiple types of transfusion reactions can occur from administering blood products as component therapy or whole blood. Overall, the transfusion reaction rate is low, reportedly 3.3–15% of recipients [20–23]. Using compatible blood products from screened donors, replacing only the necessary component(s), careful consideration of the necessity of the transfusion, and appropriate administration are the most effective means of limiting the frequency of transfusion reactions.

Monitoring for transfusion reactions is accomplished by close observation of the patient during and after the transfusion. Multiple transfusion administration patient monitoring protocols exist with the common goal of prompt recognition of a reaction. A common method of transfusion monitoring is to obtain baseline vital signs of temperature, pulse, respiration, and capillary refill time prior to administration. Five minutes following administration of the blood product, the baseline vital signs are re-evaluated. If no reaction has occurred, evaluation of vital signs is performed at 15 minutes, 30 minutes, and then every 60 minutes throughout the transfusion. In addition to these parameters, the patient should be

Table 176.2 Common transfusion reactions, symptoms, and suggested actions.

Product	Clinical signs	Response
Acute immunological reactions		
Red blood cells	Febrile non-hemolytic reactions. Other signs may include tachycardia, tachypnea, vomiting and/or diarrhea	Stop or slow transfusion rate
	Hemolytic reactions – signs may include fever, tachycardia, tachypnea, vomiting and/or diarrhea, cardiovascular collapse, pigmenturia	Discontinue transfusion
Plasma	Pruritus, urticaria, facial edema	Diphenhydramine, stop transfusion, may resume transfusion slowly
	Transfusion-related acute lung injury – most commonly reported after plasma transfusions in people	Usually develops 6–24h following transfusion
Acute non-immunological reactions		
All products	Transfusion-associated circulatory overload	Furosemide trial
	Citrate toxicity	Calcium gluconate or calcium chloride
Delayed immunological reactions		
Red blood cells (RBC)	Shortened RBC lifespan, hemolysis	Type and cross-match all future transfusions
All products	Transfusion-related immunomodulation	None
Delayed non-immunological reactions		
All products	Infectious disease transmission	Use screened donors
		Treat underlying disease

observed for vomiting, restlessness, increased respiratory effort, and/or pigmenturia (Table 176.2). In cases of life-threatening hemorrhage, rapid administration of blood products is necessary and transfusion protocols are not utilized. Chapters 170 and 177 discuss rapid administration of blood products in more detail.

Transfusion reactions can be divided into two broad categories: immunological and non-immunological. These categories can be further divided into acute (up to 48h) and delayed reactions (beyond 48h) [23,24]. Acute immunological transfusion reactions include hemolysis, fever, and urticaria. Examples of acute non-immunological reactions include transfusion-associated circulatory overload (TACO), vomiting, acute respiratory distress, and infectious disease transmission or citrate toxicity.

Red blood cell transfusion can cause two main acute immunological reactions: febrile non-hemolytic reactions and hemolytic reactions. Hemolytic reactions are the most severe transfusion reactions and can be fatal. If a reaction is suspected in patients receiving red blood cells, the transfusion should be stopped and the patient assessed for hemolysis. If hemolysis is evident, the transfusion should be discontinued immediately and the patient monitored and supported closely. Using blood from a compatible cross-match should prevent hemolytic transfusion reactions. Febrile non-hemolytic reactions are much more common. They are the result of cytokines and white blood cells in the donor unit.

The transfusion can usually be completed in the face of a febrile non-hemolytic reaction although the administration rate may need to be slowed. Premedication with glucocorticoids or antihistamine drugs will not prevent either of these transfusion reactions and is not recommended [25].

Plasma transfusion (either as component therapy or as part of whole blood) can cause acute hypersensitivity reactions manifested by urticaria and pruritus. Antihistamine administration may be of benefit for these patients. Citrate toxicity may occur with transfusion of anticoagulated blood products. Citrate chelates ionized calcium, resulting in ionized hypocalcemia. This can cause tremors, facial pruritus, hypotension, arrhythmias or any combination thereof. Citrate toxicity is treated with administration of IV calcium, in a separate line from the blood product.

The clinician must carefully evaluate the risk:benefit relationship in any potential transfusion recipient. Transfusion of red blood cells has been associated with activation of the immune system and secondary transfusion-related immunomodulation (TRIM), TACO, and transfusion-related acute lung injury (TRALI). Each of these poses serious potential risks and must be carefully considered prior to transfusion of any blood products. Use of clinical endpoints of resuscitation, such as heart rate, blood pressure, mentation, and lactate, should be emphasized over solely evaluating the HCT, PCV, or hemoglobin.

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Massive Transfusion

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Introduction

In cases of severe hemorrhage, patients may require large volumes or rapid infusions of blood products to achieve hemodynamic stabilization. This resuscitation strategy is termed *massive transfusion*, and is most commonly defined as receiving one blood volume or more of blood products within 24 hours. Receiving 50% of one blood volume within 3 hours, 150% of one blood volume regardless of time, or 1.5 mL/kg/min of blood products for 20 minutes have also been considered massive transfusion. In veterinary patients, blood volumes are approximately 80–90 mL/kg in canines and 40–60 mL/kg in felines [1].

In human and veterinary medicine, classic resuscitation strategies for patients with severe hemorrhage include crystalloid fluids followed by red blood cell transfusion, and plasma products if hypocoagulability is documented. More recently, in human medicine, review articles suggest a change in this approach, with the focus redirected at rapid surgical correction of bleeding, prevention and treatment of acidosis and hypothermia, transfusion of plasma, platelets and red blood cells in a 1:1:1 ratio, early use of fibrinogen, potential use of recombinant activated factor VII (rFVIIa), and decreased emphasis on excessive crystalloid and RBC use [2]. Some of these strategies have been incorporated into veterinary medicine in recent years, and the evidence for their use will be discussed.

Patients requiring massive transfusion are often severely affected or critically ill, and survival rates in human medicine (25–84%) and veterinary medicine (4/15 dogs in one study, 27%) reflect this [1]. Given the cost and resources associated with massive transfusion strategies, it is important to be aware of treatment recommendations and possible complications of massive transfusion to ensure the best possible outcomes.

Common Conditions Requiring Massive Transfusion

In human patients, massive transfusion is rare and is most commonly employed following hemorrhage from trauma in cases of combat. Other less common conditions requiring massive transfusion include aortic aneurysm, liver transplant, and obstetric catastrophes. In veterinary patients, data are limited and based primarily on a single retrospective study of 15 dogs [3]. In this small population, underlying causes of hemorrhage included abdominal neoplasia with resultant hemoabdomen (n=6), traumatic hemoabdomen (3), gastrointestinal hemorrhage (3), gastric dilation-volvulus (2), and septic peritonitis with severe intra-abdominal hemorrhage (1).

Diagnosis/Prediction

Patients presenting with a requirement for massive transfusion will likely demonstrate signs of severe hypovolemic shock secondary to decreased tissue perfusion and cellular hypoxia (see Chapter 153). Left untreated, hemodynamic instability will lead to organ damage and death [4]. Pale mucous membranes, prolonged capillary refill time, tachycardia (or bradycardia in cats), poor peripheral pulses, tachypnea, weakness, and mental obtundation are the classic signs of hypovolemia, but not all patients with tissue hypoperfusion as the result of massive hemorrhage present with obvious signs of shock.

Signs of blood loss may be external or may be detected via initial assessment with ultrasound (FAST scan; see Chapter 182) or rectal examination in the case of gastrointestinal hemorrhage [5]. Initial blood database should consist of packed cell volume (PCV) and total solids (TS), with a venous blood gas if possible. While low PCV

and TS are supportive of hemorrhage due to loss of both red blood cells and protein from the intravascular space, splenic contraction can lead to an increase in PCV and discordant PCV/TS (normal PCV/low TS) early on following blood loss, especially in dogs. Venous blood gas results will often be suggestive of a lactic acidosis due to tissue hypoperfusion, although other changes are possible depending on the patient's clinical signs (see Chapter 156). If hemorrhage is suspected based on history, physical exam or laboratory findings, the lack of a specific diagnosis in terms of source of bleeding should not delay resuscitation.

While hypotension (historically defined as a systolic blood pressure ≤ 90 mmHg) has classically been considered an indicator of shock, early compensation by the cardiovascular system may allow patients to maintain a relatively normal blood pressure despite significant blood loss. As such, the shock index (SI), defined as the ratio of heart rate (HR) to systolic blood pressure (SBP), has been developed in people to attempt to recognize shock earlier, during this compensatory phase. In healthy adults, normal SI ranges from 0.5 to 0.7, and human studies have identified a prehospital SI > 0.9 as a risk factor for massive transfusion [6]. Shock index has recently been evaluated in a small retrospective study of canine patients with blunt trauma requiring transfusion [7]. In that study, a SI > 1.43 was 71% accurate for predicting the need for transfusion, and the authors concluded that SI may have some utility in predicting transfusion needs following blunt trauma in dogs, although further studies are warranted (see Chapter 152).

In addition to the SI, a scoring system exists in human medicine to attempt to predict the need for massive transfusion. The Trauma-Associated Severe Hemorrhage (TASH) score takes into account a number of variables including hemoglobin concentration, base excess, systolic blood pressure, heart rate, the presence of free abdominal fluid, the presence of clinically unstable pelvic fractures or open/dislocated femur fractures, as well as gender, and calculates a score to determine the probability of massive transfusion [8]. Higher scores increase the probability of massive transfusion. No such scores have been developed for veterinary patients.

Pre-Resuscitation Complications/Acute Traumatic Coagulopathy

Even before resuscitation with fluids and blood products, patients with severe hemorrhage and shock necessitating massive transfusion are prone to coagulation abnormalities that may predispose them to further bleeding. While it was initially hypothesized that this coagulopathy was due to blood loss, hemostatic dysfunction and/or

hemodilution of coagulation factors and platelets, more recent evidence has shown that this acute traumatic coagulopathy (ATC) can occur as quickly as within 30 minutes post trauma, and is characterized by anticoagulation and hyperfibrinolysis (see Chapter 163) [9–11]. This coagulopathy occurs before resuscitation is instituted, and in human patients, its severity appears to be positively correlated with the severity of injury and degree of shock. In human trauma patients, the presence of ATC is an independent risk factor for death, and is associated with a four-fold higher risk of multiple organ dysfunction syndrome (MODS) and death [9,12].

While the exact mechanisms of ATC are not fully understood, current hypotheses include a disseminated intravascular coagulation (DIC) process with hyperfibrinolysis, an enhanced thrombomodulin-thrombin-protein C pathway, and catecholamine-induced endothelial damage from exuberant sympathoadrenal stimulation [9,11]. Hypothermia, acidosis, hemodilution, and systemic inflammation may further contribute to what has been termed a “bloody vicious cycle,” in which “bleeding leads to resuscitation, resuscitation leads to dilution and hypothermia, dilution and hypothermia lead to coagulopathy, and coagulopathy leads to bleeding” [13]. Hypothermia may worsen coagulation by inhibiting platelet function, reducing synthesis, inhibiting function of coagulation factors, and increasing fibrinolysis. In addition, acidosis impairs coagulation factor function [1,14].

In human patients with trauma, the incidence of ATC is 10–30% [15]. The incidence in veterinary medicine remains unknown, but several studies have documented the occurrence of a hypocoagulable state in canine patients with trauma. In one prospective study, spontaneously traumatized dogs had a significant reduction in all measured hemostatic factors and significant prolongations of aPTT and PT compared to a healthy control group [16]. In another study of dogs with trauma, ATC was identified in 15% of patients, and there was a correlation between prolonged aPTT times and non-survival [14].

Treatment

In human medicine, the standard treatment approach to hemorrhagic shock and those patients requiring massive transfusion historically included administration of liberal amounts of crystalloids and pRBCs followed by the administration of plasma and platelets based on coagulation testing [17,18]. Damage control resuscitation is now recommended, the purpose of which is to try to stop the “vicious bloody cycle” in which the triad of hypothermia, acidosis, and coagulopathy leads to continued hemorrhage [11,13,19,20].

Damage control resuscitation includes hypotensive resuscitation, decreased use of crystalloids, administration of fresh frozen plasma, platelets and packed red blood cells (FFP:plt:pRBC) in a 1:1:1 ratio, use of other hemostatic agents as needed, heat support, and early surgical intervention [21–23]. Based on a recent prospective observational study, the PROMMTT trial, and a prospective randomized controlled clinical trial, the PROPPR trial, it is now recommended that blood products, FFP:plt:pRBC, be administered early on in resuscitation and in a 1:1:1 ratio in human medicine to improve survival and decrease transfusion requirements [21,22]. In veterinary medicine, no studies currently exist examining blood product component therapy and transfusion ratios. However, based on the human evidence, it may be advisable to consider plasma and platelet transfusions early on in patients requiring massive transfusion, or administering whole blood when available [11,12,15,19,24].

Other blood products utilized in human medicine for massive transfusion resuscitation include cryoprecipitate, fibrinogen concentrate, rFVIIa, prothrombin complex, and antifibrinolytics [10,17,20,25–27]. Cryoprecipitate or fibrinogen concentrate is indicated when fibrinogen levels are below 100 mg/dL [17,25,27]. The fibrinogen goal is 150–200 mg/dL with the ideal range being >200 mg/dL [27]. Tranexamic acid, an antifibrinolytic, has been shown to decrease mortality in human trauma patients when used within the first 3 hours; no evidence currently exists to support the use of antifibrinolytics in veterinary patients requiring massive transfusion (see Chapter 68) [10].

Damage control resuscitation should be implemented in veterinary patients receiving or expected to receive a massive transfusion. It is recommended to optimize the use of blood products and administer them sooner to decrease the dilutional effect of large amounts of crystalloids. Transfusions should be given as needed and it is recommended that for each pRBC transfusion that is administered, a FFP transfusion be given as well. The recommended dose for FFP is 10–20 mL/kg and the dose for pRBC is 15 mL/kg to raise the PCV by 10% [28,29]. If whole blood is available, the recommended starting dose is 20–30 mL/kg. If fibrinogen is able to be measured and is low, then cryoprecipitate can be given. Tranexamic acid or aminocaproic acid can also be considered. If possible, synthetic colloids should be avoided given their reduction in fVIII and vWf activity (see Chapter 168).

Usually, it is recommended to administer a blood product transfusion slowly within a 4-hour period [30]. In stable, resuscitated patients that are meeting the criteria of massive transfusion, this recommendation should be followed (see Chapter 176). However, in unstable patients requiring massive transfusion due to hemorrhagic shock, it is the authors' recommendation

to administer blood products as fast as necessary in order to stabilize the patient as the benefit of preventing death outweighs the risk of a transfusion reaction. In the authors' experience, patients in hemorrhagic shock can be bolused pRBC transfusions within minutes without experiencing significant transfusion reactions. Hypotensive resuscitation should be implemented with a systolic blood pressure target of 90 mmHg during the early resuscitation period until hemostasis can be achieved. Additional treatments should include heat support and early surgical intervention.

Complications

Electrolyte Abnormalities

Possible electrolyte abnormalities secondary to massive transfusion include hypocalcemia, hypomagnesemia, and hyperkalemia (see Chapters 109 and 110). Citrate from pRBC units can bind to ionized calcium, causing hypocalcemia [11,13,20]. Common signs of hypocalcemia include muscle tremors, excitation, disorientation, hypersensitivity to stimuli, and facial rubbing [31]. Echocardiographic and ECG abnormalities may include evidence of decreased cardiac output, decreased contractility, arrhythmias, and a prolonged QT interval [31]. Patients with hypocalcemia showing clinical signs should be treated with calcium gluconate at a dose of 0.5–1.5 mL/kg IV administered slowly and to effect. Hypomagnesemia can also occur secondary to citrate binding [11]. Common signs are muscle fasciculations, muscle weakness, and seizures. ECG findings include arrhythmias and a prolonged QT interval [32]. Magnesium sulfate should be administered if clinical signs are present. The recommended magnesium dose for life-threatening arrhythmias is 0.15–0.3 mEq/kg diluted in 5% dextrose or normal saline and administered intravenously over 5–60 minutes [33].

Hyperkalemia can occur secondary to increased potassium levels in the pRBC supernatant [11,13]. Potassium levels increase with each day of pRBC storage and by 42 days of storage, there can be a significant amount of potassium in a unit, with studies citing 45–77 mEq/L [11,13,34]. Hyperkalemia from pRBC transfusion is thought to be less of a problem in veterinary medicine as dogs have less potassium in their red blood cells compared to humans; however, in cases of massive transfusion, potassium levels should be monitored closely [1]. If hyperkalemia occurs, it is usually transient, and resolves as potassium is redistributed in the body [34].

However, there is evidence in human medicine that cardiac arrest can occur from hyperkalemia during a pRBC transfusion [11,34]. In addition to measuring

potassium levels periodically, ECG monitoring should occur continuously in patients requiring massive transfusion. Signs of hyperkalemia on an ECG in veterinary medicine include peaked T-waves, widened QRS, atrial standstill, sinoventricular rhythm, and ventricular fibrillation [35].

Methods used to prevent hyperkalemia in human patients requiring massive transfusion include administering fresher blood, washing pRBCs to remove extracellular potassium, using in-line potassium filters, and administering insulin [13,34].

Hypothermia (see Chapter 148)

Patients in hypovolemic shock and requiring massive transfusion are likely to be hypothermic on presentation secondary to impaired tissue perfusion, and this hypothermia can be exacerbated by administering cold blood products. Complications of hypothermia include decreases in hepatic metabolism, citrate metabolism, acute-phase protein production, clotting factor production, and drug clearance [11]. Therefore, it is important to aggressively warm patients. Hypothermia should be treated with heat support, increasing the ambient room temperature, using commercial blood and fluid warmers, and humidifying air in intubated patients. Body temperature should be monitored carefully in patients with hypothermia so as not to overshoot during the rewarming process.

Acid–Base Disorders (see Chapter 107)

Both metabolic alkalosis and metabolic acidosis can develop from pRBC transfusion. A metabolic alkalosis can occur when the citrate from the pRBC unit is metabolized to bicarbonate [11,13]. Alternatively, metabolic acidosis can occur when transfusing units that are low in pH or when transfusing patients with liver dysfunction [11]. The pH of stored pRBC units can reach 6.4–6.6 due to increasing lactate and pyruvate concentrations from glucose metabolism [13]. Liver dysfunction can contribute to acidosis due to decreased ability to metabolize citrate to bicarbonate and decreased ability to metabolize

lactate [11]. Patients requiring massive transfusion should have venous or arterial blood gas values monitored regularly.

Transfusion Reactions (see Chapter 176)

Transfusion reactions, such as multiple organ failure (MOF), transfusion-related acute lung injury (TRALI), acute respiratory distress syndrome (ARDS), and transfusion-associated cardiac overload (TACO), can occur from blood product administration, and adverse events may be increased in patients requiring massive transfusion due to the increased amount of blood products administered. In human medicine, blood transfusion is an independent risk factor for MOF, and massive transfusion is independently associated with death [2]. Blood transfusion and increased total blood volume infused in human trauma patients are associated with increased incidence of SIRS and mortality [11].

In the single veterinary study on massive transfusion, the complications found among the population included hypocalcemia (10/10 dogs), hypomagnesemia (9/9), hyperkalemia (2/10), metabolic acidosis, thrombocytopenia (5/5), prolonged PT/aPTT (7/10), and transfusion reactions. The transfusion reactions were fever (3), delayed hemolysis (3), vomiting (1), and facial swelling (1) [3].

Prognosis

The prognosis for veterinary patients receiving massive transfusion is guarded and depends on the underlying cause. In the authors' opinion, prognosis is guarded to poor if hemorrhage is secondary to underlying disease, whereas patients requiring massive transfusion secondary to trauma may have a guarded to fair prognosis. In the veterinary study mentioned above, the mortality rate was 73% and no dog with a PT/PTT > 150% prolonged survived [3]. However, these results should be interpreted with caution as more recent advances in recognition of the need for transfusion and treatments may help to improve outcomes.

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Section 6

Emergency Room Procedures

178

Vascular Access*Matthew W. Beal, DVM, DACVECC**College of Veterinary Medicine, Michigan State University, East Lansing, MI, USA***Introduction**

Patients presented to veterinarians on an emergency basis often have severe physiological derangements necessitating rapid access to vascular structures in order to deliver fluids, blood products, and potentially life-saving medications. Vascular access devices can also provide valuable monitoring information about intravascular pressures on both the venous and arterial sides of the circulation. Gaining efficient vascular access using appropriate devices facilitates the rapid delivery of care and thus contributes to positive outcomes in this often unstable patient population. The following pages will describe various methods and devices for venous and arterial access that may be utilized on an emergency basis.

Venous Access**Considerations for Venous Access**

Patients presenting on an emergency basis are often under extreme stress due to their underlying condition(s), pain, transportation, and the emergency room environment. In this patient population, venous access must be performed efficiently while causing as little discomfort and stress to the patient as possible. Despite the availability of devices that are placed using creative techniques and advanced technology, “keeping it simple” is a guiding principle when dealing with this patient population. Placing short, over-the-needle IV catheters in easily accessed (cephalic, saphenous) veins meets these requirements. Concurrent administration of oxygen (see Chapter 181) in patients with cardiorespiratory compromise and the judicious use of analgesics and sedatives will also help minimize stress (see Chapter 193).

Vascular access sites are a potential source of hospital-acquired infection in veterinary patients [1].

While rapid acquisition of vascular access is important in the patient population that presents on an emergency basis, adherence to strict asepsis may help minimize the chance of catheter-related complications in the days following admission. The proposed vascular access site should be clipped very widely, allowing for a large sterile area within which to work. Full surgical preparation in accordance with institutional guidelines is indicated. Use of sterile gloves and a sterile drape during placement of routine peripheral venous access devices is indicated. However, at minimum, examination gloves should be utilized. All measures of sterile technique (sterile surgical gowns, caps, masks, sterile gloves, and wide draping) further minimize the chance of contamination and should be used in more complex access procedures (central venous access, dialysis access).

The access site should be evaluated critically at least once daily and the vein proximal to the site should be evaluated multiple times daily for evidence of thrombophlebitis (redness, pain, swelling, thrombosis).

Choice of vascular access site and device type placed on an emergency basis is determined by numerous factors including, but not limited to, the pathophysiology of major problems (need for rapid infusion, presence of hemostatic abnormalities, etc.), ease of device placement, need for ability to monitor central venous pressures, need for ability to reliably sample, and patient stability.

Hypovolemia is one of the most common cardiovascular derangements encountered on an emergency basis (see Chapter 153). The ability to rapidly infuse large volumes of crystalloid fluids or blood products is often needed for the management of this condition.

The vascular access device and placement location can have significant influence on the maximum rate of fluid administration. Flow of fluid through rigid tubes is governed by the Hagan–Poiseuille equation [2]. Although the IV infusion system, IV catheter, and vasculature

are not rigid tubes, the equation still provides valuable insights into the physics of flow. Flow (Q) is determined by the pressure differential across the tube ($P_{in} - P_{out}$), the radius of the tube (raised to the fourth power, r^4), the length of the tube (L), and viscosity of the fluid flowing through the tube (μ) according to the equation below

$$\text{Flow rate}(Q) = \frac{(P_{in} - P_{out})\pi r^4}{8\mu L}$$

Simply stated, this equation indicates that increasing pressure at the inlet of a tube (squeezing or elevating an IV fluid bag), increasing the radius of the “tube” (larger bore IV placed in large vessels), infusing fluids with low viscosity (for example, diluting with saline and warming packed red blood cells), and minimizing length of the system (not choosing long central venous catheters when rapid infusion is needed) will facilitate rapid infusion of IV fluids and blood products. Of note, the radius of the “tube” has greatest influence on flow as it is raised to the fourth power. Simply doubling radius results in a 16-fold increase in flow rate.

Approaches and Techniques for Venous Access

Venous catheters may be placed via three major approaches.

The percutaneous approach is most commonly utilized. In this technique, the IV catheter is placed directly through the skin into the venous structure.

The percutaneous facilitative technique involves creation of a small skin defect of similar diameter to the IV catheter using a sharp instrument such as a #11 scalpel blade through which the IV catheter is placed. When performing the percutaneous facilitative technique, the skin should be tented over the vessel prior to incision to minimize the chance of underlying vascular injury (Figure 178.1). The percutaneous facilitative technique decreases resistance caused by the skin during attempts to penetrate it and advance a catheter through it while also decreasing the chance of trauma to the catheter itself while penetrating the skin. The facilitative technique is very useful in thick-skinned patients and in areas of the body with thicker skin, including the cervical region. The technique should always be used when placing larger diameter access devices.

The third approach is a surgical cut-down. Cut-down may need to be performed on an emergency basis when no other access device can be placed and immediate patient stability hinges on gaining vascular access. The emergency cut-down procedure involves creation of a generous incision slightly lateral or medial to the anatomical location of the preferred vein. In peripheral sites (cephalic or saphenous vein), after incision, the skin may



Figure 178.1 Percutaneous facilitative approach to the jugular vein in a dog. A small skin defect is created using a sharp instrument such as a #11 scalpel blade through which the IV catheter is placed. When performing the percutaneous facilitative technique, the skin should be tented over the vessel prior to incision to minimize the chance of underlying vascular injury.

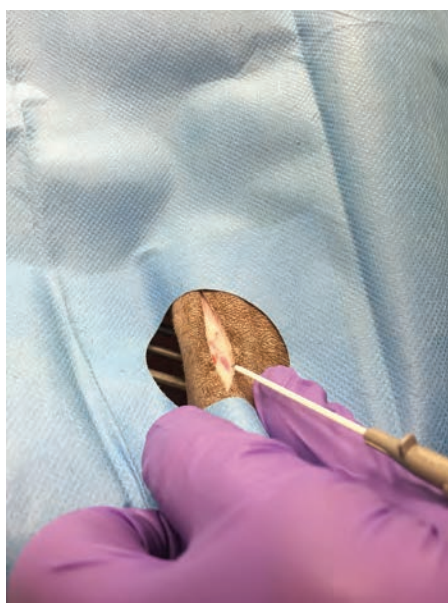
be rolled slightly to facilitate visualization of the vein (Figure 178.2a). The IV catheter is then placed (preferably) through the skin distal to the cut-down site, into the site, and then into the vein (Figure 178.2b). This allows the cut-down site to be closed without the IV catheter penetrating through the incision.

The author finds that in the most urgent situations when an emergency cut-down is needed, the jugular vein provides a very reliable access site that allows for the placement of a large-bore venous access device. The anatomical location of the jugular vein is easily determined by identifying the angle of the mandible and drawing a line between it and the thoracic inlet (Figure 178.3a). Cut-down over the jugular vein is performed as described above for a peripheral vein, but some blunt dissection will be necessary to strip away subcutaneous fat and adventitial tissue from the vessel itself to optimally visualize the vessel (Figure 178.3b). Dissection around the vessel allows for placement of a monofilament suture or silicone vessel loop for facilitating control of the vessel prior to catheter placement (Figure 178.3c).

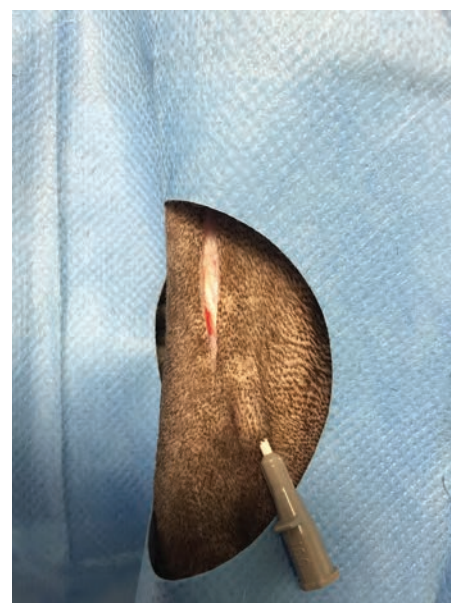
The emergency cut-down procedure should be performed with adherence to strict asepsis. However, on an emergency basis, if the situation precludes adherence to strict asepsis, then after resuscitation, alternative sterile access should be attained and the catheter placed via emergency cut-down should be removed.

The aforementioned approaches may be utilized for the placement of a variety of types of catheters using a

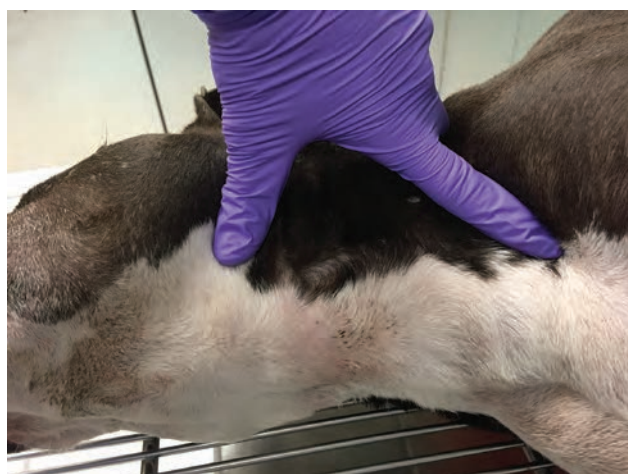
Figure 178.2 (a) Cut-down just medial to the cephalic vein. After incision, the skin is rolled slightly to facilitate visualization of the vein. (b) The IV catheter is placed through the skin distal to the cut-down site, into the site, and then into the vein. This allows the cut-down site to be closed without the IV catheter penetrating through the incision.



(a)



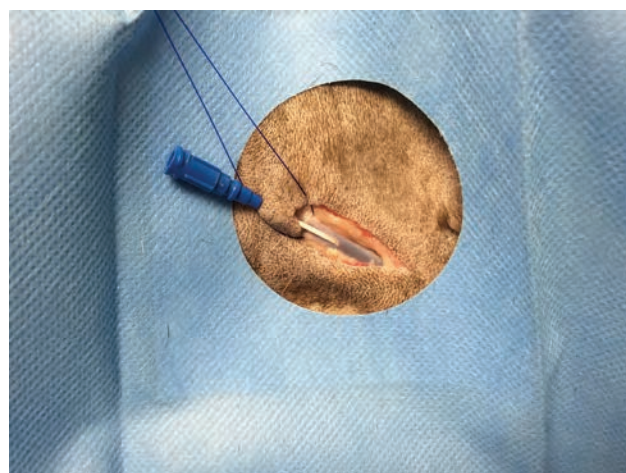
(b)



(a)



(b)



(c)

Figure 178.3 (a) Jugular cut-down procedure. The anatomical location of the jugular vein is easily determined by identifying the angle of the mandible and drawing a line between it and the thoracic inlet. (b) Cut-down over the jugular vein is performed as described above for a peripheral vein, but some blunt dissection will be necessary to strip away subcutaneous fat and adventitial tissue from the vessel itself to optimally visualize the vessel. (c) Dissection around the vessel allows for placement of a monofilament suture or silicone vessel loop to facilitate control of the vessel prior to catheter placement. Note that the catheter has been placed distal to the cut-down site.

variety of techniques. As previously mentioned, the most commonly utilized catheters in the small animal emergency room are over-the-needle IV catheters placed in peripheral vessels. These catheters are generally placed using direct visualization and palpation of the target vessel. The over-the-needle catheter is directed into the target vessel at approximately a 20° angle to the skin. When a flash of blood is visualized in the chamber of the needle, the entire system is advanced 1–3 mm and then the catheter is fed over the needle into the vessel and secured and dressed using standard techniques.

Through-the-needle catheters were once used for the placement of a variety of types of central venous catheters and peripherally inserted central catheters (PICCs). These catheters are economical but they create a larger defect in the vessel than the catheter occupies after placement and, as a result, may be associated with more hemorrhage than catheters placed using other techniques. Through-the-needle catheters have decreased in popularity as veterinarians and veterinary technicians have become increasingly comfortable with catheters placed using the Seldinger technique.

The Seldinger or modified Seldinger techniques are also called “over-the-wire” techniques. They are utilized for the placement of a variety of types of catheters but most commonly, central venous catheters and PICCs use this technique [3]. The author uses this technique for the placement of large catheter introducers (also called sheath introducers) in the jugular vein of patients with severe hypovolemia, allowing for extremely rapid volume expansion.

The following are the major steps in the Seldinger technique.

1. Surgical preparation.
2. +/- Local anesthetic infiltration.
3. Prepare the IV catheter for insertion. Flush all lumens with heparinized saline. Moisten catheters and dilators with saline.
4. Make a small 2–4 mm incision with a #11 blade over the vessel (percutaneous facilitative approach). Note that this step may be performed or the incision may be expanded after step 6.
5. Insert the needle or catheter into the blood vessel. Blood should flow freely from the needle/catheter.
6. Feed a flexible “J-tip” guidewire or other soft tip guidewire through the needle into the blood vessel. For all future steps, the guidewire should be held by the operator to eliminate the chance of dislodgment or inadvertent loss in the patient.
7. Withdraw the needle/catheter over the guidewire. Mild hemorrhage may be noted. Direct pressure can be applied after needle/catheter withdrawal.
8. Advance a dilator or combination dilator/catheter over the guidewire into the blood vessel.

9. Remove the dilator over the guidewire and advance a prepared catheter (step 3) over the wire into the vessel.
10. Remove the guidewire.
11. All ports should then be flushed with saline or heparinized saline.
12. Suture the catheter in place and apply a sterile dressing.

Advanced imaging techniques may be useful for gaining vascular access. Ultrasound-guided vascular access is especially useful in patients in which the vessel to be punctured cannot be visualized or palpated [4]. The author uses this technique most often to access the jugular, maxillary, or femoral veins in patients with deep vessels, obesity, or edema. Briefly, a high-frequency, linear array transducer with a sterile cover is used to identify the target vessel and is placed over it and in a longitudinal plane. Vessel puncture is performed using one of the aforementioned techniques behind (upstream from) the transducer. The puncture needle or catheter is visualized entering the vessel during placement. The ultrasound transducer is then removed and catheter placement proceeds according to manufacturer instructions.

Fluoroscopy-assisted vascular access in the emergency room is most often utilized during placement of dialysis catheters for intermittent hemodialysis or continuous renal replacement therapy (CRRT) in patients with acute renal injury. Fluoroscopy allows for optimal positioning of the catheter tip during placement.

Locations for Venous Access

As previously stated, venous access locations should be chosen to minimize stress to the patient while meeting the given goal of the access device (administration of medications only versus rapid fluid infusion, versus monitoring of central venous pressure, etc.). Peripheral veins are the most common sites for venous access, with the cephalic vein, accessory cephalic vein, and saphenous vein most often utilized. Using these sites allows the patient to remain sternal which is often helpful when there is respiratory compromise. Box 178.1 indicates peripheral venous access sites that may be considered.

The use of highly mobile sites such as the auricular vein or common digital veins will require the utilization of a splint. Securing the IV catheter to the pinna with rolled gauze placed beneath it is helpful for auricular venous access. A simple spoon splint will help immobilize the carpus when utilizing the common digital veins.

Central venous access is not often utilized in the initial minutes after a patient presents on an emergency basis. However, central venous access is often performed soon thereafter in patients in which central venous pressure

Box 178.1 Peripheral venous access sites.

Cephalic vein
Accessory cephalic vein
Medial saphenous vein
Lateral saphenous vein
Dorsal common digital vein
Auricular vein
Jugular vein

monitoring is indicated and in those which require a highly reliable catheter for repeated blood sampling. Some central venous catheters allow for the monitoring of central venous oxygen saturation which has potential as a monitoring tool in the emergency room and intensive care unit.

The jugular vein is the most commonly utilized site for central venous access, but a catheter placed in the saphenous vein (or rarely cephalic) can be advanced into the central circulation (PICC). The author also utilizes the maxillary vein in dogs that have a temporary tracheostomy and require central venous access. In these patients, the jugular vein is in close proximity to the temporary tracheostomy site and thus puts a catheter placed in this location at significant risk for contamination.

When considering utilizing the jugular or maxillary veins for central venous access, hemostasis should be assessed (platelet count and coagulation through assessment of ACT or PT/aPTT). Significant hemostatic abnormalities are a contraindication to jugular, maxillary, and femoral vein access.

Intraosseous Access

Considerations for Intraosseous Access

Intraosseous access to the rich sinusoidal network of the marrow cavity allows for the delivery of fluids, blood products, and medications in patients in which venous access is not possible or is technically challenging. This may include patients that are extremely small (neonates) and those with severe chronic vascular injury or severe hypovolemia where venous access is challenging. Intraosseous access can often be achieved very rapidly. Most often, intraosseous access is used until traditional venous access can be acquired. Contraindications to placement of IO devices include fracture of the proposed insertion bone, injury or disease at the proposed insertion site, and sepsis. This being said, access is needed and IO catheters may be placed despite the possibility of sepsis, especially in neonatal patients.

Approaches and Techniques for Intraosseous Access

Spinal needles or standard hypodermic needles (20–22 G) in neonates and Jamshedi bone biopsy/bone marrow aspiration needles in larger patients are commonly utilized for IO access. The stylet in these devices (except hypodermic needles) prevents bone spicules from clogging the needle itself.

Briefly, the proposed insertion site is aseptically prepared and aseptic technique is practiced. Most patients requiring IO access are moribund and local anesthesia is not utilized. However, in the more alert patient, local infusion of 1 mg/kg lidocaine in the skin and down to the periosteum is indicated if time permits. If using the intertrochanteric fossa of the femur, the greater trochanter is palpated and the needle is directed through the skin and onto the greater trochanter. Then, the needle is simply “walked” medially until it falls into the fossa (Figure 178.4). This technique may help avoid injury to the sciatic nerve. Short 90° oscillations of the needle are applied while gentle pressure is directed down the axis of the femur. Palpation of the medial aspect of the femur helps identify unintended penetration of the medial cortex. The stylet is removed and the catheter is gently flushed to ensure patency. If not patent, rotate the catheter 90° to ensure that the bevel is not closely apposed

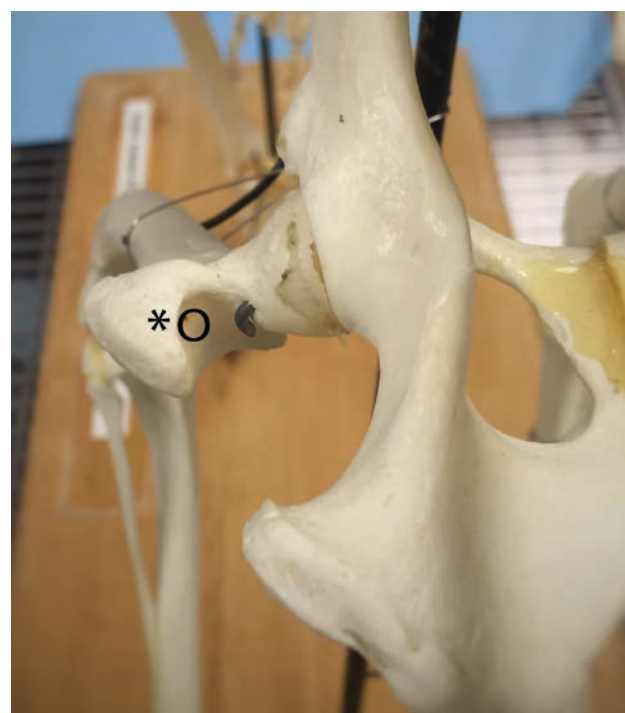


Figure 178.4 Intraosseous landmarks for IO catheter insertion at the intertrochanteric fossa of the femur. The greater trochanter is palpated and the needle is directed through the skin and onto the greater trochanter (*). Then, the needle is simply “walked” medially until it falls into the fossa (O).

to the inner cortex. If fluid accumulates subcutaneously at the insertion site, an alternative site should be considered. Once in place, a sterile dressing should be applied. The author secures these catheters in place using a tape butterfly and sutures.

Alternative devices, including spring-loaded impact penetration devices and powered drivers, are commercially available for very rapid placement of IO catheters (Veterinary BIG, WaisMed Ltd, Rosh Ha'Ayin, Israel; EZ-IO by Vidacare, Mila International, Erlanger, KY, USA). These devices most often utilize the flat, proximal aspect of the tibia or the proximal humerus at the level of the greater tubercle. Collectively, they allow for very rapid, successful placement of IO catheters in non-neonatal dogs and cats [5].

Arterial Access

Arterial access is acquired in the emergency room for monitoring of direct arterial blood pressure and for sampling for analysis of arterial blood gases. The dorsal pedal artery is most commonly utilized in veterinary patients for arterial access because it is superficial and peripheral. The puncture site is usually just distal to where the artery dives between metatarsals II and III (Figure 178.5). The anatomy facilitates easy compression should access be unsuccessful or when catheter removal is necessary.

Alternative peripheral sites for arterial puncture include the radial artery and auricular artery. More proximal sites for arterial access include the femoral artery and brachial artery. These sites, especially the femoral artery, are easily accessed, but high motion makes catheter dislodgment a problem in mobile patients. The author only uses proximal arterial sites for access in patients that are moribund or immobilized (ventilator-dependent patients, CRRT patients) and only longer catheters should be utilized to minimize the chance of dislodgment with motion. Proximal arterial access sites are difficult to compress should placement be unsuccessful or when catheter removal is necessary, making bleeding a significant risk of placement.

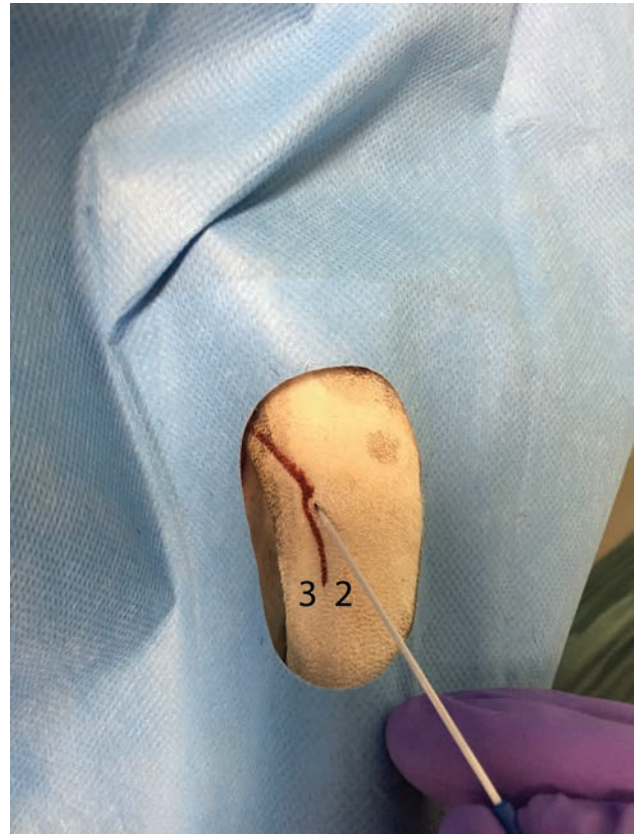


Figure 178.5 Path of the dorsal pedal (metatarsal) artery of the right pelvic limb. The catheter indicates the direction of puncture. Numbers 2 and 3 indicate the location of the proximal aspect of the second and third metatarsals.

Hemostasis should be completely assessed if proximal arterial access sites are chosen.

Over-the-needle catheters are most often placed for arterial access. However, kits that utilize the Seldinger technique are also available. Aseptic technique should be adhered to during placement and similar monitoring should proceed as described above for venous access. Arterial catheters are optimally connected to a continuous blood pressure monitoring system which provides a continuous low-volume heparinized saline flush to the system.

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Intraosseous Catheters

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Introduction

The ability to obtain rapid vascular access in an emergency setting is of paramount importance to allow for the administration of resuscitative drugs and fluids. Obtaining prompt intravenous access can be difficult, especially in patients that present with cardiovascular collapse. Other challenges such as small patient size, trauma to commonly used vascular sites, obesity, or peripheral edema can also hinder gaining rapid intravenous access. Multiple attempts at gaining intravenous access lead to delays in treatment, and can increase morbidity and mortality.

There are several ways to gain vascular access percutaneously, ultrasound guided, or surgically (see Chapter 178). When intravenous access is not possible, intraosseous (IO) catheterization is a viable alternative to obtain vascular access [1–11]. In fact, due to IV access limitations in small patients, the IO catheter in avian, exotic mammals, and some reptile patients is well utilized [12].

Human medicine now widely accepts IO catheterization when IV access is not obtainable and several IO insertion devices (automated bone injection guns) have been developed to allow for rapid IO catheterization [2,4,5,7,8]. It has been demonstrated that when using an automated bone injection gun in pediatric patients, it takes between 10 seconds to 1 minute to place an IO catheter with 70–80% success rate [6]. In adults requiring resuscitation from trauma, one study showed that the IO catheterization success rate was 85% on first attempt with a mean of 2.0 minutes, compared to 60% success rate and a mean of 8.0 minutes for central line placement [7]. Due to the speed with which an IO catheter can be placed, the American Heart Association finds the use of an IO catheter a reasonable alternative if venous access cannot be obtained peripherally [4,5].

At the time of writing, there is limited information on the use of IO catheters in veterinary patients. Olsen

et al. demonstrated that the placement of an IO catheter in dogs using an automated bone injection gun provided reliable vascular access [13], and another study using feline cadavers identified that the use of a bone injection gun to facilitate IO catheter placement allowed for rapid placement [14]. Both studies suggest that the use of an IO catheter in animals suffering from cardiac arrest may be a viable alternative to an IV catheter.

Physiology

The rationale that IO catheterization provides rapid accessible vascular access is due to the rigid nature of bone which prevents bone marrow vessels from collapsing [1,2,15]. Administration of drugs and fluids into bone marrow is effective because bone marrow has a well-defined venous system that empties quickly into the systemic circulation [3]. Intraosseous infusions achieve similar onset of action time to peripherally or centrally administered fluids or drugs [15].

Blood analysis can also be performed from the bone marrow aspirate and studies have shown that in comparison to peripheral blood analysis (electrolytes, blood gas, blood typing), the values are similar, especially if drawn at time of insertion; however, blood gas and electrolyte levels may not be accurate if the sample has been collected after the administration of fluids or drugs.

Indications

The indications for IO catheterization have been extrapolated from human medicine as there are no veterinary studies documenting the impact of IO placement. The American Heart Association recommends a central line during resuscitation because it allows for higher peak

drug concentrations and shorter circulation times. However, due to its time-consuming nature, peripheral access is recommended. Often, peripheral access is not obtainable, so an IO catheter is a reasonable alternative in these settings.

An IO catheter is indicated when a critically ill patient of any age requires intravascular access that cannot be secured in a timely fashion. Common conditions where an IO catheter might be warranted include life-threatening cardiovascular collapse (cardiopulmonary arrest, shock, sepsis), unique patient conformation (edematous or obese states or small/neonate patients), and thrombosis, trauma or severe burns or skin disease at conditional catheter sites.

Contraindications

There are few contraindications to intraosseous catheterization. The primary one is if the IO site has a fractured bone or one suspected to be fractured because infused medication or fluids may not make it to the systemic circulation and it may also lead to compartment syndrome or extravasation.

Medications

Most drugs that can be administrated intravenously can also be safely administered intraosseously (Table 179.1), although certain drugs, mostly limited to hyperosmolar drugs, can cause tissue necrosis if extravasation occurs [16].

Methods

Intraosseous catheter sites that are easily accessible in dogs and cats include the humeral head, the flat medial surface of the proximal tibia, and the trochanteric fossa of the femur. The skin is clipped and aseptically prepared as it would be for placement of an intravenous catheter. The bone is palpated for a flat spot and the limb is supported so that it will not move under pressure. The needle is then drilled into the bone either manually or through the use of an insertion device. In the avian species, care must be taken to avoid insertion of an IO into pneumatic bones.

Devices for IO placement range from the traditional manually placed hypodermic needle to battery-operated automatic drills. A variety of needles can be utilized for IO catheterization including butterfly, spinal, standard, and bone marrow needles. Additionally, there are commercially available IO needles that come with a stylet to avoid occlusion of the catheter with bone material in

Table 179.1 Medications that can be given via the intraosseous route.

Therapy	Limitations
Medication	
Adenosine	
Amiodarone	
Atropine	
Bretylium	
Calcium chloride	
Cisatracurium	
Dextrose	Reported tissue necrosis with extravasation
Dobutamine	
Dopamine	
Epinephrine	
Etomidate	
Fentanyl	
Heparin	
Insulin	
Lidocaine	
Naloxone	
Norepinephrine	
Phenytoin	
Propofol	
Rocuronium	
Sodium bicarbonate	Reported tissue necrosis with extravasation
Succinylcholine	
Tenecteplase	
Vasopressin	
Vecuronium	
Fluid therapy	
Albumin	
Fresh frozen plasma	
Hypertonic saline	Reported tissue necrosis
Lactated Ringer's solution	
Normal saline	
Packed erythrocytes	

adults; however, regular hypodermic needles (18–20 G) will suffice for the soft bony cortex of neonates or small dogs or cats. Needles of smaller size often bend under the strain of insertion and can become occluded during placement.

In addition to standard needles and commercially available needles, other devices have been manufactured that improve ease and shorten access times, such as the bone injection gun (BIG, WaisMED, Houston, TX), drill (EZ-IO, Vidacare, San Antonio, TX), and sternal IO

device (FAST1, Pyng Medical, Richmond, Canada). The BIG is a spring-loaded needle with a pre-fixed depth that is propelled at high speed into the bone marrow. It was found to be significantly faster at gaining IO access than a Jamshidi bone marrow needle in a dog tibia [13].

The EZ-IO is a small, battery-powered drill that has needles of varying length. The needle hub is secured on the drill and penetrates through the cortex into the bone marrow. The stylet is then removed. A study using feline cadavers identified that the use of a EZ-IO gun to facilitate IO catheter placement allowed for rapid placement compared to the BIG and manual IO needle placement, while a dog cadaver study found that the EZ-IO gun facilitated faster IO catheter placement compared to a jugular venous cut-down technique regardless of experience level of the operative [12,17].

There are a variety of ways to ensure proper placement of an IO catheter. The needle should be well implanted so that it moves in the same motion if the limb is moved forward and backward. It should also stand on its own because when properly seated in the medulla, it is laterally supported by the rigid cortex. Along with this maneuver, correct placement can be verified by infusion of fluid and monitoring for extravasation.

Possible Complications

Complications after proper IO catheterization are rare, with a low overall incidence of <1% [18]. They include:

- extravasation
- fracture

- osteomyelitis
- skin abscess
- cellulitis
- fat embolism.

The primary complication of intraosseous catheters is extravasation of infusions (drugs, fluids, blood, etc.) into the soft tissue which infrequently leads to compartment syndrome [19]. Osteomyelitis reports are rare (incidence of 0.6%) and it most likely occurs subsequent to leaving an IO catheter in for greater than 24 hours, poor aseptic technique or multiple IO attempts at the same location [2,18]. Other complications include cellulitis and skin abscesses [20]. The longer an IO catheter is left in place, the higher the chance of adverse events. For this reason, it is recommended to replace the IO catheter with a peripheral or central catheter as soon as possible, but as standard within 24 hours. There have been no ill effects for bone deformity/growth arrest secondary to intraosseous placement in patients as evidenced by long-term follow-up [21].

Intraosseous Catheter Care

Alternative IV access should be sought as soon as feasible. While in place, the site should be kept clean and standard hand hygiene for handling the catheter should be employed. Flushing of the catheter should be performed as with an IV catheter with either heparinized or saline solutions. Securement or wrapping of the IO may or may not be feasible, depending on the IO site and the patient's size or critical state.

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Airway Management

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Introduction

Airway management may be broadly defined as ensuring that the patient has a patent airway from nose to alveoli; methods of oxygen supplementation are discussed in Chapter 181. Oxygen therapy is theoretically not required with airway obstruction, but may decrease the work of breathing and limit upper airway swelling associated with increased inspiratory efforts. The emergency specialist should be familiar with indications and techniques to identify and maintain the airway.

The airways may be divided into the upper and lower airway, with the thoracic inlet being the dividing point. Upper airway obstruction causes difficulty on inspiration due to collapse associated with negative inspiratory pressure, while lower airway obstruction causes obstruction on expiration (see Chapters 28 and 30–32). Normal expiration is passive but with obstruction, there may be active expiratory “push.” Most of airway management involves treatment of upper airway obstruction and/or maintenance of a tracheostomy tube. Animals with airway obstruction have increased inspiratory effort and typically loud breathing. Hyperthermia may develop due to increased respiratory efforts and the inability to effectively cool, but it is possible that aspiration pneumonia may have developed as well. The possibility of pneumonia should be considered if temperature fails to normalize after respiratory efforts improve, or as a possible cause of exacerbation of stable upper airway disease.

The decision to manage the airway should be made early; often the recommendation is that if you consider intubation, you should do it! In general, outside routine general anesthesia for diagnostics or therapy, intubation is performed for dynamic upper airway obstruction or to

provide for positive pressure ventilation (PPV) for either respiratory or ventilatory failure. A tracheostomy may be required to bypass a fixed upper airway obstruction or in a patient with dynamic collapse such as severe laryngeal collapse or cervical tracheal collapse (see Chapters 30 and 32).

Healthy Dog or Cat

Normal dogs and cats may require airway management if they are sedated or anesthetized for diagnostics or treatment. Clients often perceive sedation to be “safer” than general anesthesia; this is not always true. While light sedation may be inadequate to permit orotracheal intubation, it is still essential to carefully monitor heavily sedated patients until they are able to adequately maintain sternal recumbency. Airway occlusion/obstruction is considered to be a principal cause of unexpected death during the perianesthesia period. Brachycephalic dogs should always be intubated and monitored closely until recovery; they often tolerate endotracheal tubes even after they are able to sit sternal and occasionally even walk around (see Chapter 28). Oxygen helmets, high-flow oxygen or heliox may facilitate anesthetic recovery when available (see Chapter 181) [1–3].

Upper Airway Obstruction (see Chapters 28 and 30–32)

Upper airway obstructions (UAOs) are more frequently dynamic in dogs and fixed in cats. Common UAOs in dogs include brachycephalic syndrome, tracheal collapse, and laryngeal paralysis. In cats, UAO is

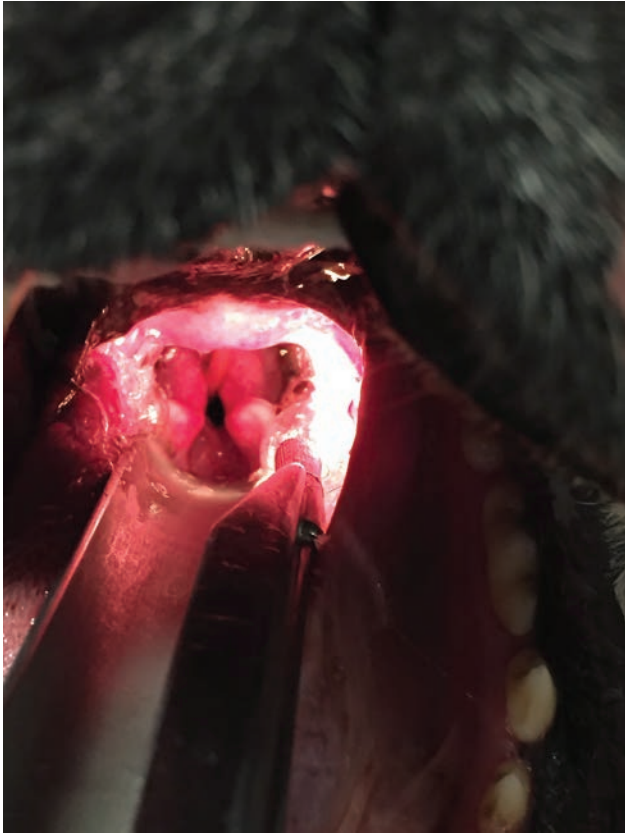


Figure 180.1 Oral view of a nasotracheal catheter.

often harder to appreciate initially due to lower inspiratory flow rates and subsequently less upper airway noise. Cats may have a wheeze associated with a fixed UAO which is commonly mistaken for bronchoconstriction associated with asthma. Emergency clinicians should recall that feline asthma rarely develops late in life in cats.

The decision to intubate a patient with UAO should be made confidently, but ideally with a plan in mind for follow-up for patient care. Follow-up will depend on what is identified at the point of oral examination but may include surgical palliation, biopsy, temporary tracheostomy or other supportive care. In particular, in cats with suspected laryngeal masses, the need for a temporary tracheostomy is very common, and should be discussed with the family *before* undertaking an oral examination under heavy sedation.

Nasal oxygen alone is rarely helpful in the treatment of airway obstruction as the obstruction is not bypassed. Nasotracheal intubation is commonly performed in people and in larger animals such as horses,

but it is difficult to place a tube to provide an adequate airway via the nasal route in small animals. However, nasotracheal tubes may be placed for provision of supplemental oxygen, which may prevent the need for intubation or help a patient with a compromised airway recover from surgery [4]. Nasotracheal tubes require anesthesia and direct visualization of the glottis for placement. From an emergency room perspective, nasotracheal oxygen may prevent the need for intubation or a temporary tracheostomy in animals with upper airway obstruction although intubation may be practically easier!

In order to place the nasotracheal tube, the patient needs to be under anesthesia or otherwise obtunded enough to permit oropharyngeal manipulation. The nasotracheal tube is placed by passing a red rubber catheter through the nasal cavity and then retrieving it with hemostats and then directing it down the trachea, approximately to the level of the carina (Figure 180.1). Successful placement can be verified by direct visualization and by confirmation of the presence of end-tidal CO₂.

Difficult Intubation

If adequate oxygenation and ventilation cannot be achieved with sedation/anxiolysis and supplemental oxygen, intubation and/or tracheostomy may be considered. However, if respiratory arrest is imminent, then intubation should be urgently attempted. However, if time permits, collection of supplies before efforts are made is useful for cases of suspected difficult intubation. Dogs with laryngeal masses or severe brachycephalic syndrome are most commonly associated with intubation difficulty, so the clinician should be prepared to “capture the airway” by a variety of methods as the clinical course dictates.

Prior to efforts to intubate, it is prudent to have a variety of supplies available including a number of tube sizes, as well as a guidewire (or long polypropylene catheter for a guidewire exchange-based intubation), and surgical instruments and supplies in case tracheostomy becomes necessary. If direct visualization of the laryngeal lumen is not possible, it may be possible to digitally palpate and introduce an endotracheal tube in larger dogs. Endoscopic assistance may also be used, although this technique is best accomplished after some prior practice. Finally, before a tracheostomy is performed, if preferred, retrograde tracheal intubation may be performed by placing a needle into the trachea and then directing a guidewire orally to permit placement of an endotracheal tube over the guidewire or alternatively, supplemental

oxygen may be provided via a long catheter directed towards the carina.

Laryngeal mask airways (LMAs) are used occasionally in small animals and may be a useful tool to provide ventilation [5,6]. LMAs are composed of a standard tube with an inflatable “mask” which is designed to preferentially cover the larynx in order to provide oxygen and inhalational anesthetic agents. LMAs are also useful for intubation of smaller species such as rabbits, or in cases where it is difficult to open the mouth adequately to directly visual the larynx. In the emergency setting, LMAs are useful to have in stock, particularly in practice settings with fewer personnel or less comfort with surgical airways. As with any airway, ensuring adequate oxygenation and ventilation is important.

Following successful intubation in a patient with a difficult airway, it is essential to determine what the next steps in patient care should include. It may be that successful extubation is possible if a foreign object is removed or that surgical intervention is required to facilitate restoration of an airway lumen. Pharyngeal abscesses are common in dogs, particularly in stick chewers, and these may result in airway impingement and require temporary tracheostomies until resolution of the swelling. Percutaneous drainage may result in immediate improvement.

Tracheostomy

Temporary tracheostomy is commonly performed in the emergency room, and while a discussion of the specific procedure is beyond the scope of this chapter, it is essential that an ER clinician understands how to perform the procedure urgently and does not need to review the procedure in the event of an airway occlusion. Key tips include staying on midline, making a long incision, and placing labeled stay sutures to permit easy replacement of the tube if it is dislodged.

Permanent tracheostomy is rarely performed in the emergency room, but it may be wise for the ER clinician to discuss permanent tracheostomies as a possible endpoint for therapy in order to have owners consider the implications and commitment required.

Management of the Tracheostomy Tube

Patients that have a tracheostomy tube in place should be closely observed as occlusion or dislodgment can prove fatal. Unless the patient is undergoing mechanical ventilation or lacks a gag reflex, the cuff should not be inflated in case the lumen of the tube becomes occluded with

secretions. All personnel working in an ER should be trained in managing or replacing a tracheostomy tube. Supplies for replacement of the tube, suction, cotton swabs, and propofol should be kept close to the cage or run.

The lumen of the tube may be easily occluded by mucus or blood/blood clots. As the role of the upper airway includes humidification of inspired air, tracheal tubes are prone to becoming obstructed. Obstruction may build up slowly and then result in apparent acute blockage. Tracheostomy tubes should be suctioned and/or changed as needed. Routine suctioning is not required.

When the airway obstruction has resolved, the tracheostomy tube may be removed and the site allowed to heal by second intention. It is important not to close the skin, as until the tracheal incision heals, closing the skin will permit the development of subcutaneous emphysema. It is uncommon in the emergency room to both place and remove the tracheostomy tube unless it was urgently placed to remove a foreign body.

Pharmacological Therapy

No medical therapy exists to directly help dilate the upper airway. Theophylline and albuterol/terbutaline have no direct benefit for any upper airway obstruction. Dogs are not thought to develop naturally occurring bronchoconstriction, so bronchodilators are usually of no benefit, although additional effects (mucus clearance, diaphragmatic strength) may be helpful in some dogs with generalized lower airway disease, although not tracheal collapse. Cats do suffer from bronchoconstriction so in cats with true asthma, bronchodilators are useful.

Anxiolytics may be helpful to decrease the anxiety associated with respiratory distress. Acepromazine is widely used in the emergency setting, and butorphanol may also have some benefit from this perspective. Trazadone has been gaining popularity as a mild sedative/anxiolytic and may help some dogs with more minor airway obstruction. Doxepin has been proposed as an adjuvant therapy for dogs with laryngeal paralysis. At the time of this writing (June 2016), there is an ACVIM Foundation/Zoetis-funded grant by Rishniw evaluating the efficacy of this therapy in a randomized clinical trial.

Glucocorticoids are the mainstay therapy for lower airway obstruction and may help with upper airway obstruction associated with swelling, such as with brachycephalic airway obstruction or tracheal collapse. Laryngeal paralysis does not benefit from glucocorticoids unless severe swelling is observed.

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Oxygen Therapy

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Introduction

Oxygen supplementation is widely used in veterinary medicine to relieve hypoxia and increase oxygen delivery to the tissues. For patients presenting to the emergency room who are triaged with signs of respiratory distress, oxygen administration during the assessment process can be beneficial and even life saving to the patient. As there are few contraindications to short-term oxygen administration, oxygen supplementation should be initiated in patients presenting with signs of respiratory distress until the status of the patient's respiratory system can be determined.

Oxygen therapy increases the fraction of inspired oxygen (FiO_2) delivered to the alveoli. Causes of respiratory distress and decreased delivery of oxygen to the tissues are often multifactorial in the patient presenting to the emergency room (see Chapter 4). Whatever the cause of respiratory distress, an increase in FiO_2 to the patient can be beneficial. The oxygen content in arterial blood (CaO_2) along with cardiac output (CO) is a major determinant of oxygen delivery (DO_2) to the tissues. CaO_2 is defined as $(\text{Hb} \times 1.34 \times \text{SaO}_2) + (\text{PaO}_2 \times 0.003)$ which factors in the amount of hemoglobin (Hb), the arterial oxygen saturation of hemoglobin (SaO_2), and the amount of oxygen dissolved in plasma. An increase in FiO_2 will lead to an increase in SaO_2 in most situations. With supplemental oxygen, there is an increase in the partial pressure of arterial oxygen (PaO_2) and a subsequent shift of the oxyhemoglobin dissociation curve to the left, facilitating the binding of oxygen to hemoglobin and leading to a subsequent increase in SaO_2 [1]. The increase in SaO_2 is more profound with primary pulmonary disease or injury causing a defect in gas exchange versus disease or injury causing anemia or a decrease in binding of oxygen to hemoglobin such as carbon monoxide poisoning (see Chapter 139). In the emergency setting, whether the effect of oxygen therapy is large or small, oxygen

administration is an important part of stabilization in patients presenting with signs of respiratory distress.

Non-Invasive Oxygen Therapy

Non-invasive oxygen delivery methods are readily available in most emergency clinics. These methods vary in the ease of oxygen administration to the patient and patient tolerance. They also vary greatly with regard to the FiO_2 delivered to the patient. Most of these oxygen delivery methods are inexpensive and are easy to set up and use. Prior to the initiation of non-invasive oxygen therapy, the patency of the upper airway must be assessed. If a partial or complete upper airway obstruction is present, a patent airway must be quickly established with intubation or, if unable to intubate, emergent tracheostomy (see Chapter 180). The patient's ability to ventilate also needs to be quickly established. The non-breathing or hypoventilating patient should be immediately intubated and resuscitation methods started.

Flow-By Oxygen

Flow-by oxygen is delivered via a tube placed in the vicinity of the patient's nose or mouth. The tube is connected to an oxygen source such as oxygen tank, wall-mounted oxygen or an anesthesia machine. A humidifier can be placed in circuit to provide humidified air. Oxygen flow rates are set by the clinician and can deliver an FiO_2 of 25–40% [2]. Benefits of flow-by oxygen are ease of use and quick implementation. Disadvantages include variable FiO_2 , oxygen waste, and patient tolerance. Providing flow-by oxygen can be labor intensive in that an assistant is required to remain by the patient's side at all times holding the tube to the patient's face for oxygen administration. Because of the ease and speed with which flow-by oxygen can be administered, it is a reasonable

first line of oxygen therapy for the emergency patient presenting with signs of respiratory distress, allowing for an immediate increase in FiO_2 during assessment, stabilization, and placement of IV catheter. Flow-by oxygen therapy is a temporary delivery method that can be utilized until a method of long-term oxygen therapy can be implemented.

Face Mask

A face mask can be attached to an oxygen source for delivery of higher FiO_2 compared to flow-by oxygen. Oxygen delivery with face mask provides for a variable FiO_2 of 35–60%, depending on how tight fitting the mask is around the face [2]. With a face mask, oxygen administration flow rates are typically set at 200 mL/kg/min but can be set higher. Oxygen delivery with a face mask is easy to use and quick to set up, providing an immediate increase in FiO_2 to the emergency patient presenting in respiratory distress (Figure 181.1). Patient tolerance of the face mask, especially a tight-fitting mask, can be a limiting factor with this oxygen delivery method. Care should be taken when using a face mask on patients presenting with facial trauma. With a tight-fitting face mask there is a risk of rebreathing of CO_2 and hyperthermia. Use of a non-rebreathing circuit with a face mask can prevent rebreathing of CO_2 and limit hyperthermia.

Due to its quick implementation and ease of use, oxygen delivery by face mask is a good first-line method of oxygen therapy in the emergency setting. Like flow-by oxygen, face mask oxygen delivery requires the constant presence of an assistant for administration in the awake and alert patient. For long-term oxygen delivery, face mask administration is usually only tolerated in the obtunded patient. Face mask oxygen delivery is



Figure 181.1 Canine patient receiving oxygen via a loose-fitting face mask.

a reasonable first line oxygen delivery method in the patient presenting to the emergency room with signs of respiratory distress but most patients will require other delivery methods if long-term oxygen support is needed.

Oxygen Hood

An oxygen hood can be constructed using an Elizabethan collar and covering the opening 75–90% with clear plastic wrap. An oxygen source is placed within the collar and secured to the patient. Use of an oxygen hood can deliver an FiO_2 of 30–40% with flow rates of 1–2 L/min once the hood has been flooded with oxygen [3]. With an oxygen hood, there must be a sufficient opening to allow for escape of CO_2 and heat. This method of oxygen delivery is well tolerated by most patients, can be used for long-term oxygen therapy, and does not require specialized equipment.

Nasal Oxygen

Delivery of oxygen through a nasal cannula is a common supplementation method in veterinary patients. This method of oxygen delivery is well tolerated and can be used for long-term administration. Oxygen delivery through a nasal cannula is technically easy, inexpensive, limits oxygen waste, is well tolerated and can provide a FiO_2 of up to 70% [4–6]. However, the FiO_2 delivered to the patient can be variable and is influenced by flow rates, panting, and respiratory rate [6,7]. Patients receiving nasal oxygen are readily accessible to the clinician for assessment and diagnostics without disruption of oxygen therapy.

Nasal cannula placement can be unilateral or bilateral. Nasal cannulae are usually placed up to the level of the medial canthus of the eye although they can be placed into the pharyngeal region at the level of the ramus of the mandible. Nasal prongs are also available for oxygen administration and do not require advancement into the nasal cavity. Prongs most likely deliver a comparable FiO_2 to nasal cannula oxygen but no studies have evaluated their use in oxygen delivery. The nasal cannula or nasal prong size should be no more than half the diameter of the nares. A humidification source such as a bubbler humidifier is recommended to prevent drying of the nasal mucosa.

Contraindications for nasal oxygen include facial trauma or other nasal obstruction precluding placement of nasal cannula or prongs. Recommended flow rate through each nasal cannula is 100 mL/kg/min. At higher oxygen flow rates the nasal mucosa are unable to adequately heat and humidify the incoming air. This can lead to patient discomfort, drying of the nasal mucosa and a decrease in pulmonary compliance and conductance [6].

Oxygen Cage

Oxygen cages are a stress-free method of oxygen supplementation. Emergency patients presenting in respiratory distress can be quickly triaged and placed in an oxygen cage, allowing for immediate delivery of a FiO_2 up to 60% [5,7]. Oxygen cages can range from expensive commercial cages that control FiO_2 , CO_2 , heat, and humidity to a simple plastic-wrapped cage door, pet carrier or incubator with an external oxygen source. When using an oxygen cage that does not control heat and CO_2 , care must be taken to prevent hyperthermia and rebreathing of CO_2 . A commercial CO_2 monitor and thermometer can be placed in the oxygen cage with the patient to monitor temperature and carbon dioxide levels.

The ease and stress-free nature of oxygen administration using an oxygen cage is appealing and often necessary in the patient presenting in respiratory distress. However, the clinician should be cautioned that cage oxygen administration severely limits hands-on access to the patient. Opening of an oxygen cage causes a precipitous drop in FiO_2 that can be detrimental to the patient. Emergency patients present with varying degrees of pulmonary injury and disease and can quickly decompensate with a sudden drop in oxygen levels. The clinician must weigh the benefits of oxygen cage use against the inability to interact with the patient and provide basic stabilization. In the emergency patient requiring immediate cage oxygen support, careful visual monitoring of the patient is necessary to monitor for signs of decompensation. The use of continuous electrocardiogram, pulse oximetry, and blood pressure connected to a monitoring device may aid the clinician with monitoring of patient status and response to therapy. A step-wise plan for the stabilization and assessment of these patients should be organized and implemented as soon as possible.

Advanced Oxygen Delivery Methods

When conventional oxygen delivery methods are not adequate for relief of hypoxia or if the patient has facial injury or deformities precluding conventional therapies, advanced non-invasive oxygen delivery methods should be considered. Advanced non-invasive oxygen delivery methods are popular in people failing conventional oxygen therapies as these methods can avoid intubation which comes with increased risk for morbidity and mortality [8,9]. Advanced oxygen delivery methods such as transtracheal oxygen and high-flow nasal cannula have been used with success in veterinary patients failing conventional therapies and may be useful when escalation of oxygen therapy in patients presenting to the emergency room in respiratory distress is required.

Transtracheal Oxygen Administration

Oxygen administration through a transtracheal catheter (TTC) can be considered in patients requiring oxygen support where a nasal cannula cannot be placed or for those patients failing conventional oxygen therapies. The main benefit of transtracheal oxygen delivery over conventional therapies is that the placement of the TTC into the lower airways bypasses a significant portion of the upper airway. This limits the mixing of oxygen with deadspace and delivers an increased FiO_2 of up to 80% compared to nasal oxygen at similar flow rates [10]. TTCs are reported to be well tolerated by both dogs and cats and allow for easy clinician access to the patient [10]. They require expertise to be placed and injury to the trachea and surrounding tissues has been reported [7].

Oxygen flow rates using TTCs have been reported to be lower than with nasal cannulae. The recommended starting oxygen flow rate for a TTC is 50 mL/kg/min which is comparable to an oxygen flow rate of 100 mL/kg/min through a nasal cannula [10]. The use of TTCs completely bypasses the upper airway, allowing for delivery of cold, dry air directly to the lungs, so proper humidification of oxygen is recommended. Reported complications with use of a TTC include kinking of the catheter, tracheitis, subcutaneous emphysema, catheter dislodgment, and obstruction of catheter with secretions [7,10]. Because a TTC can deliver a FiO_2 of greater than 60%, oxygen toxicity is a concern.

High-Flow Nasal Cannula

High-flow nasal cannula (HFNC) has been used in people since the early 2000s as an advanced oxygen delivery method to avoid intubation. More recently, HFNC has found utility in the human emergency setting when conventional oxygen therapies fail and escalation of oxygen therapy is needed [11,12]. High-flow nasal cannula accurately delivers humidified and heated oxygen via nasal prongs to the patient, allowing for safe delivery of higher oxygen flow rates. The delivery system humidifies the air to 99% relative humidity, allows for adjustment of the gas temperature and for adjustment of FiO_2 from 21% to 100%. Oxygen flow rates vary with the system used and the size of the nasal prongs, ranging from 1 to 60 L/min.

The proposed mechanism for the improvement in oxygenation and ventilation parameters seen with HFNC is based on the higher flow rates achieving deadspace wash-out [13]. With complete deadspace wash-out, the desired FiO_2 is delivered to the lungs without any mixing of end-expiratory gas. Studies in people have also shown a potential pressure benefit with HFNC which can vary with flow rate and open or closed mouth [14].

There are limited studies in veterinary medicine looking at the use of HFNC and none specifically looking at the use of high-flow oxygen therapy in veterinary patients presenting to the emergency room for respiratory distress [15,16]. One study reported the use of HFNC in a dog presenting to the emergency room with polytrauma including pneumothorax, severe pulmonary contusions, and pelvic fractures after a motor vehicle accident. The pneumothorax was continuous, necessitating chest tube placement prior to initiation of HFNC but remained continuous for several days until oxygen flow rates were less than 10L/min [16]. The use of HFNC therapy in patients with existing pneumothorax should be undertaken with caution.

Advantages to the use of HFNC in the emergency patient include possible avoidance of intubation in those failing conventional oxygen therapies, patient comfort with higher oxygen flow rates, ease of use comparable to conventional nasal oxygen administration and delivery of higher and accurate FiO_2 . Disadvantages includes expense of equipment, risk of oxygen toxicity with $\text{FiO}_2 > 60\%$, and risk of exacerbation of pneumothorax.

Invasive Oxygen Delivery Methods

Patients presenting with severe work of breathing, hypoxemia ($\text{PaO}_2 < 60\text{mmHg}$ or $\text{SpO}_2 < 90\%$) or hypercapnia ($\text{PaCO}_2 > 60\text{mmHg}$) unresponsive to non-invasive oxygen support may require intubation and positive pressure ventilation (PPV) (see Chapter 188). In addition, previously stable patients presenting to the ER may decompensate and require invasive oxygen support. Invasive oxygen administration involves intubation of the patient. Intubation has been associated with an increase in morbidity and mortality due to loss of normal airway defense mechanisms, risk of pneumonia and prolonged immobility secondary to heavy sedation required for intubation [1,17]. Despite these risks, in the severely unstable patient, intubation and PPV can be life saving until the patient can be stabilized.

Positive Pressure Ventilation

Positive pressure ventilation can help improve hypoxemia in dogs and cats with severe hypoxemia unresponsive to conventional oxygen support (see Chapter 188). Overall, in dogs and cats undergoing mechanical ventilation for pulmonary pathology, regardless of the cause, reported survival rates are 20–30% [18,19]. Caution should be exercised when using PPV in veterinary trauma patients with existing pneumothorax or who are at risk for pneumothorax. PPV can worsen an existing pneumothorax or cause a pneumothorax requiring continuous suction while the patient is being ventilated (see Chapter 44). Constant attention to patient pulmonary function is of the utmost importance

and pneumothorax should be highly considered in any patient receiving PPV that undergoes acute desaturation.

The use of PPV requires a level of expertise to operate, expensive equipment, and intensive patient care and monitoring. Complications associated with PPV include ventilator-acquired pneumonia, pneumothorax, and effects of prolonged sedation and immobility.

Hyperbaric Oxygen

With the increasing availability of portable hyperbaric oxygen chambers specifically engineered for veterinary patients, hyperbaric oxygen (HBO) is finding utility in veterinary medicine. The utility of HBO in improving oxygen delivery is based on the effect of pressure on the various gas laws (Fick, Henry, Boyle) [20,21]. Hyperbaric oxygen leads to changes in oxygen solubility and pressure. By increasing atmospheric pressure beyond 1 atmosphere (1 atm), more oxygen can be dissolved in and transported by plasma. In addition, the increased amount of oxygen dissolved in blood will increase the partial pressure of oxygen as measured by PaO_2 . This allows for improved diffusion of oxygen into the tissues compared to oxygen being transported by hemoglobin. And indeed, it has been proposed that at $2.5 \times$ atmospheric pressure (2.5 atm) with an FiO_2 of 100%, the amount of dissolved oxygen in plasma is adequate to meet the resting requirement of the tissues without the need for hemoglobin [20,21]. In people, hyperbaric oxygen is used in the treatment of carbon monoxide poisoning, wound healing, gas bubble reduction, enhancement of antimicrobial function, modulation of inflammation, and angiogenesis. Veterinary publications on the use of hyperbaric oxygen therapy in small animals are mostly limited to case reports and to date no controlled studies have been published.

Complications with HBO include oxygen toxicity, barotrauma, decompression sickness, and oxygen-induced seizures [20,21]. While patients are undergoing HBO therapy, the clinician does not have hands-on access and in an emergency it can take several minutes to decompress the chamber. Monitoring equipment is generally not available in veterinary HBO chambers. In the veterinary emergency setting, HBO may have a utility in smoke inhalation, post cardiopulmonary arrest, envenomations, and sepsis [22,23].

Monitoring Response to Oxygen Therapy

When starting supplemental oxygen therapy, regardless of the cause, the patient must be carefully and continuously monitored for response to therapy. Lack of

patient response to therapy must be quickly recognized and requires an escalation to more advanced or invasive methods of oxygen administration.

Response to oxygen therapy can be monitored using several methods. The easiest and less stressful method is continuous visual monitoring of the patient. This is particularly important for the patient in an oxygen cage or in severe distress. For a patient in an oxygen cage, any intervention that requires opening of the cage door can lead to a detrimental decrease in FiO_2 . For this reason, observation of response to therapy is key for these patients. In addition, patients in severe respiratory distress may not tolerate blood draws for arterial blood gas or application of a pulse oximetry probe.

In the author's opinion, visual inspection of the patient is one of the most useful and non-stressful tools for evaluation of response to oxygen therapy. Attention should be paid to the patient's respiratory rate and effort and color of the gums or tongue. Patients which are showing a positive response to oxygen therapy should have a decrease in their respiratory rate and improvement in their respiratory effort. Patients with cyanosis responding to oxygen therapy should have improvement in the color of their gums or tongue. Patients responding to oxygen therapy should be willing to lie down and sleep as well as eat and drink. Other vital parameters such as heart rate and blood pressure should normalize with response to oxygen therapy. Persistent signs of respiratory distress warrant escalation of oxygen therapy.

Pulse oximetry is a non-invasive monitoring method which, using spectrophotometry, detects the saturation of hemoglobin with oxygen (SpO_2). SpO_2 readings of less than 92% with continued signs of respiratory distress indicate the need for escalation of oxygen therapy. Inaccuracies associated with pulse oximetry can be seen with patient motion, pigmented skin, hypothermia, vasoconstriction, bright lights, and poor cardiac output (Editors' note: Carbon monoxide toxicity can result in inaccurate pulse oximetry readings). The probe is typically placed on the tongue or gums but can also be placed on the pinna, webbing of the toes, prepuce or vulva. SpO_2 readings are a useful tool for monitoring response to oxygen therapy but do not give information regarding the efficiency of gas exchange or ventilation [24].

Arterial blood gas monitoring is the gold standard for determining oxygenation and ventilation parameters. This requires blood sampling from an arterial vessel. The dorsal pedal artery in the hind foot is typically used for arterial blood sampling but arterial blood can also be sampled from the femoral, auricular, lingual and digital arteries of the front foot (see Chapter 178).

For patients receiving oxygen therapy, a PaO_2 of less than 70 mmHg with continued signs of respiratory distress requires escalation of oxygen therapy. A PaCO_2 of greater

than 50 mmHg indicates hypoventilation and mechanical ventilation should be considered for these patients.

Oxygen Toxicity

Oxygen is directly toxic to the pulmonary epithelium secondary to the formation of free oxygen radicals. The degree of damage to the lungs is related to both the duration of oxygen therapy and the FiO_2 . In animals receiving 100% oxygen for 4 days almost total destruction of type I epithelial cells was seen. In contrast, exposure of animals to 60% oxygen for 7 days produced few morphological changes to the lungs [25]. Sensitivity to oxygen toxicity varies between species and between neonates and adults. Neonates seem more resistant to oxygen toxicity compared to adults of the same species [26].

To avoid oxygen toxicity, FiO_2 should be kept below 50% whenever possible. The majority of the oxygen delivery methods available in veterinary medicine are not able to consistently deliver a FiO_2 of more than 60% to the patient. However, transtracheal oxygen, high-flow nasal cannula and intubation with or without positive pressure ventilation have the capacity to consistently deliver an FiO_2 of greater than 60% and consideration must be given to the development of oxygen toxicity.

Conclusion

Oxygen supplementation should be administered to all tachypneic patients presenting to the emergency room. For initial triage and stabilization, flow-by and face mask oxygen can be rapidly instituted to provide an increase in FiO_2 to the patient. An oxygen cage can be used as a fast and stress-free method of oxygen delivery in the patient presenting in respiratory distress but lack of hands-on access needs to be weighed against the ease of use. Hood oxygen and nasal oxygen are reasonable long-term oxygen delivery methods in patients requiring ongoing oxygen support.

In patients failing these conventional oxygen delivery methods, oxygen supplementation via transtracheal catheter can be considered. High-flow nasal cannula is a novel oxygen delivery method in veterinary medicine and may be useful for providing oxygen support to emergency patients failing conventional therapies. With severe respiratory distress not responsive to other methods of oxygen supplementation or with hypoventilation, intubation and positive pressure ventilation should be considered.

The emergency clinician must carefully monitor patient response to oxygen therapy and be prepared for escalation of oxygen therapy if improvement is not seen.

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Sonography in the Emergency Room

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Terminology

The terminology for standardized focused and complete veterinary ultrasound examinations and ultrasound signs and terms used during global FAST is shown in Table 182.1.

Abdominal Focused Assessment of Sonography for Trauma (FAST)

Target-Organ Approach

The use of the target-organ approach (naming abdominal FAST (aFAST) views by internal anatomy rather than external sites) maximizes the amount of clinical information gained during aFAST far beyond a simplistic approach of fluid positive or fluid negative (Figure 182.1) [1–6]. The author's recommended way to perform each aFAST view, their respective strengths, weaknesses, pearls, and pitfalls have been described [3,4]. Each aFAST view should be imaged in a standardized manner with dogs and cats placed in lateral recumbency (right generally preferred) [1–6] by fanning away and toward the table top in longitudinal orientation (same as sagittal) followed by rocking the probe cranially at each respective view [3,4]. The use of transverse orientation is likely unnecessary based on the landmark publication by Boysen et al. in which 397/400 views matched comparing longitudinal to transverse orientation when fluid was detected [7]. Lastly, pleural and pericardial effusion may be detected via the FAST diaphragmatico-hepatic (DH) view and all sonographers performing aFAST should make it habitual to look beyond the diaphragm into the thorax [3,4,6–9]. Goal-directed templates for recording aFAST findings keep veterinarians on task, give clinical value to initial and serial examinations, and provide a means for ultrasound program surveillance (detecting strengths and weaknesses in training) [2–4,6,8–10].

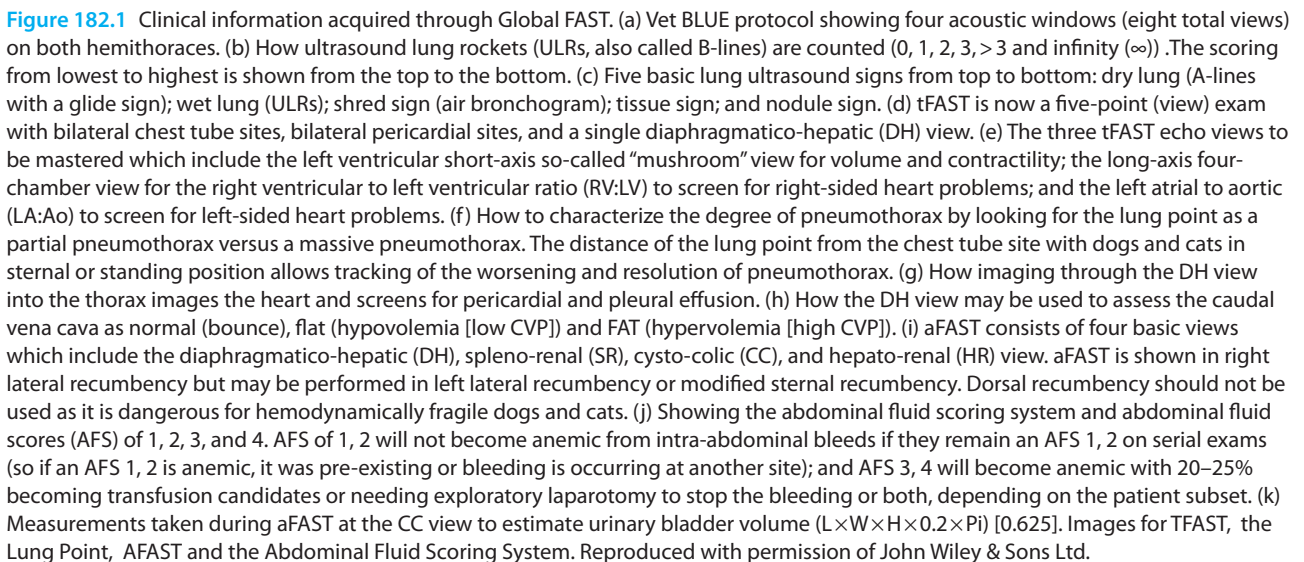
Abdominal Fluid Scoring System

The abdominal fluid scoring (AFS) system was developed to better characterize bleeding dogs because of the higher rate of hemoabdomen than previously reported pre-FAST (pre-FAST ~20% compared to a FAST rate of 45%) [1]. The scoring system is simple (0–4 scale) for dogs and cats placed in either lateral recumbency (see Figure 182.1) and includes positive intra-abdominal fluid (retroperitoneal fluid is not scored) [1]. Importantly, low-scoring dogs and cats (abdominal fluid score of 1,2) will *not* become anemic from their intra-abdominal bleed as long their AFS *remains* 1,2 on serial exams [1–3,11]. Therefore, if an AFS 1,2 dog or cat is anemic or becomes anemic, then pre-existing anemia was present or bleeding is occurring at another site (another space or cavity, gastrointestinal tract, reproductive tract, fracture site(s), or externally), respectively (or there is hemodilution due to large volumes of intravenous fluids) [1–3,11].

Conversely, higher-scoring dogs with AFS 3,4 will predictably become anemic and ~20–25% of bluntly traumatized dogs with AFS 3,4 will become anemic enough to require blood transfusion(s) [1–3] and, uncommonly, surgical exploratory surgery [1–3,6,7]. In contrast, higher scoring AFS 3,4 dogs bleeding postinterventionally or from penetrating trauma or ruptured tumors generally require resuscitation and exploratory surgery to stop the bleeding [3]. Exceptions would include coagulopathic dogs, including those with anaphylaxis [3,12]. These same principles likely hold true for cats, but felines are less likely to survive acute large-volume blunt trauma-induced bleeds (hemoabdomen FAST rate of 14% compared to dogs FAST rate of 27–45%) [5,11]. A similar human scoring system also aids in decision making (blood transfusion, exploratory surgery) [13] and any positive AFS should always be considered as major intra-abdominal injury until proven otherwise.

Table 182.1 Terminology for standardized focused and complete veterinary ultrasound examinations and ultrasound signs and terms used during global FAST.

Terminology for standardized ultrasound exams	
Abdominal FAST	aFAST
Thoracic FAST	tFAST
Veterinary bedside lung ultrasound exam	Vet BLUE
Global FAST	aFAST, tFAST and Vet BLUE combined
Complete abdominal ultrasound	
Complete echocardiography	
Ultrasound signs and characterizations used during global FAST	
A-lines	Hyperechoic horizontal equidistant lines extending from the pulmonary-pleural line representing a strong air interface
Caudal vena cava (CVC) characterization	<p>Bounce: expected ~35–50% dynamic changes in CVC diameter during inspiration and expiration</p> <p>Flat: lacks dynamic change in CVC diameter (<10%) during inspiration and expiration having an abnormally small diameter</p> <p>FAT: lacks dynamic change in CVC diameter (<10%) during inspiration and expiration having an abnormally large diameter</p>
B-lines (also called ultrasound lung rockets)	Hyperechoic vertical lines originating from the pulmonary surface that extend through the far field and swing in synchronization with inspiration and expiration, obliterating A-lines representing strong acoustic impedance between air and fluid at the lung surface
Bull's eye sign	Sign indicative of pericardial effusion at the right tFAST PCS view (directing the probe toward the sternum) through the observation of the heart's apex rounded by free fluid contained within the pericardial sac
Cardiac bump	Observation at the FAST DH view in which the muscular apex of the heart beating and indenting along the diaphragm is observed; helps rule in or out pericardial effusion
Gall bladder halo sign	<p>Occurs with the presence of gall bladder wall edema and supports the diagnosis of anaphylaxis (flat CVC) vs right-sided heart failure/generalized systolic dysfunction, pericardial effusion (FAT CVC) vs right-sided volume overload (FAT CVC) in collapsed, weak, hypotensive dogs</p> <p><i>Note:</i> There are other causes for gallbladder wall edema</p>
Glide sign	Observation of the to-and-fro motion of the lung sliding along the thoracic wall at the pulmonary-pleural interface in concert with inspiration and expiration; also called lung sliding
Lung point	Transition point where lung recontacts the thoracic wall evidenced most commonly by the observation of either the glide sign or B-lines (ultrasound lung rockets) ventrally (or toward the sternum) and lack of both dorsally (or toward the spine); the lung point increases the sensitivity for the diagnosis of pneumothorax and semi-quantitates/allows tracking of the degree of pneumothorax by its distance from the chest tube site
Nodule sign	Observation of a round anechoic structure off the pulmonary surface that has a hyperechoic far border often with air reverberation artifact appearing as a B-line (ULR) through the far field; most commonly represents neoplastic abscess and granulomatous conditions
Racetrack sign	Sign indicative of pericardial effusion at the FAST DH view through the observation of the heart's apex rounded by free fluid contained within the pericardial sac
Shred sign	Observation of irregularities along the normal expected linear continuity of the pulmonary surface with variable degrees of echogenicity and hyperechoic foci contained within, representing lung consolidation with air bronchograms
Tissue sign	Observation of irregularities along the normal expected linear continuity of the pulmonary surface with variable degrees of echogenicity often appearing like soft tissue (liver-like) without hyperechoic foci, representing severe lung consolidation without an air bronchogram
Tree trunk sign	Observation of distended hepatic veins as they drain into a distended (FAT) caudal vena cava (abnormal finding); represents conditions impeding blood flow from the liver to the right heart (most commonly right-sided failure, pericardial effusion)
Ultrasound lung rockets (ULRs) (also called B-lines)	Hyperechoic vertical lines originating from the pulmonary surface that extend through the far field and swing in synchronization with inspiration and expiration, obliterating A-lines representing strong acoustic impedance between air and fluid at the lung surface
Urinary bladder volume estimation formula (mL)	$\text{Length (cm)} \times \text{Width (cm)} \times \text{Height (cm)} \times 0.2 \times \text{Pi (0.625)}$



blood is rapidly absorbed from the abdominal cavity in <48 hours [2,3,6]. If free fluid is safely accessible, abdominocentesis and fluid analysis should be performed in order to accurately characterize the effusion (ultrasound cannot reliably characterize free fluid) [2,3,5,6].

Blunt Versus Penetrating Trauma

There are gross differences in the coagulation cascade that occur between blunt trauma, in which blood is rapidly defibrinated by the mesothelial cells (and thus seen during aFAST as black anechoic triangulations), versus penetrating trauma, in which the crushing, tearing or shearing of tissue result in clotted blood (and thus is often missed during aFAST since clotted blood appears like adjacent soft tissue) [3,6,14]. In time, however, clotted blood will defibrinate and thus be apparent as free fluid and detected during serial aFAST [3,6,14]. Likewise, ruptured abdominal viscera will in time leak their contents and be detectable during serial aFAST (septic, exudative effusions) [15] and vascular injuries may in time, with cicatrization, lead to portal and hepatic hypertension (transudate/modified transudate) [16–19]. In other words, serial aFAST allows for the detection of a wide range of intra-abdominal injury when free fluid is not initially present, and detected free fluid may be characterized for a diagnosis and decision making regarding medical versus surgical conditions [2]. For these reasons, the liberal use of serial exams and serial aFAST for up to 24–48 hours is imperative for all at-risk dogs and cats [2,3,6,14,15,20,21], and 4-hour postadmission FAST exams have been standard of care since 2001 in human medicine [22] and are recommended for dogs and cats [2,3,6,11].

In summary, the recommended approach is to rehydrate, resuscitate, and re-evaluate with serial aFAST exams [2,3,6]. It is important to record the AFS in a systematic method because dogs and cats with small-volume bleeding or suspect for ruptured abdominal viscous (acute abdomen), especially when dehydrated, often develop marked effusions over the next 2–6 hours when placed on even modest intravenous fluid rates [2,3,6]. If free fluid becomes safely accessible, then abdominocentesis and fluid analysis are recommended in order to accurately characterize the effusion (ultrasound cannot reliably characterize free fluid) [2,3,5,6].

Triage or Non-Trauma Subsets: Collapsed, Weak, Hypotensive

The use of FAST formats for triage (non-trauma) subsets of dogs and cats as a first-line screening test has been advocated for several years [2,3,6]. In a recent clinical study, it was found that 75% of unstable and 9% of stable dogs and cats undergoing the combination of aFAST and tFAST had clinically relevant findings that helped direct care and diagnostics [5]. In another non-trauma study, pericardial effusion was detected in dogs at a much higher frequency when aFAST and tFAST were applied at triage than prior to using FAST (28 cases in 2011 versus three cases in 2005) [9].

In addition to detecting free fluid in the peritoneal cavity and retroperitoneal space, and in the pleural cavity and pericardial sac, the observation of gallbladder wall edema (so-called gallbladder halo sign) alerts the sonographer to the possibilities for anaphylaxis [23] in dogs, and right-sided heart conditions (dysfunction, failure/volume overload, pericardial effusion) in dogs [3,24] and, although rare, cats [24]. Importantly, anaphylactic dogs not uncommonly develop hemoabdomen that range from low-scoring AFS 1,2 to high-scoring AFS 3,4 with variable findings on traditional coagulation times (PT, aPTT) [3,12]. The pathogenesis has not been sorted out but is likely a combination of severe hepatic venous congestion from massive histamine release, coupled with heparinization from mast cells and the subsequent effects of tryptase and bradykinin resulting in diapedesis of blood into the peritoneal cavity. Mistaking an anaphylactic hemoabdomen for a surgical case will likely lead to a fatal patient outcome [12].

Moreover, the target-organ approach lends itself to detecting incidental and unexpected findings triggering continued imaging and diagnostics for many conditions, including as examples: DH view – liver (masses, cysts), gallbladder (choleliths, sludge, mucocoeles); SR view – spleen (masses), left kidney (cortical cysts, pyelectasis/hydronephrosis, nephroliths); CC view – urinary bladder (thrombus, intraluminal debris, wall abnormalities); HR view – splenic masses, midabdominal masses, pyometra, right kidney (same as left kidney). In a human FAST study, ~8% of patients undergoing FAST had clinically relevant incidental findings detected [25]. Published aFAST goal-directed templates have a “comments section” to record suspect incidental findings [2–4,6,10].

Thoracic FAST

Thoracic FAST is a five-point exam that includes bilaterally applied chest tube sites (CTS) for rapid detection of pneumothorax (PTX) (highest point to which air would rise) and pulmonary contusions; bilaterally applied pericardial sites (PCS) for echocardiographic views of the left and right heart, pleural effusion (PE), and pericardial effusion (PCE); and singly applied diaphragmatico-hepatic (DH) view for PE and PCE, volume status (caudal vena cava and hepatic veins), and a deep window into the lung (see Figure 182.1) [2,6,8,26]. tFAST views, their strengths, and the clinical information garnered from them are listed in Table 182.2.

Thoracic FAST PCS and DH Views

Pericardial Effusion

The gold standard for the diagnosis of PCE is ultrasound [9]. For non-radiologist and non-cardiologist

Table 182.2 Thoracic FAST: how to perform, strengths, pearls, and pitfalls.

tFAST views	How to perform	Strengths	Pearls	Pitfalls
Left and right chest tube site (CTS) *Air rises	<ol style="list-style-type: none"> 1. Place probe directly above xiphoid in upper 1/3 of the thorax either in lateral or standing or sternal recumbency where the cap of air would rise if PTX was present 2. With the probe perpendicular to the long axis of the ribs, establish the gator sign orientation to identify the lung line (pulmonary-pleural interface) 3. The glide sign is best observed by scattering the echoes by placing the rib head in the middle of the field (one-eyed gator) or oblique the echoes by fanning the probe to make the lung line less bright white and more gray 	Diagnosis of PTX by A-lines without a glide sign	<ol style="list-style-type: none"> 1. A-lines with a glide sign rule out PTX 2. ULRs (also called B-lines) rapidly rule out PTX 3. ULRs support the present of pulmonary contusions 4. If suspected PTX then search for the lung point generally evidenced by the resumption of the glide sign, ULRs, but also any lung signs including shred and tissue 	<ol style="list-style-type: none"> 1. Imaging too far caudally over the abdomen 2. Imaging too far dorsally over the hypaxial muscles 3. Rapid shallow breathing makes it difficult to see the glide sign 4. Safe sedation such as butorphanol slows the breathing to better search for the glide sign
Left pericardial site (PCS) *Fluid falls to the most gravity-dependent sites	<ol style="list-style-type: none"> 1. Left PCS in right lateral recumbency – palpate for the apical beat with your left hand with your fingers on the right thoracic wall and your thumb on the left thoracic wall 2. Your thumb on the left thoracic wall will guide you on where to place the probe 3. Image the heart with the marker toward the elbow 4. Increase depth to be able to see the bright pericardium in the far field so the heart is clearly seen in its entirety 	Diagnosis of pleural effusion *Diagnosis of PCE better via the right PCS view and the DH View	<ol style="list-style-type: none"> 1. Moving the probe closer to the sternum and directing toward the heart helps avoid air interference from lung 2. One view is no view – use multiple views to diagnose PE and PCE 	<ol style="list-style-type: none"> 1. Mistaking the major fluid-filled structure in the thorax, the heart, for free fluid, leading to the most catastrophic of mistakes – performing centesis on a heart chamber
Right pericardial site (PCS) *Fluid falls to the most gravity-dependent sites	<ol style="list-style-type: none"> 1. Right PCS in right lateral recumbency – palpate for the apical beat with your left hand with your fingers on the right thoracic wall 2. Where your middle 2 fingers palpate the apical beat guides you on right thoracic wall to where to place the probe 3. Increase depth to be able to see the bright pericardium in the far field so the heart is clearly seen in its entirety 4. Image the heart with the marker toward the elbow for the short-axis view 5. Image the heart with the marker toward the spine for the long-axis view 	<ol style="list-style-type: none"> 1. Diagnosis of PE and PCE 2. Volume and contractility via the left ventricular short-axis mushroom view 3. Left-sided hypertension (LA:Ao ratio) 4. Right-sided hypertension (RV:LV ratio) 	<ol style="list-style-type: none"> 1. Only diagnose PCE if (a) imaging toward the muscular apex of the heart (bull's eye sign) or (b) imaging the long-axis 4-chamber view if all 4 chambers are clearly identified or (c) using the DH view (racetrack sign) <p>*The pericardium attaches at one atrium and then rounds the apex of the heart to attach at the other atrium</p>	<ol style="list-style-type: none"> 1. Mistaking the major fluid-filled structure in the thorax, the heart, for free fluid, leading to the most catastrophic of mistakes – performing centesis on a heart chamber

(Continued)

Table 182.2 (Continued)

tFAST views	How to perform	Strengths	Pearls	Pitfalls
Diaphragmatico-hepatic (DH) view	<ol style="list-style-type: none"> 1. Place the probe immediately caudal to the xiphoid and direct the probe toward the head of the patient 2. The curvilinear white line indicating the diaphragmatic–air-filled lung interface should be observed 3. Increase depth to be able to see into the thorax (25–33% of the far field) for PE 4. Rock the probe toward the sternum (parallel to it) to observe the “cardiac bump” (the muscular apex of the heart indenting into the diaphragm) to be able to interrogate for PCE 5. Fan through the gall bladder in both directions to observe for free intra-abdominal fluid 6. Look for the CVC for volume status as a bright white equals sign (=) made by the near and far CVC walls as the CVC traverses the diaphragm 	<ol style="list-style-type: none"> 1. Diagnose PE and PCE 2. Diagnose free intra-abdominal fluid 3. Volume status via the CVC 4. Gall bladder edema (halo sign) for anaphylaxis or right-sided heart conditions 5. DH view has less air interference than PCS views 6. The DH view performed similarly in sternal or standing as in lateral recumbency with imaging of the gall bladder, cardiac bump, and CVC 	<ol style="list-style-type: none"> 1. May be used as a single diagnostic view for PCE because the view interrogates the muscular apex of the heart making it much less likely to mistake a heart chamber for PCE 2. Mirror image artifact along the diaphragm immediately rules out PE 	<ol style="list-style-type: none"> 1. Mirror image artifact (created by the strong air–soft tissue interface of air-filled lung and diaphragm) can be a major confounder especially when free intra-abdominal fluid, the gall bladder, and the hepatic venous system are reflected into the thorax 2. Gall bladder wall edema (halo sign) is <i>not</i> pathognomonic for anaphylaxis

Ao, aorta; CVC, caudal vena cava; LA, left atrium; LV, left ventricle; PCE, pericardial effusion; PE, pleural effusion; PTX, pneumothorax; RV, right ventricle; ULR, ultrasound lung rocket.

sonographers, it is imperative to know how to properly diagnose PCE without mistaking the heart, the major fluid-filled structure in the thorax, for free fluid (Table 182.3) [6,8,9,27]. Such a misdiagnosis of a heart chamber for PCE (or PE) potentially leads to the most catastrophic of mistakes – performing centesis on the heart [6,8,9].

To maximize a correct diagnosis of PCE, the sonographer should adhere to the following tenets:

- image the heart at the right PCS view in its entirety with adequate depth to visualize the bright (hyperechoic [white]) pericardium in the far field [6,8,9,27]
- image toward the muscular apex of the heart where no fluid-filled heart chambers are likely to be mistaken for free fluid (bull’s eye sign at the right PCS view, race-track sign at the DH view) [8,9]
- use the long-axis four-chamber view only if all four heart chambers are clearly identified [9,27,28].

The sonographer should know that the pericardium is attached at one atrium and then courses toward and

around the muscular apex of the heart to attach to the other atrium [8,9,27,28]. Adhering to the sage axiom that “one view is no view,” using combinations of the aforementioned strategies also prevents mistakes.

Finally, the diagnosis of PCE should never be made solely on short-axis views other than by imaging toward the muscular apex of the heart because it is easy to mistake the right ventricle (or other heart chambers/structures) for free fluid [8,9].

If a diagnosis cannot be made, then a cardiologist or radiologist should be consulted.

Pleural Effusion

The gold standard for the diagnosis of PE is debatable and suggestions have included thoracoscopy, ultrasound, and computed tomography (CT) [29]. The diagnosis of PE follows the tenets for diagnosing PCE (see Table 182.3) [6,8,27]. However, in contrast to PCE in which the free fluid is contained within the pericardial sac, PE is uncon- tained and unrestrained unless compartmentalization is

Table 182.3 Diagnosis of pericardial and pleural effusion.**Diagnosis of pericardial effusion**

The gold standard for the diagnosis of pericardial effusion is ultrasound

Radiography is poor

Pericardial effusion is contained in the pericardial sac that attaches at one atrium and rounds the apex of the heart to attach to the other atrium

Imaging strategy	FAST DH view	tFAST PCS view
Image toward the muscular apex of the heart where no heart chambers can be mistaken for free fluid	FAST DH view – racetrack sign	tFAST right PCS view – bull's eye sign
Long-axis 4-chamber view where all 4 chambers are identified		tFAST right PCS view
Increase depth to view the heart in its entirety using the bright white (hyperechoic) pericardium in the far field as a landmark		

Diagnosis of pleural effusion

The gold standard for the diagnosis of pleural effusion is computed tomography

Radiography is generally good

Pleural effusion is uncontained and unrestrained unless compartmentalized

Imaging strategy	FAST DH view	tFAST PCS view
Increase depth to image the heart in its entirety using the bright white pericardium in the far field as a landmark		tFAST right and left PCS – anechoic (black) triangulations
Image toward the muscular apex of the heart where no heart chambers can be mistaken for free fluid	FAST DH view – anechoic (black) triangulations	

DH, diaphragmatico-hepatic; PCS, pericardial site; tFAST, thoracic FAST.

present [6,8,27]. At the left and right PCS views, depth should be increased so the heart is clearly imaged in its entirety by observing the bright (hyperechoic [white]) pericardium in the far field [6,8,27]. The diagnosis of PE on PCS views is made by observing free fluid outside the heart and its pericardium.

The DH view is advantageous because it is much more difficult to mistake the heart for free fluid when compared to the transthoracic PCS views [8,9]. At the DH view, PE is observed as anechoic triangulations (in contrast to the rounding of PCE and its racetrack sign) [6,8,9]. Pitfalls of the DH view include mistaking the caudal vena cava for PE as it traverses the diaphragm [4]. However, by fanning through the diaphragm with a more liberal use of the DH view, the diagnosis of PE may be more confidently made, and the savvy sonographer knows that a mirror image artifact at the DH view immediately rules out PE along that plane.

Finally, PE on ultrasound may look like a large-volume effusion when in fact the effusion is minimal (and sonographers should be familiar with the centimeter scale on their machine). In questionable cases, thoracic radiography, although less sensitive, is a readily available modality to perform on stable patients [30].

If a diagnosis still cannot be made, then a cardiologist or radiologist should be consulted.

FAST DH View and CVC for Estimating Volume Status

The DH view is part of both tFAST and aFAST and eyeball characterization estimates central venous pressure (CVP) at the point where the caudal vena cava (CVC) traverses the diaphragm (see Figure 182.1) [2,3,26,27,31]. The CVC is characterized as having a normal bounce (~50% variation in diameter with phases of respiration), being flat with <10% change and small sized (volume depleted (low CVP)), or being FAT with <10% change and enlarged (volume overloaded (high CVP)) [27,31–34]. The hepatic veins should likewise be characterized as unremarkable (typically only evident in patients with high CVP) or distended (tree trunk sign) [3,6,8,31,33,34]. Distension of hepatic veins should concurrently have a FAT CVC [3,8,27,31,34]. Whenever a FAT CVC and hepatic venous distension are observed on admission prior to volume resuscitation, right-sided heart problems, PCE, or vascular obstruction between the diaphragm and the pulmonary outflow track should be suspected [3,6,8,26,27,31,33,34]. When a FAT CVC and hepatic venous distension occur following fluid resuscitation or while dogs and cats are receiving intravenous fluid therapy during hospitalized care, right heart volume overload is present until proven otherwise [26,27,31,33–35].

tFAST Basic Echo Views

Three views at the right PCS view are taught: the short-axis left ventricular view (so-called mushroom view), the short-axis quick-peek LA:Ao view, and the long-axis four-chamber view (RV:LV) (see Figure 182.1) [6,26,27,35]. These views provide information regarding volume and contractility, and left-sided and right-sided hypertension, respectively [26,27,34–36]. The eyeball approach generally gives ample information during patient resuscitation and monitoring when complete echocardiography is not readily available or is too risky for an unstable patient [6,8,26,27,33–37]. The eyeball approach (subjective assessment) has been shown to reliably give similar information as obtained by more technically challenging measurements using M-mode and color flow Doppler [37]. If concern regarding cardiac function and volume overload persists, then complete echocardiography should be performed by a sonographer with advanced training (cardiologist or radiologist). When echocardiography views are too risky or indeterminate, then the fallback strategy of using Vet BLUE for left-sided failure/overload and the caudal vena cava and hepatic venous congestion for right-sided failure/overload should be used (see Figure 182.1).

tFAST CTS Views

Pneumothorax and Lung Point

The CTS is designated as the highest point on the thorax to which the cap of air would rise when free air (pneumothorax (PTX)) is present within the pleural space (see Figure 182.1) [2,8,27,38]. The observation of either the glide sign or ultrasound lung rockets (ULRs), also called B-lines, rules out PTX at that specific point along the thoracic wall [2,8,38]. Thus, if the glide sign or ULRs are observed at the highest point to which air would rise in that positioning, then PTX is ruled out [2,8,38]. If A-lines without a glide sign are observed, then PTX is likely and with the patient in sternal or standing position, the sonographer should search for the lung point [2,8,26,39].

The lung point is the location where lung recontacts the thoracic wall and is most often evidenced through either observation of the glide sign or presence of ULRs (see Figure 182.1) [2,8,26,39]. The lung point increases the sensitivity for the diagnosis of PTX, semi-quantitates its degree (partial versus massive), and serially allows for tracking worsening or resolving PTX [39]. When the lung point is in the middle one-third or midthorax from the CTS to the sternum or further ventrally, thoracocentesis generally should be performed.

Pulmonary Contusions

The presence of ULRs rapidly rules out PTX at the CTS view but the presence of ULRs supports the diagnosis

of pulmonary contusions (PCs) [2,8,40,41]. Numbers of ULRs likely correlate with severity of PCs and through the use of Vet BLUE, the total number of ULRs is used to assign the patient a “pulmonary contusion score” [2,8,40]. Serial exams allow for tracking PCs as worsening (increasing ULRs) or resolving (decreasing ULRs). In severe PCs, additional lung ultrasound signs of consolidation, referred to as the shred sign and the tissue sign, are observed (see Figure 182.1) [8,40,42,43].

Vet BLUE

Vet BLUE (bedside lung ultrasound exam) should be considered as an extension from the CTS to better characterize patient respiratory status (see Figure 182.1) [6,40,42,44–46]. Using lung ultrasound (LUS) and the Vet BLUE pattern-based approach screens for respiratory conditions and developing complications during hospitalized care [26,44–48]. Dogs and cats should have dry LUS profiles (infrequent to no ULRs) during Vet BLUE [44,45]. LUS findings may include the following: dry lung (A-lines with a glide sign; normal patients), wet lung (ULRs, also called B-lines; patients with interstitial lung fluid), shred sign (analogous to air bronchograms), tissue sign (consolidation with no aeration, referred to as hepatization [30]), and nodule sign (nodular infiltration) (see Figure 182.1) [2,40,43,49,50]. The wedge sign is a subset of the shred sign and strongly suggests the presence of pulmonary thromboembolism (vascular infarction) [42].

Assumptions, Strengths, and Weaknesses of Lung Ultrasound

Lung ultrasound has been shown to be diagnostically more sensitive than both lung auscultation and chest radiography for common respiratory conditions in human patients [49,51]. The LUS assumption is that acute pathology makes it peripherally to the outer 1–3 mm of lung, and thus may be detected by LUS [40,43–47,49,51,52]. Conversely, if the pathology does not make it to peripheral lung then abnormalities will be missed [49,51,52]. However, most acute respiratory conditions in people, and apparently with dogs and cats, extend to peripheral lung and may be detected using LUS [44–47,49,51]. Serial Vet BLUE exams should be used in suspect cases [26,35,40].

Importantly, ULRs are non-specific LUS findings and generally represent a fluid–air interface at the lung periphery [2,40,43–47,49,51]. Conditions associated with the presence of ULRs include cardiogenic and non-cardiogenic pulmonary edema, hemorrhage, pneumonia, and inflammation [2,8,40,41,44–47,49,51]. Thus, a Vet BLUE pattern-based approach best characterizes the

likely diagnosis, for example cardiogenic edema is more dorsal or generalized with bacterial bronchopneumonia being more ventral [30,42,44–46]. ULRs are counted (1, 2, 3, > 3, infinity (∞)) over a representative single intercostal space during Vet BLUE (see Figure 182.1) [40,44–46,48]. ULRs are counted because their numbers correlate with the degree of alveolar-interstitial edema on CT [53]. Recently, a simplistic strong positive approach of having two or more positive sites (positive being > 3 or infinity ULRs) on both hemithoraces was shown to have comparable sensitivity and specificity to thoracic radiography for the diagnosis of left-sided congestive heart failure in cats [46].

Vet BLUE is advantageous over radiography because it is point of care, requires minimal to no restraint, and is rapid (<60–90 sec) [40,44–46]. Through use of the Vet BLUE pattern-based approach and proper LUS training for learning additional LUS signs (shred sign, wedge sign, tissue sign, and nodule sign), a more accurate LUS conclusion may be drawn [40,42,43,49,50,54].

Finally, atelectic lung may result in ULRs, shred sign or tissue sign [30,48,55,56] but in most instances, these LUS findings resolve within 2 hours post-sedation anesthesia [56].

Global FAST

Global FAST for Patient Monitoring

Through the use of aFAST, its fluid scoring system, and the cystocolic view urinary bladder volume estimation formula [57,58], tFAST and Vet BLUE patient surveillance for developing complications and volume status may be better ascertained and should be included in daily rounds following physical examination (see Figure 182.1) (Table 182.4) [6,26,27,54–56,59,60]. Global FAST evaluates volume status and cardiac contractility, left-sided heart status (Vet BLUE (ULRs) and LA:Ao), right-sided heart status (CVC and hepatic veins), the possibility of

Table 182.4 Use of global FAST for rapid assessment and monitoring of the critical dog and cat modified from the RUSH exam [33].

Global FAST evaluation	Hypovolemic shock	Cardiogenic shock	Obstructive shock	Distributive shock
Pump – how contracting?	Works	Deficient	Works –Overloaded	Works – Deficient
Inotropy	Hypercontractile heart	Hypocontractile heart	Hypercontractile heart	Hypercontractile heart (early sepsis)
	Small chamber size	Dilated heart	PCE/tamponade	Hypocontractile heart (late sepsis)
	Dry lung	Wet lung	RV strain (increased RV:LV) when PTE, cardiac thrombus	Dry > wet lung
			Dry >> wet lung	
Tank – how full?	Empty	Overfilled	Overfilled	Empty or Overfilled
Volume	Flat CVC	Distended CVC	Distended CVC	Normal or small CVC (early sepsis)
	Flat jugular veins	Distended jugular vein	Distended jugular	Peritoneal fluid (exudate/ sepsis source)
	Dry lung	ULRs (lung edema)	PTX (A-lines and no glide sign)	PE (exudate/ sepsis source)
		Wet lung	Dry or wet lung	Dry or wet lung
Pipes – leaky?	Leaky	Normal	Obstructed	Leaky or Distended
	Peritoneal fluid (loss)	Peritoneal fluid (ascites)	Thromboembolism	ARDS
	PE (loss)	PE		Third spacing
	Splenic or other intra-abdominal bleeding tumor			
Comments	Use Vet BLUE and AFS	Use Vet BLUE and AFS	Vet BLUE can detect PTE	Vet BLUE and tFAST can detect non-cardiogenic edema

AFS, abdominal fluid scoring; ARDS, acute respiratory distress syndrome; BLUE, bedside lung ultrasound exam; CVC, caudal vena cava; LV, left ventricle; PCE, pericardial effusion; PE, pleural effusion; PTE, pulmonary thromboembolism; PTX, pneumothorax; RV, right ventricle; ULR, ultrasound lung rocket.

drug reactions (dogs and the gallbladder halo sign), and assessment for effusions in four spaces (abdominal, retroperitoneal, pleural, and pericardial) plus lung edema [7,26,27,35,56,59,60]. The abdominal fluid scoring system allows for predicting the need for blood transfusion by differentiating small-volume bleeders (AFS 1,2) from large-volume bleeders (AFS 3,4) [2,3,6]. The cystocolic view urinary bladder volume estimation formula allows for estimating urine output when measurements are performed over time (see Figure 182.1)[57,58].

Lastly, global FAST may be performed with the abdominal preset and a single microconvex probe in <5–7 minutes by properly trained veterinarians [2,6,26,59,60] and global FAST accomplishes many of the same objectives as the combined use of FAST and the RUSH exam used by physicians (see Table 182.4) [26,33,59,60].

Global FAST for CPR and Advanced Life Support

When dogs and cats have unexplained hypotension, appear close to cardiopulmonary arrest (CPA) or have experienced CPA, minutes count and global FAST rapidly screens for potentially treatable conditions,

Table 182.5 Use of global FAST for rapidly ruling out your Hs and Ts in patients nearing cardiopulmonary arrest and during cardiopulmonary resuscitation. Source: Modified from AHA CPR guidelines.

The Hs	The Ts
Evaluated for using venous blood gas, physical exam, vital signs	Evaluated for using global FAST
Hypothermia	Tension pneumothorax
Hypotension	Trauma, hemorrhage
Hyperkalemia, hypokalemia	Thromboembolism
Hypoglycemia	Tamponade, pericardial effusion
Hydrogen ion (acidosis)	Toxin, anaphylaxis

including tension PTX, pulmonary thromboembolism, internal hemorrhage, pericardial effusion/tamponade, and anaphylaxis (Table 182.5) [6,26,54,59,60]. Moreover, global FAST serves as a monitoring tool directing fluid resuscitation and inotropic and vasopressor therapy through principles previously discussed and as shown in people (see Figure 182.1) [26,33,59–62].

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Thoracocentesis

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Introduction

Thoracocentesis is a straightforward procedure that is widely performed in veterinary practice, particularly in the emergency setting. Indications include the alleviation of respiratory distress due to pleural space disease, as well as to aid diagnosis. The procedure is rapid, relatively technically simple, and usually associated with minimal complication. Thoracocentesis does not require highly specialized equipment. It can be performed with or without ultrasound guidance and under light sedation and/or local anesthesia.

Recently, a veterinary thoracocentesis simulator model was validated for training purposes as part of an entry-level clinical skill set checklist [1]. Such simulator-based training has been demonstrated to significantly improve an individual's performance and level of comfort with the procedure [2]. However, most clinicians will learn to perform thoracocentesis on patients, either during veterinary school or in the early days of practice.

Indications

The goals of thoracocentesis may be therapeutic, diagnostic, or both. Animals with signs of respiratory difficulty due to pleural space disease are candidates for therapeutic thoracocentesis and animals with an unclear diagnosis and pleural effusion may have a thoracocentesis performed for diagnostic purposes, specifically to look for infection or neoplasia. Pleural space disease is typically suspected on physical examination and confirmed by point-of-care ultrasound or radiography (see Chapter 182). Dogs and cats being supported by positive pressure mechanical ventilation are also at increased risk of barotrauma, which may result in pneumothorax; this is more commonly a concern in longer duration ventilation (see Chapter 188).

Diagnostic thoracocentesis can be performed in patients with pleural space disease in the absence of significant respiratory signs. These patients usually have smaller volume effusions and do not require a therapeutic procedure. However, in any patient which undergoes thoracocentesis, it is important that samples are collected for fluid analysis (to include cell and protein counts), cytology, and bacterial culture and susceptibility if indicated. Brief in-house cytology is useful and can, for instance, aid in making the presumptive diagnosis of pyothorax if intracellular bacteria are present in the sample or neoplasia, such as lymphoma, in a cat with a mediastinal mass. If chylothorax is suspected, triglyceride and cholesterol concentrations should be submitted on both the fluid and serum for definitive diagnosis.

Contraindications

Thoracocentesis can exacerbate clinical bleeding in cases of coagulopathy, severe thrombocytopenia, or thrombocytopathia. In young dogs with pleural effusion, the clinician should be sure to rule out anticoagulant rodenticide toxicity prior to thoracocentesis as pleural hemorrhage is a common site for bleeding in such cases (see Chapter 130). Additionally, fractious or anxious patients must be adequately sedated and safely restrained to minimize risks of procedure (see Chapter 192).

Preparation and Considerations

Preparedness is strongly advocated in all aspects of clinical medicine, and may be life-saving in the event of fulminant pleural space disease, particularly if a tension pneumothorax is present (see Chapter 44, Pneumothorax). Emergency thoracocentesis set-ups, or "chest-tap kits" (Figure 183.1),

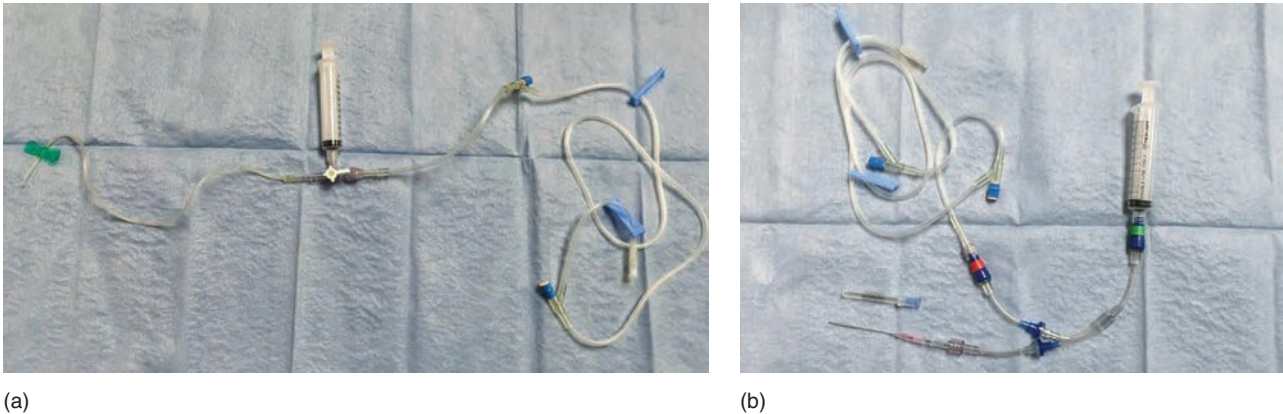


Figure 183.1 (a,b) Example of an emergency chest tap set-up which can be stored on a crash cart where it can be easily accessed, accompanied by butterfly catheter set-up.

should be assembled and stocked in easily accessible locations, such as within a crash cart or in a drawer next to the main triage area, as well as in the intensive care units. Sedation and analgesics may be indicated to reduce anxiety, treat pain, and minimize movement during the procedure (see Chapter 193). Local anesthesia may also be used.

Procedure

Gather supplies and prepare the patient (see Table 183.1 and Box 183.1 for a thoracocentesis procedure checklist and equipment options). Ensure anyone assisting with the procedure is comfortable with patient restraint, monitoring, and basic equipment handling (e.g. aspirating syringe, managing three-way stopcock). An area over

the appropriate rib spaces is clipped, typically between the seventh and ninth intercostal spaces, and aseptically prepped. This location over the thorax is chosen in order to avoid the heart and to avoid inadvertent sampling of the abdominal cavity. Ideal positioning will be somewhat

Table 183.1 Thoracocentesis procedure equipment options.

	Pros	Cons
Needle with extension tubing	Allows rapid penetration of chest wall without tissue drag, does not kink	Risks laceration of lung or blood vessels
Butterfly catheter	Ideal for small patients	May not be long enough for use in larger patients, risks laceration of lung or blood vessels
Over-the-needle catheter	Removal of stylet reduces risk of intrathoracic laceration, attachment of active suction for drainage of large-volume or chronic effusions	Often kinks once stylet removed, risks tissue drag through skin with wider bore catheters (≥ 16 G)

Box 183.1 Thoracocentesis equipment checklist.

- Clippers
- Aseptic scrub for prepping thorax
- Sterile gloves
- #11 scalpel blade (optional); only if large-gauge catheter use planned
- Syringes (10–60 mL; may depend on size of animal and volume of effusion)
- Three-way stopcock or smart “Y” bi-clave adapter
- Sterile needle, over-the-needle IV catheter or butterfly catheter
- Sterile extension tubing
- Collection bowl for fluid
- Supplies for fluid sample submission:
 - Red- and lavender-top tubes for fluid sample submission
 - Culturettes (aerobic and anaerobic)
 - Glass slides for cytology
- Oxygen (flow-by mask and/or cage for recovery)
- Assistant(s):
 - Help with restraint
 - Administer sedation as needed
 - Operate syringe and three-way stopcock
- Ultrasound machine (optional)
- Sedation or local anesthesia if desired

dictated by what is most comfortable for the patient. If a pneumothorax is present, air will rise to the top of the chest, making sternal or lateral recumbency acceptable. Conversely, effusion is gravity dependent and accumulates ventrally, making sternal recumbency better; dogs may stand if preferred. However, as the mediastinum is not complete in dogs and cats, fluid and air may usually be aspirated successfully from any location. Inadvertent abdominocentesis is more common if there is a large amount of ascites which results in the forward displacement of the diaphragm. Care must be taken to prevent undue stress caused by restraining a patient in lateral recumbency that is having difficulty breathing.

Identify Anatomical Landmarks

The point of entry for draining pleural effusion is just above the costochondral junction at approximately the seventh or eighth intercostal space. A more dorsal approach may be needed if treating pneumothorax, about halfway between the spine and the costochondral junction between the eighth and ninth intercostal space (Figure 183.2). The intercostal blood vessels run along the caudal border of the ribs and should be avoided.

Once the point of entry is identified, a local anesthetic block can be administered if desired and applied to the depth of the pleura. In unstable patients with the need to evacuate the chest urgently, this step should be skipped. Local anesthetics do cause a sting at the site of administration, and this additional stress may be counterproductive to the procedure. One part sodium bicarbonate may be mixed with nine parts lidocaine to reduce injection discomfort when used to block the intended thoracocentesis site.

Sterile gloves are often used for the procedure to permit palpation of the thoracic wall prior to thoracocentesis. The

point of entry site is palpated and the needle is advanced through the skin cranial to the adjacent rib to avoid lacerating intercostal vessels running caudally. For thoracocentesis, a 20 or 22 gauge needle with an attached extension set, a butterfly catheter or over-the-needle IV catheter may be used based upon clinician preference (see Figure 183.1). In cats, a butterfly catheter (21 gauge) is most commonly used, with the exception of large cats, where a 1.5" needle may be required to gain access to the pleural space.

For cases with large-volume effusions, the extension tubing may be attached directly to an active suction unit to expedite drainage. Since negative pressure will not be detected with this method, the collection canister is monitored and once fluid production ceases, the suction unit is switched off and a final attempt at hand aspiration is made. If pleural evacuation endpoints are unattainable in the presence of a large-volume pneumothorax, or if repeated thoracocentesis is required within a short period of time, thoracostomy tube placement and continuous suction are likely indicated.

Complications

In general, thoracocentesis is a low-risk procedure, but complications can occur. The most common acute complication is iatrogenic pneumothorax due to laceration of the pulmonary parenchyma or excessive generation of negative intrathoracic pressure and subsequent ripping of unexpandable lung [3]. While iatrogenic laceration is easy to understand, the concept of unexpandable lung is perhaps less so. In this scenario, long-standing effusion results in small restricted lungs, covered with fibrotic pleura. In people, unexpandable lung is further divided into trapped lung and entrapped lung. Entrapped lung occurs during active pleural disease, and trapped lung develops following recovery from prior pleural space disease. Increasing pleural effusion results in a positive intrathoracic pressure. As this fluid is drained, the pressure in the chest becomes increasingly more negative, and this will result in the formation of pleural–pneumo fistulae that permit air leakage. Iatrogenic hemorrhage from laceration of intrathoracic blood vessels can occur, but is usually mild and self-limiting. Occasionally, stress caused by restraint may lead to rapid decompensation and even death from respiratory arrest in unstable patients. It is important to note that *more* complications are associated with not performing thoracocentesis and permitting persistent respiratory distress.

Postprocedure Monitoring

Patients should be monitored closely following thoracocentesis for signs of new or progressive



Figure 183.2 Thoracocentesis procedure performed with polypropylene over-the-needle catheter and a smart “Y” adapter instead of a three-way stopcock.

respiratory distress. Such signs may represent an iatrogenic complication, such as pneumothorax or hemothorax, or re-expansion pulmonary edema (less common). Postprocedure thoracic FAST can be used to reassess the residual volume of effusion, aid in detection of pneumothorax, and help guide the deci-

sion on whether or not to re-tap (see Chapter 182). Additionally, postprocedure radiographs may be obtained and compared with baseline images to optimize detection of soft tissue mass lesions that may have been obscured by the presence of effusion prior to thoracocentesis.

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Thoracostomy Tube Placement

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Indications for Thoracostomy Tubes

Thoracostomy tubes, also referred to as chest tubes or thoracic drains, are used to remove air and/or fluid from the pleural space [1]. The evacuation of the pleural space may be a life-saving intervention, specifically when the continuous presence of air or effusion cannot be managed by intermittent thoracocentesis alone. In practice, this may include cases in which frequent intermittent thoracocentesis is necessary (e.g. >3 thoracocentesis procedures performed in 12–24h). In these cases, the presence of an indwelling thoracostomy tube may be associated with improved patient comfort and welfare compared to performing repeated thoracocentesis procedures. Thoracostomy tubes may also be utilized therapeutically for locoregional analgesia and pleurodesis. Pleurodesis involves the delivery of a substance (e.g. whole blood, chemotherapy) via a thoracostomy tube into the pleural space with the intention of artificially obliterating the space by promoting adhesion of the pleural membranes.

Pneumothorax

Pneumothorax may be considered spontaneous [2–5], traumatic [6] or iatrogenic [7] (e.g. during mechanical ventilation or following thoracocentesis) (see Chapter 44). Intermittent thoracocentesis may be sufficient for the management of non-recurrent and low-volume pneumothorax in animals. Thoracostomy tubes are indicated when there is large-volume and/or rapid accumulation of air in the pleural space causing respiratory embarrassment. This typically occurs in animals with spontaneous pneumothorax (e.g. secondary to ruptured pulmonary bullae) and in patients recovering from thor-

acotomies rather than in cases of traumatic pneumothorax [8]. Local analgesia can also be provided safely via thoracostomy tubes (i.e. interpleural block) in patients recovering from lateral thoracotomies and following trauma [9]. Alternative approaches to analgesia in these patients, including subcutaneous wound soaker catheters, intercostal analgesia, and systemic analgesia, may also be reasonable depending on specific patient considerations and clinician preference (see Section 7).

Thoracostomy tubes can be used for autologous blood patch in cases of recurrent spontaneous pneumothorax or persistent pneumothorax in the patient recovering from pneumectomy [10]. This technique has been described in dogs with persistent pneumothorax with a reported good success [10], although it is likely inferior to definitive surgical treatment of spontaneous pneumothorax in most cases.

Pleural Effusion (see Chapter 45)

Pleural effusion, irrespective of the etiology, may benefit from thoracostomy tube placement if the effusion is persistent, rapidly accumulating or necessitating frequent thoracocentesis procedures. Continued drainage is additionally beneficial in some specific situations such as pyothorax [11], where drainage of infected material helps with source control. The presence of the thoracostomy tube in specific patients following surgery may also be advantageous. For instance, a thoracostomy tube in a dog recovering from an esophagotomy enables the clinician to monitor the characteristics of any pleural effusion (e.g. cellularity, presence of bacteria) in a minimally invasive way. In this example, the thoracostomy tube may enable the clinician to identify dehiscence of the surgical site definitively if new septic suppurative effusion develops.

Thoracostomy tubes can also be used for the delivery of chemotherapy drugs (e.g. cisplatin, carboplatin) into the pleural space in cases of chronic, recurrent malignant pleural effusions [12,13].

Preparation for Placement

Thoracostomy tubes are usually placed under sedation or general anesthesia [8] (see Chapters 190–193). It is advisable to have the patient intubated when using large-bore trocar type tubes to allow temporary intermittent positive pressure ventilation and brief apnea. The patient should not receive any assisted breaths during the insertion and advancement of the thoracostomy tube. The lateral aspect of the thorax should be clipped between the sixth and 10th intercostal spaces and aseptically prepared. Systemic opioids and locoregional analgesia (e.g. intercostal block) can be considered prior to placement of the tube. Preoxygenation is advisable prior to induction of anesthesia.

Tube Types

Several tubes can be considered for use in small animals: trocar type, small-bore wire-guided tubes placed using the Seldinger technique [14], and red rubber catheter tubes. Thoracostomy trocar tubes are stiffer than the wire-guided and red rubber catheters, so are less prone to kinking. Stiffer tubes are associated with increased discomfort and do require general anesthesia for placement.

Tube size will depend on patient size and is roughly comparable to the diameter of the mainstem bronchi [8]. A 14–16 French tube is suitable for cats and small dogs, while large dogs can take a 24–26 French tube. Other items required include Christmas tree connectors, tubing with a Luer-Lok, a non-collapsing extension set, and a three-way stopcock [11]. A pack with the aforementioned materials, blades (both number 10 and 15), sterile thoracostomy tubes, sterile gauze, instrument set consistent with a hemostat, needle holder, scalpel holder, suture scissors, and tube clamp should all be readily available for use [11].

Tube Placement Techniques

Trocar Tubes

Trocar tubes should be placed under general anesthesia (see Chapter 191). The patient is placed in lateral recumbency and an assistant pulls the skin cranially. A midthoracic area should be clipped and aseptically prepared.

Different techniques can be used for the placement of these tubes. One technique involves making a full-thickness incision at approximately the 10th to 11th intercostal space. The trocar tube is advanced through the skin incision and then advanced to the level of the seventh or eighth intercostal space.

An alternative technique involves the use of a Kelly hemostat to bluntly dissect through a partial-thickness intercostal space incision. The tube should be gripped with the non-dominant hand close to the distal end of the tube to prevent accidental overadvancement into the thoracic cavity.

Once the thoracostomy tube is in place, it can then be reorientated so it may be advanced off in a cranio-ventral direction. Once in place, the assistant can stop pulling the skin forward, enabling the skin to retract back and thus creating a tunnel for the tube. A connector with three-way stop cock and syringe can be attached to ensure air and/or fluid is collected, depending on the underlying disease. Postprocedural thoracic radiographs are recommended to verify tube position. The tube can be secured with a purse-string suture around its base and then further secured with a finger trap pattern [11].

Wire-Guided Tube

These tubes are becoming increasingly popular in small animal emergency practice given the technical ease with which they can be placed compared to trocar style tubes. These smaller bore tubes also appear to be less painful compared to the larger bore tubes.

A small incision can be made in the skin using a #11 blade in the skin overlying the intended intercostal space (e.g. seventh to ninth). A standard over-the-needle style catheter is inserted through this incision into the pleural space. The stylet is removed from the catheter, enabling passage of a guidewire into the pleural space. The catheter is then removed over this guidewire, allowing for the insertion of a pliable thoracostomy tube over the guidewire. Once the tube is in the pleural space, the guidewire can be removed, a closed valve attachment is applied to the end of the tube, and the tube is secured to the external chest wall. A specific plastic butterfly attachment included in the thoracostomy tube kit is usually secured to the tube itself. This enables the placement of nylon skin sutures through the attachment securing the tube to the skin.

Red Rubber Catheter

A simple sterile red rubber catheter may also be used as a chest tube if no other options are available. To make it more functional as a chest tube, additional fenestrations can be added to the end of the catheter. The tube

can be placed in a similar fashion to the trocar tube by making a skin incision over the appropriate intercostal space. A tunnel can be created with blunt dissection using a Carmalt or Kelly forceps, allowing passage of the catheter to about the level of the seventh intercostal space.

Thoracostomy Tube Maintenance and Care

Strict aseptic care of the thoracostomy tube is required after placement, although prophylactic antibiotics are uncommonly recommended. A barrier over the tube itself (e.g. body stocking, self-adhesive bandage) can be considered and changed daily if used. A tubing clamp is usually recommended in addition to the three-way stopcock. An e-collar should be used to prevent patient interference. Analgesia is essential for these patients as well as close monitoring of respiratory rate and effort (see

Chapter 193). Chest tubes should be removed as soon as they are no longer needed [1]. For cases of pneumothorax, usually no or very mild air production is necessary before a tube is removed. In cases of pleural effusion, it should be remembered that the presence of the tube itself will be associated with some mild effusion. In these instances, a low volume of effusion that is not causing respiratory distress is usually acceptable.

Complications

Thoracostomy tubes are usually well tolerated but potential complications include infection, hemorrhage, visceral injury during placement, and re-expansion pulmonary edema [1]. Additionally, the clinician should recall that the presence of a thoracostomy tube does not exclude clinically significant pleural space disease, as a tube may kink or become occluded.

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Pericardiocentesis

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Etiology and Indications for Pericardiocentesis

Pericardial effusion can be caused by cardiac neoplasia such as hemangiosarcoma, chemodectoma, lymphoma, ectopic thyroid carcinoma, mesothelioma, and several non-neoplastic disorders such as idiopathic pericarditis, constrictive pericardial disease, congestive heart failure, left atrial tear, hypoproteinemia, and infection [1–3]. Causes of pericardial effusion are described in greater detail in Chapter 54.

Pericardiocentesis is warranted when pericardial effusion is causing cardiac tamponade (Figure 185.1). The European Society of Cardiology (ESC) has established guidelines for management of pericardial diseases in people as well as indications for pericardiocentesis; cardiac tamponade is considered a class I indication (i.e. very strong recommendation) [4,5]. Cardiac tamponade occurs when intrapericardial pressure exceeds the

pressure within the right atrium and/or right ventricle during diastole, leading to reduced right heart filling and a resultant decrease in cardiac output. Cardiac tamponade can occur with either a large or small volume of pericardial effusion, so the volume of effusion should not be the main trigger for pericardiocentesis. Cardiac tamponade is present when hemodynamic compromise is evident; clinical signs consistent with tamponade include hypotension, jugular venous distension, tachycardia, tachypnea, and cardiogenic shock [6–8]. Signs of right-sided congestive heart failure such as ascites may be identified and may indicate chronic cardiac tamponade. The degree of hemodynamic compromise depends upon both the volume of effusion and the rate of fluid accumulation, with acutely developing effusions causing tamponade with relatively small volumes of effusion.

Cardiac tamponade can be suspected based on clinical examination findings such as pulsus paradoxus, tachycardia, muffled heart sounds, jugular venous distension, or mucous membrane pallor [7,8]. Electrocardiographic signs that may be observed include sinus tachycardia, low-voltage QRS complexes, electrical alternans, or ST segment changes, and radiographic findings can include cardiomegaly with globoid cardiac silhouette or a distended caudal vena cava [7,8]. Confirmation of cardiac tamponade is usually made by assessment with echocardiography with classic findings of an anechoic or hypoechoic space between the pericardium and epicardium and collapse of the right atrial and/or right ventricular wall (Video Clip 185.1). A complete echocardiogram is ideally performed prior to pericardiocentesis as cardiac masses are easier to visualize with the pericardial effusion still present, but in unstable cases pericardiocentesis should be done immediately.

Pericardiocentesis may be performed to relieve tamponade or in order to obtain a diagnostic sample for fluid analysis and cytology. It is less frequently indicated in cats for tamponade, and should be performed with caution as

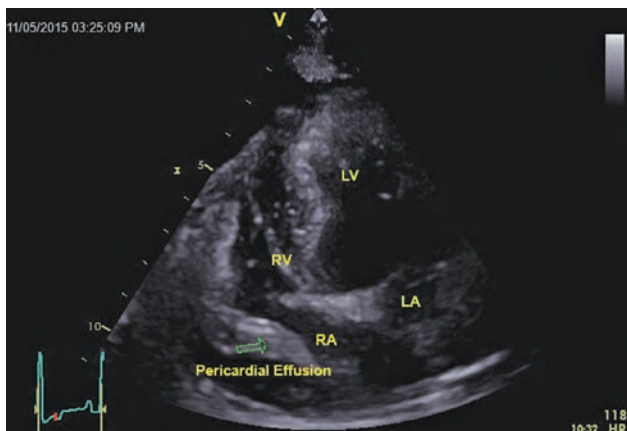


Figure 185.1 Still image of echocardiogram from the left apical view depicting presence of pericardial effusion and collapse of the right atrial wall (arrow) consistent with cardiac tamponade.

the space between the pericardium and the epicardium can be less than 0.5 cm, increasing the chance for cardiac trauma during pericardiocentesis.

Contraindications

Pericardiocentesis is contraindicated or relatively contraindicated in animals with active hemorrhage into the pericardial sac and those with coagulopathy. The most common situation where active bleeding might preclude pericardiocentesis is cardiac tamponade secondary to left atrial splitting/left atrial rupture (Video Clip 185.2). The typical example might be a geriatric, small-breed dog with degenerative mitral valve disease, pericardial effusion, thrombus in the pericardial space, and signs of hemodynamic compromise. If a left atrial tear is suspected then pericardiocentesis should be withheld, except in animals with cardiogenic shock at risk for cardiopulmonary arrest in which case the benefits of pericardiocentesis might outweigh the concerns of hemorrhage into the thoracic cavity after pericardiocentesis. Suspected or known coagulopathy is another relative contraindication for pericardiocentesis (e.g. vitamin K rodenticide intoxication). Finally, if pericardial effusion is secondary to congestive heart failure (CHF), then the effusion might resolve with treatment of CHF and pericardiocentesis might not be required (especially in cats).

Sedation (see Chapter 192)

Sedation may be indicated to perform pericardiocentesis and should be assessed on a case-by-case basis. Evaluation of the patient's stability, alertness, temperament, and potential for sudden movements may determine whether sedation is indicated and to what degree. In severely ill or decompensated patients, sedation is often not required. The authors prefer to use an opioid or a combination of an opioid with a benzodiazepine (e.g. butorphanol 0.2 mg/kg with midazolam 0.2 mg/kg). Drugs that might compromise hemodynamic situation such as alpha-2 agonists should be avoided.

A local anesthetic block can be performed within the intercostal space with lidocaine or bupivacaine. Sodium bicarbonate can be added to the local block to neutralize the acidic pH and reduce discomfort associated with the block (1 part sodium bicarbonate to 9 parts lidocaine).

Equipment

Supplies for pericardiocentesis can vary based on clinician preference and availability of certain equipment. In

most situations, necessary supplies include clippers and antiseptic solution(s) for aseptic skin preparation, sterile gloves, #11 scalpel blade for stab skin incision, catheter with stylet for pericardiocentesis (e.g. 16 gauge $\times$ 5½ inch IV catheter with stylet, large-bore trocar catheter, or a specific centesis catheter), three-way stopcock, extension set, syringes of varying sizes to aspirate the effusion, sample collection tubes (red top tube and EDTA tube), and a container to collect fluid. The size of the syringes may be based on clinician preference, size of patient, and volume of pericardial effusion present. If indicated in a cat, pericardiocentesis is typically performed using a smaller catheter or needle (e.g. 18 or 20 gauge 1.5 inch needle or catheter).

Ideally, ultrasound imaging is available for ultrasound-guided pericardiocentesis and electrocardiographic monitoring.

Procedure

Ideally, pericardiocentesis would be performed in a quiet setting or environment to avoid sudden movement secondary to loud stimuli. The patient should be sedated if indicated, local anesthetic block drawn up, electrocardiographic (ECG) monitoring hooked up to observe for cardiac arrhythmias, the patient properly positioned, and all supplies gathered and readily accessible. The patient should have a peripheral intravenous catheter already in place to allow for administration of sedation and venous access in case emergency antiarrhythmic or resuscitation drugs are indicated. A defibrillator should be readily accessible if possible.

Positioning

The patient can be positioned in sternal or lateral recumbency as determined by clinician preference. A right-sided approach is preferred, between the third and fifth intercostal spaces, typically at the left fifth intercostal space. Patients with dyspnea may prefer to be positioned in sternal recumbency. A right-sided approach is preferred based on anatomy as the cardiac window (cardiac notch) is larger on the right hemithorax [8,9]. Approach via the left hemithorax is less desirable due to the anatomical location of the coronary arteries and risk of vascular damage with the catheter or needle.

Procedural Monitoring

Prior to performing the pericardiocentesis, ECG monitoring should be established to identify baseline arrhythmias and observe for ventricular arrhythmias during the procedure. A 2 mg/kg dose of lidocaine should be drawn

up and on hand in case it is required during the procedure. Arrhythmias may indicate that the catheter tip is in contact with the myocardium and when noted they should trigger a relocation of the catheter or a temporary termination of aspiration on the syringe. Typically, patients with cardiac tamponade are tachycardic and as the tamponade is relieved, the heart rate should decrease and return to normal. ECG monitoring should be continued in the postprocedural period as arrhythmias may develop post pericardiocentesis.

Technique

The right hemithorax is shaved and a location for the pericardiocentesis is chosen between the third and fifth intercostal spaces, ideally based on ultrasonic guidance (Figure 185.2). A mental note of this location can be made or it can be demarcated with a permanent marker. A local anesthetic block can be administered, and the chest should be prepped in an aseptic fashion.

Sterile gloves should be worn and the syringe can be attached to the extension tubing and three-way stopcock.

At the desired site for centesis, a #11 blade is used to make a hole in the skin large enough to accept the stylet and catheter, such that the catheter is not burred as it advances through the skin. With the stylet advanced all the way into the catheter, the catheter and stylet are advanced through the skin and subcutaneous tissues, through the intercostal space and into the pleural space. Occasionally, a “pop” is felt as the catheter enters the

thoracic cavity and/or the pericardial space. This deliberate puncture should be slow but continuous as the catheter is inserted ~2.5–5 cm into the thoracic cavity. As the catheter is being inserted and enters the pericardial space, the stylet should be removed from within the catheter. After puncture and flashback, the position of the needle can be confirmed via agitated saline under echocardiographic guidance [6]. A modified transudate of pleural effusion may be seen before pericardial effusion is noted.

A syringe, three-way stopcock, and extension tubing are attached to the catheter and gentle negative pressure is applied to obtain samples for fluid analysis and assessment of clotting of the effusion. If ventricular arrhythmia is observed on the ECG or if it feels as though there is tissue against the catheter tip, the catheter should be slightly pulled outward.

If there is uncertainty whether the catheter is appropriately located within the pericardial space, the ultrasound probe can be placed near the catheter and a contrast echocardiogram can be performed. Ultrasonography can be used to assess if the amount of effusion is reduced and whether there is resolution of cardiac tamponade. Femoral pulses and mucous membrane color should be assessed for improvement post pericardiocentesis. Clinical improvement, ultrasonographic evidence of improvement, lack of additional fluid being obtained, or resistance at the catheter tip may all be used to determine that the catheter should be retracted from the thoracic cavity.

Samples to Obtain and Submit

At a minimum, the pericardial effusion obtained from the pericardiocentesis should be placed in an EDTA lavender top for cytology and fluid analysis and within a non-additive red top tube. The effusion placed within a non-additive tube should be assessed for the presence of clotting versus non-clotting hemorrhagic effusion during pericardiocentesis. Fluid obtained from within the pericardial sac should be non-clotting in most cases, and if the fluid does clot then this is indicative of an intracardiac puncture or active ongoing bleeding from the source (i.e. a mass). If clotting of the aspirated fluid occurs then the catheter should be immediately retracted and the animal should be re-evaluated.

Postprocedure Monitoring

Within the 12–36 hour post pericardiocentesis, continuous ECG (telemetry) monitoring is advised to evaluate for ventricular arrhythmias, which are sometimes severe enough to require treatment. The mucous membrane color and refill time, heart rate, respiratory rate, and

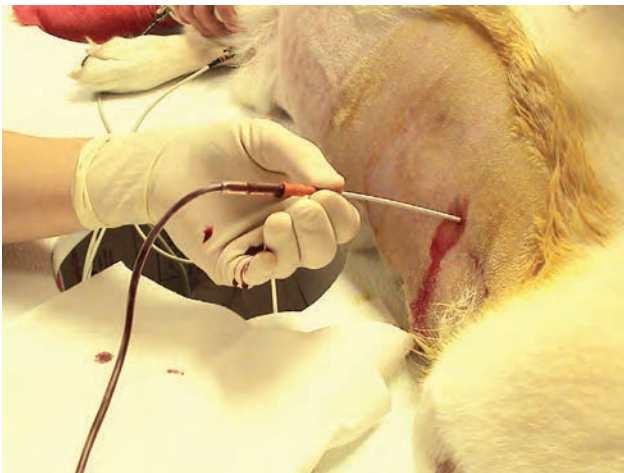


Figure 185.2 Image depicts a pericardiocentesis being performed at the level of the fifth intercostal space. Patient is positioned in left lateral recumbency with the right hemithorax clipped and aseptically prepared. ECG leads are attached to the patient. The clinician is wearing sterile gloves to hold the catheter in place. A hemorrhagic effusion is being aspirated and visualized within the extension tubing.

femoral pulse quality should be monitored to assess for evidence of recurrent effusion. Serial ultrasound evaluation should be performed if recurrence is suspected or if hemodynamic instability develops. Pleural effusion may develop if ongoing bleeding from the heart leaks from the hole made in the pericardial space and into the pleural cavity. Volume support with administration of intravenous fluids may be indicated, based on clinical signs or clinician preference.

Complications

Potential complications resulting from pericardiocentesis include ventricular arrhythmias, sudden death, laceration or perforation of the myocardium or great vessels, hemorrhage into the pleural space or recurrent pericardial effusion, pneumothorax, or introduction of infection into the pericardial space.

The rate of major complications following pericardiocentesis using ultrasonic guidance in people is 1.3–1.6% compared to 20.6% rate of life-threatening complications with an unguided, blind approach [9]. For veterinary patients, ultrasound guidance, if available, is recommended in order to minimize the risk of complications and determine the best window for pericardiocentesis.

In a study by Humm et al., the incidence of adverse events was 10.7% within 1 hour of pericardiocentesis and 15.2% (17 out of 85 dogs) within 48 hours, based on retrospective evaluation of 85 dogs (112 episodes of pericardiocentesis) with varying etiologies of pericardial effusion [3]. The most commonly observed complication was arrhythmia requiring drug therapy in 11 out of the 17 patients with observed complications, followed by cardiopulmonary arrest in four patients, and continued bleeding into the pericardium which resulted in euthanasia in three out of 17 cases. There was no significant difference between frequency of pericardiocentesis and etiology of pericardial effusion in relation to the risk of adverse events in this study [3].

Pearls of Wisdom

Ultrasound-guided pericardiocentesis is preferred to determine the most appropriate window with the least chance for cardiac trauma or perforation. During pericardiocentesis, if there is concern regarding location of the needle or catheter, contrast echocardiography can help to determine whether they are within the pericardial space. Injection of a small volume of agitated saline through the catheter should result in visualization of microbubbles within the pericardial sac via ultrasonography.

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Abdominocentesis*Karl E. Jandrey, DVM, MAS, DACVECC**School of Veterinary Medicine, University of California, Davis, CA, USA***Introduction**

The decision to take a patient with abdominal disease to emergency surgery is predicated on the accuracy of the diagnosis. The challenge is to determine when surgery is indicated based on vague abdominal signs. Besides serial physical examinations for the assessment of increasing abdominal size or progressive pain, samples of peritoneal fluid obtained by abdominocentesis or diagnostic peritoneal lavage can yield the specific diagnosis of an abdominal disease process and lead to focused surgical or medical intervention.

Indications

Indications for abdominocentesis are listed in Box 186.1 [1]. In general, blind abdominocentesis is considered when free abdominal fluid is suspected or unknown abdominal disease is present. Periumbilical ecchymosis (Cullen's sign) may be associated with hemorrhage in the peritoneum or retroperitoneum and can be an indication

Box 186.1 Indications for abdominocentesis [1].

- Radiographic loss of serosal detail
- Free abdominal fluid detected on ultrasound
- Abdominal injury without obvious peritoneal entry wounds
- Shock, multiple injuries, or signs of abdominal injury after blunt trauma
- Head or spinal injury precluding reliable abdominal examination
- Persistent abdominal pain or fluid distension of unknown cause
- Postoperative complications possibly caused by leakage from an enterotomy or anastomotic site

for abdominocentesis. Relative contraindications to abdominocentesis include coagulopathy, organomegaly, and distension of abdominal viscera. Intestinal or uterine penetration is rare unless the viscus is dilated and/or adherent to the abdominal wall [2]. Ultrasound-guided abdominocentesis allows directed aspiration of abdominal free fluid. With ultrasound-guided techniques, the risk of abdominocentesis is considered far less than blind techniques. Proper technique attempts to prevent the introduction or spread of infection, laceration of an organ, or hemorrhage from a punctured vessel.

Technique

Abdominocentesis is completed using a single paracentesis (open or closed needle technique) or a four-quadrant approach. Ultrasound guidance can highlight a smaller accumulation of fluid and allow for a more directed approach. The site for blind single paracentesis lies caudal to the umbilicus to avoid the falciform fat. Four-quadrant abdominocentesis encircles the umbilicus. Use of ultrasound may more directly guide the best location based on the size and accessibility of the fluid pocket within the peritoneum.

Focused Assessment with Sonography for Trauma (see Chapter 182)

The focused assessment with sonography for trauma (FAST) protocol was studied in dogs to prove that it is a rapid and simple technique to allow veterinary clinicians with minimal previous ultrasound experience to detect free abdominal fluid in the emergency room [3]. This technique scans four regions (caudal to the xyphoid process, midline over the urinary bladder, and each flank) in longitudinal and transverse planes of the abdomen with

patients in lateral recumbency. If free abdominal fluid is detected, ultrasound-guided abdominocentesis may be indicated.

Preparation of the Patient

Patient positioning in left lateral recumbency may be most effective to avoid puncture of the spleen. This is particularly relevant to blind abdominocentesis. Restraint may be completed manually or with the use of sedatives and analgesics (see Chapters 192 and 193). Prior to penetration of the abdomen, a wide surgical clip and preparation of the site using aseptic technique must be completed in the region identified for paracentesis. If using a blind technique, this will be along the ventral midline centered at the umbilicus. Alternatively, if an abdominal ultrasound has identified a focal pocket of fluid, a standard aseptic clip and preparation at that location is prudent.

Closed-Needle Abdominocentesis

A closed-needle diagnostic abdominocentesis can be completed using a 22 or 24 gauge needle attached directly to a 3, 6 or 12 ml syringe, or attached to a syringe via an extension set. Local anesthetic infusion of 2% lidocaine may be used at the abdominocentesis site. With a blind approach, penetration of the abdominal cavity can be completed on the midline, caudal to the umbilicus. The location of abdominocentesis is ideally determined by ultrasound guidance.

The needle is gently inserted completely at this site and further movement of the needle tip is avoided to prevent laceration of internal structures. The syringe is aspirated to remove peritoneal fluid. If the fluid is hemorrhagic it should be observed for the formation of clots. Ideally, the hemorrhagic fluid should be placed in a glass container such as a plain blood tube to evaluate for clot formation. Free fluid within the abdominal cavity should not clot while hemorrhagic fluid obtained from puncture of the spleen, liver or any vessel will readily clot. If clotting of the abdominal fluid is observed, the needle should be removed and abdominocentesis attempted in another location. Cytological, biochemical analysis and culture of the abdominal fluid should be performed, as indicated, on the collected fluid.

The advantages of the closed needle technique include greater ability to avoid contamination of the fluid sample or abdominal cavity. It may also require less manipulation of the needle while it is in the abdomen so it may be less likely to be traumatic. Free gas should not be evident on radiographs after a closed-needle abdominocentesis.

A closed-needle abdominocentesis can also be used for therapeutic removal of peritoneal fluid. Therapeutic

removal of large volumes of fluid may be indicated if the abdominal distention impairs diaphragmatic motion, increases intra-abdominal pressure impeding blood flow to the visceral organs, or is painful for the patient. To maintain a closed system, a three-way stopcock can be placed between the syringe and extension set. Another extension set placed on the stopcock can be directed into a bowl or graduated cylinder. A large over-the-needle catheter may be preferable to the use of a hypodermic needle as it may reduce the risk of internal organ injury.

Open-Needle Abdominocentesis

An open-needle abdominocentesis is an alternative method for blind abdominocentesis. It is completed in a similar fashion to that described for a closed-needle technique, except the needle alone is inserted into the peritoneal cavity. Fluid from the peritoneum is allowed to flow freely through the needle into a container or sample submission tube. Rotation of the needle hub may facilitate flow. This technique may help prevent occlusion with or aspiration of omentum or intestinal viscera. It may be a more successful technique as false-negative results are more likely to occur if suction is applied during paracentesis [4]. Free abdominal gas on radiographs is possible after this procedure.

Four-Quadrant Abdominocentesis

A modification of the open-needle technique is the four-quadrant abdominocentesis. Instead of one open needle, four open needles are placed simultaneously in each quadrant surrounding the umbilicus. Gravity dependency or changes in transabdominal pressure between the needles may increase the likelihood of obtaining fluid. One study using a four-quadrant technique in dogs showed that fluid was obtained in 78 of 100 needle paracenteses when 5.2–6.6 mL of abdominal fluid/kg body weight was present [5].

Alternative Techniques for Abdominocentesis

The use of a peritoneal dialysis catheter for abdominocentesis has been shown to detect 1.0–4.4 mL of abdominal fluid/kg body weight, so it may increase the sensitivity of a blind technique [6]. A larger diameter and multiple fenestrations make this apparatus more reliable for detecting smaller volumes of peritoneal fluid compared to a standard needle or catheter. Commercial peritoneal dialysis catheters work well, but over-the-needle catheters can be carefully fenestrated and used with good results. The use of a 14 or 16 gauge, over-the-needle catheter with multiple, small fenestrations placed manually using a #10 scalpel blade can increase the surface area for

drainage. There are also commercially available, fenestrated paracentesis catheters available for this purpose. The use of a fenestrated catheter increases the likelihood of fluid collection compared to needle abdominocentesis alone [7]. A fenestrated catheter can also be a useful technique for therapeutic abdominal fluid removal.

Diagnostic Peritoneal Lavage

Diagnostic peritoneal lavage (DPL) is performed when alternative diagnostic methods such as sonography are unavailable, or when the patient's condition does not allow other diagnostics or imaging to be performed. Patient positioning, use of sedatives, and preparation of the site are similar to abdominocentesis. Local anesthetic infusion of 2% lidocaine should be placed at the puncture site either at the umbilicus or 2–3 cm lateral to it to avoid the falciform fat.

A small stab incision is made in the skin with the #11 scalpel blade at the site of local anesthetic infusion. The fenestrated catheter, such as a commercially available peritoneal dialysis catheter, is introduced through the incision completely into the abdomen. Slow gentle rotation of the closed-end, dialysis catheter is needed to overcome considerable resistance from fascial planes and the linea alba. If a fenestrated over-the-needle catheter is used, the catheter is advanced completely off the stylet once the tip of the catheter has penetrated the peritoneal cavity. A syringe may be attached to the catheter at this point. If no peritoneal fluid is obtained, saline is infused into the abdomen through the catheter. A volume of 22 mL/kg of warm, sterile 0.9% sodium chloride is infused by gravity through a drip set attached to the catheter. The abdomen is gently massaged or the patient is rolled without dislodging the catheter to distribute the saline throughout the abdomen. A syringe is attached and gently aspirated or fluid is allowed to flow by gravity into a collection container or back into the drip set and fluid bag.

Large volumes of fluid are generally not obtained due to the wide dispersion throughout the abdomen. Any amount retrieved should be submitted for biochemical and cytological evaluation including culture and sensitivity testing. Fluid samples from a DPL must be interpreted in light of the dilution effect of this collection method.

Abdominal Fluid Analysis

Paracentesis Sample

Packed cell volume (PCV), total protein (TP), creatinine, glucose concentration, and blood urea nitrogen (BUN) should be measured from the peritoneal fluid sample.

Potassium and lactate are other biochemical markers that can be tested to add diagnostic value to the fluid sample. If the PCV of the peritoneal fluid exceeds the peripheral PCV, it is suggestive of parenchymal organ laceration or large vascular disruption. Hemodilution with urine may cause a decreased PCV of abdominal fluid in patients with both abdominal hemorrhage and urological injury. Uroabdomen can be diagnosed from simultaneous measurement of creatinine and potassium in both the abdominal fluid and peripheral blood. Because of its high molecular weight, a creatinine concentration in the abdominal fluid higher than twice that of peripheral blood is highly suggestive of free urine in the abdominal cavity [8]. An increased ratio of potassium in the abdominal fluid compared to peripheral blood (greater than 1.4:1) also suggests urological injury [8]. Rapid assessment and comparison of the BUN in abdominal fluid and peripheral blood can be completed using reagent strip technology. However, BUN can readily equilibrate across the peritoneal lining and is less reliable for the diagnosis of uroabdomen.

Cytological Analysis

Cytological analysis of cellular effusions is always recommended and culture of abdominal fluid with susceptibility testing should be submitted if sepsis is possible. Emergency cytological analysis often assists the clinician in initiating appropriate therapy. In many cases, the decision for medical versus surgical therapy can be readily apparent before official clinical pathological analysis.

The gross appearance of the fluid should be examined. An abdominal fluid sample that is completely clear and colorless makes the diagnosis of peritonitis, severe intra-abdominal injury or perforation, and leakage from the gastrointestinal tract less likely [4]. Fluid that appears opaque, cloudy, or flocculent should be examined immediately. Since accurate hemocytometer analyses are less commonly completed in practice, the cell concentration must be estimated. The higher the cellularity ($>10,000/\mu\text{L}$) and protein concentration ($>3.5\text{ g/dL}$), the more likely the fluid is an exudate; surgical therapy may be indicated, especially if the microscopic analysis shows intracellular bacteria. The lowest cell ($<2,500/\mu\text{L}$) and protein concentrations ($<2\text{ g/dL}$) may be transudates; therefore, continued therapy is more likely to be medical. Modified transudates may have more cells and a lower protein concentration (or fewer cells and a higher protein). Other clinical data may be needed in these cases to more clearly direct the next therapeutic step.

A direct smear that has been dried and stained appropriately can be examined at low power for large particulate material such as plant material or crystals. High-power magnification is used to identify

bacteria, fungi, and blood cells. Intracellular bacteria (with or without extracellular bacteria) and degenerate neutrophils characterize a septic effusion. Surgical intervention should be considered and undertaken immediately if this is found, often prior to confirmation by a reference laboratory. Surgery is not necessarily indicated when only extracellular bacteria are found in the fluid sample.

Glucose and lactate measurements on peritoneal fluid can also aid in the diagnosis of septic peritonitis. In one prospective analysis of 18 dogs with septic effusion, peritoneal fluid glucose concentration was always lower than the blood glucose concentration [9]. A blood-to-peritoneal fluid glucose difference >20 mg/dL was 100% sensitive and 100% specific for the diagnosis of septic peritoneal effusion in dogs.

With gall bladder or common bile duct injury, the clinical signs of icterus may be delayed. A dark green to black or dark amber color of peritoneal fluid suggests the presence of bile pigments. Peritoneal fluid can be analyzed for total bilirubin. If the abdominal fluid bilirubin is significantly greater than peripheral bilirubin, then bile peritonitis is present.

Diagnostic Peritoneal Lavage Samples

Cytological characteristics of the white cells are more meaningful than absolute cell counts due to dilutional consequences of a DPL [2,10]. In a study comparing pre- and postoperative DPL samples, recent surgery increased the white blood cell count from normal (1000 cells/mm³)

to usually less than 10000 cells/mm³ [11]. Elevations in the peritoneal white blood cell count in response to sepsis occur over variable time periods [5] that overlap these normal ranges. Due to dilution, the PCV of the DPL fluid cannot be directly compared with the peripheral blood PCV. It has been reported that a PCV of the DPL fluid of greater than 5% is indicative of significant hemorrhage [10]. Serial assessments of the abdominal fluid with increasing PCVs may more clearly define continuing hemorrhage.

Creatinine and potassium elevations in the lavage fluid are more difficult to interpret due to dilutional effects of the 0.9% NaCl. Excretory urography, retrograde contrast cystourethrography or surgical intervention may be indicated.

Conclusion

Serial physical examinations and diagnostic studies are required to decide when acute abdominal disease should be surgically explored versus treated medically. Blunt abdominal trauma cases are challenging diagnostic problems because the clinical manifestations may be delayed for hours or days. Abdominocentesis is a valuable tool to obtain a sample for laboratory and cytological analysis in the emergency room or intensive care unit. A diagnostic peritoneal lavage may be indicated in a patient where significant abdominal injury has occurred but no diagnostic sample was identified by FAST or obtainable via abdominocentesis.

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Urethral Catheterization (Including Urohydropulsion)

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Introduction

Placing a catheter into the urethra via the urethral opening is indicated in a number of emergent conditions (Box 187.1). The condition will often dictate if single, intermittent, or indwelling urethral catheterization is required and therefore determine the type of catheter used. Species and sex differences play a role in catheter selection and placement technique. Catheter selection and placement technique also can limit complications such as lower urinary tract trauma and catheter-associated urinary tract infections.

Indications for Urethral Catheterization

Urinary retention is a common emergent presentation and can be caused by anatomical pathologies, such as physical obstructions to include urolithiasis, neoplasia, inflammation, and trauma, or functional pathologies,

such as myogenic neurological or dyssynergic pathologies. One-time, intermittent or indwelling catheterization may be needed to relieve the urinary retention, but care must be taken to prevent trauma to lower urinary structures [1–3]. A catheter should not be used directly to dislodge calculi; instead, use retrograde urohydropulsion, which uses water pressure via the catheter to dilate the urethra and move the obstruction into the bladder [4].

Contrast diagnostic imaging may be useful in assessing urinary retention or trauma to the lower urinary tract. This may be a one-time catheterization and the catheter is fed just into the urethra for a urethrocystogram or advanced into the bladder for a cystogram [5].

Indwelling catheterization may be warranted in critically ill patients to monitor urine output, determine fractional excretions (e.g. of free water), or measure intra-abdominal pressure [6,7].

Bladder decompression and maintenance of urine output may be considered in a number of conditions. In surgeries of the urinary tract or associated structures, prolonged procedures or in anesthetized patients with increased urine output, an indwelling catheter may be warranted [1,2]. Additionally, keeping the bladder empty via an indwelling urinary catheter will hasten elimination of toxins (e.g. methylxanthines) that are reabsorbed from the bladder [8]. While urethral catheterization should not be a substitute for nursing care, it is reasonable to utilize one intermittently or long term in cases where the benefits in patients who are immobilized or who have wounds that would be compromised with normal urination outweigh the risks [1,2,9,10].

Although urine samples may be obtained from an indwelling urethral catheter, urethral catheterization should not be performed for the sole purpose of routine urine sampling as cystocentesis yields a superior sample and free-catch sampling avoids the risks of catheterization [11].

Box 187.1 Indications for urethral catheterization.

- Relief of urinary retention
 - Anatomical
 - Functional
- Contrast imaging study of the lower urinary tract
- Monitoring of critically ill patients
 - Urine output
 - Intra-abdominal pressure
- Keep urinary bladder decompressed or empty
 - Perioperative
 - Urogenital surgery
 - Prolonged surgery or possible large intraoperative urinary output
 - Intoxications
 - Selected patients that are immobilized

Risks of Urethral Catheterization

Urethral catheterization carries the risk of trauma to the lower urinary tract or catheter-associated urinary tract infection (CAUTI).

Stylets, stiff catheters (e.g. polypropylene), excessive force, lack of lubrication, and diseased tissue can lead to urethral or bladder trauma (see Chapter 100). Stylets should be designed for urethral catheter use and not extend outside the catheter. Excessive force should also be avoided if an anatomical obstruction is encountered, but even with appropriate placement technique and when indicated to obtain cytological samples, diseased tissue may be more friable [3,4,12]. In one retrospective study, the most common cause of urethral tears in cats was secondary to catheterization in patients with urethral obstruction [13]. Lower urinary tract tears should be recognized as a potential complication of urethral catheterization, especially when localized pathology is suspected.

The length of catheter to be inserted into the urethra should be premeasured prior to placement to limit trauma to the bladder. Additionally, this step can prevent overinsertion resulting in the catheter kinking, knotting or folding back onto itself and traveling antegrade down the urethra. If the catheter has folded onto itself, advancing another catheter alongside the original and applying gentle traction under anesthesia may successfully remove the catheter in these instances; otherwise, surgery is indicated [12].

Microorganisms may be introduced into the urinary tract during catheter placement and one study reported a 20% incidence of a UTI in a one-time catheterization of female dogs [14] (see Chapter 96). Subsequently, microorganisms may migrate along the external or internal surface of the catheter with biofilm, thus offering resistance to the host defenses. Veterinary studies have reported the incidence of CAUTIs to be up to 55% with indwelling urinary catheters. As with any intervention, the risks must be weighed against the benefits. Placing a catheter only when it is indicated, using it for only as long as necessary and following aseptic placement and maintenance protocols will limit complications. Studies utilizing this approach have reported the incidence of CAUTI in veterinary intensive care units in patients with an indwelling urethral catheter >24 hours to be as low as 10% [9,10,15–22].

Catheter Considerations

Urethral catheters are made from various materials and available in different diameters and lengths, and with balloon tips.

Size

Urinary catheters diameters are expressed in French (Fr) scale. The French scale value divided by 3 is the outside diameter of the catheter in millimeters; so, a 6 Fr catheter would have an outside diameter of 2 mm. Cats generally need a 3.5–5 Fr, female dogs a 3.5–14 Fr, and male dogs a 3.5–10 Fr. Especially in dogs, males require a longer catheter than females. Some catheters may be too short to reach the bladder in large male dogs and therefore premeasurement to the center of the bladder or desired location in the urethra should be made to ensure the catheter on hand is of adequate length.

Materials

Urinary catheters are made from a variety of materials that affect stiffness, urethral reactivity, and resistance to bacterial swarming and biofilm formation. While commonly available urethral catheters can be used for a single (in and out) catheterization, indwelling catheters are ideally soft for patient comfort and to decrease the potential for urethral trauma, biologically inert to limit urethral inflammation, and resistant to biofilm and bacterial adherence to reduce CAUTIs. Silicone and polyurethane catheters are therefore preferred for long-term indwelling catheters. Other commonly used materials include hydrogel, siliconized and Teflon-coated latex, latex, red rubber, and plastic/polypropylene. Antimicrobial and antiseptic-coated urethral catheters are available to reduce CAUTIs but they are reserved as a supplemental intervention in long-term catheterizations due to their increased cost, potential to induce reactions and effectiveness of primary interventions such as hand washing and placement and maintenance protocols [1,2,23,24].

Foley Catheters

In 1934, Dr Frederic Foley developed a balloon-tipped catheter with a distal port. Modern veterinary versions include smaller diameters and longer lengths to address anatomical differences from humans. They offer the advantage of anchoring the catheter within the bladder with the balloon inflated near the distal end. This eliminates the need to secure the catheter at the vulva or prepuce. They are ideal when an indwelling catheter is needed but the balloon offers the potential for some unique considerations. The balloon should ideally be filled with a sterile solution (versus air or tap water) as it is non-compressible and stays in the balloon longer compared to air and prevents contamination in case of balloon leakage or rupture. There is some debate between sterile water and saline as the ideal filling solution; sterile

water has been proposed to be the preferred solution as it maintains balloon inflation longer and avoids the potential of balloon valve or lumen occlusion due to salt crystals. Proper inflation volumes indicated on the catheter should be observed. Overfilling the balloon can lead to occlusion of the catheter lumen from the balloon itself or contact with the bladder wall or even balloon rupture. Underfilling the balloon can lead to displacement from the bladder [24,25].

Placement Technique

Universal

While there are technical differences in the placement of urethral catheters, a universal protocol emphasizing asepsis is the foundation to limit complications, namely CAUTIs (Box 187.2) [18,20]. Considerations for technique are also based on patient signalment and cardiopulmonary stability.

Male Dogs

Male dogs tend to tolerate catheterization with simple restraint and comforting; sedation may not be necessary. The urethral opening in a male is at the distal penis and is easily accessed by extruding the penis from the prepuce. After clipping and scrubbing the distal prepuce and surrounding area, the penis is extruded, wiped of gross contamination and the internal prepuce is flushed with a 0.05% chlorhexidine solution. With the penis still extended (and barrier drapes in place), the catheter is guided into the urethral opening and advanced to the desired location.

Female Dogs

Female dogs present an anatomical challenge of identifying the urethral papilla which is usually on the ventral floor at the junction of the vaginal vestibule and vault. The author prefers to perform urethral catheterization in lateral recumbency with the pelvic limbs in a neutral position using a digital technique. It requires no

Box 187.2 Universal protocol for urethral catheterization.

1. Premeasure length of catheter needed by estimating the length from the urethral opening to the bladder or intended distal tip, following the path of the urethra.
 2. Assemble needed supplies (+/- sedatives PRN).
 - a. Sterile drapes/barrier for work area and patient
 - b. Sterile urinary catheter
 - If Foley catheter, syringe and sterile water for balloon, test balloon
 - c. Clippers
 - d. Gauze sponges
 - e. Chlorhexidine surgical scrub and water rinse
 - f. Lidocaine or water-based lubricant (single use)
 - g. Sterile gloves
 - h. Solution of 6.25 mL of 2% chlorhexidine in 250 mL sterile water (0.05% solution)
 - i. Syringe for flushing prepuce
 - j. If performing urohydropropulsion:
 - Sterile lubricant mixed with sterile saline 1:1 in a syringe
 - Exam/sterile gloves for transrectal/vaginal urethral palpation
 - Syringes (depending on signalment, 1–60 cc)
 - Flush solution (saline for irrigation, isotonic IV solutions)
 - Assistant(s) as this is a team effort
 - Additional urinary catheters for urohydropropulsion or indwelling
 - k. If indwelling, closed collection system
 - Collection bag (appropriate size for animal)
- If bag does not have tubing, aspiration port or male adapter for catheter:
- Male (referring to adapter) connector for urinary catheter
 - Extension tubing (1 or 2)
 - Three-way Luer-Lok stopcock
 - Infusion plug
 - Cable tie(s) and application gun
- l. If non-Foley indwelling catheter
 - Skin forceps
 - Needle drivers/hypodermic needle
 - Scissors
 - Suture, e.g. 3-0 nylon
 - Commercial “butterfly” adapter or tape
 3. Wash hands (before and after procedure).
 4. Clip a 3–5 cm border of hair from the catheter insertion site, i.e. the preputial or vulvar area.
 5. Utilize a chlorhexidine scrub and tap water solution to prepare the area with three washes and subsequent rinses.
 6. Flush the area of the urethral opening (vaginal vestibule or prepuce) with a 0.05% chlorhexidine solution five times.
 7. Use a sterile barrier drape, gloves, and single-use water-based lubricating jelly to aseptically place urethral catheter.
 8. Once the catheter is successfully in the urethral opening, it is advanced until the premeasured length or resistance is encountered.
 9. Secure the catheter if indwelling.

specialized equipment and is an easy technical skill to learn. Keeping the digit, hand, and forearm in line and along with the catheter parallel to the work surface, the initial approach is at an angle to access the vaginal vestibule then straighten to approach the urethral papilla. Others prefer visualization of the urethral papilla with the patient in dorsal recumbency with the caudal extremities elevated cranially or in ventral recumbency with the caudal extremities hanging off the work surface.

The external genital area is clipped and scrubbed (gently) and the vestibule is flushed with 0.05% chlorhexidine solution. The urethral papilla may be palpated digitally or directly visualized with a light source and vaginal speculum or a sterilized otoscope. Once the papilla is identified, the catheter is advanced into the urethral opening. Successful placement is confirmed by following the catheter from the vulva and hitting a rim of tissue. Sedation is often warranted for female patients; flushing the area of the urethral papilla with lidocaine (injectable) solution or jelly (not to exceed 4mg/kg) with a lubricated syringe (without a needle) has anecdotally been suggested for patient comfort. When a patient is too small to accommodate a digit or equipment as above, a blind technique where the catheter is advanced along the ventral midline of the vaginal vestibule is utilized.

Male Cats (see Chapter 98)

Male cats are rarely amenable to urethral catheterization without sedation unless the cat is obtunded. Placement in male cats is like that of dogs, keeping in mind that the penis in cats has a more caudal angle than dogs and extrusion should follow suit, that is the prepuce is retracted craniodorsally. Gentle caudoventral traction of the penis may further facilitate catheterization.

Female Cats

Female cats are also rarely amenable to urethral catheterization and sedation is warranted unless the cat is obtunded. Unless the cat can accommodate a digit or viewing device, the blind technique is utilized as described above.

In all cases, if the catheter is advanced into the bladder, urine should flow; alternatively, flushing sterile saline and subsequent aspiration, radiography (with or without contrast), and ultrasound can be used to assess catheter placement. Once the catheter is in place, it should be connected to a closed collection system and secured.

Retrograde Urohydropropulsion

If the catheter is being placed to relieve an anatomical obstruction due to a urethral plug or calculus, it

is advanced to the area of obstruction under general anesthesia or heavy sedation (see Chapter 191). Injecting a sterile physiological solution through the catheter to dilate the urethra and move the obstruction towards the bladder is referred to as retrograde urohydropropulsion. It is preferred to using the catheter to physically move or bypass the obstruction to minimize the risk of urethral trauma, including tearing or subsequent stricture formation. If urohydropropulsion is unsuccessful, using the catheter to manipulate or bypass the obstruction should be weighed carefully against repeated decompressive cystocentesis or a tube cystotomy until definitive surgery can be performed (see Chapter 106).

Decompressive cystocentesis to a modest residual volume is recommended in cases of bladder overdistension prior to retrograde urohydropropulsion as it decreases the pressure against the obstruction, accommodates the volume of flushing solution, provides for a pure urine sample, and relieves the pathologies associated with an overdistended bladder and obstructive uropathy.

Once the catheter tip is just distal (with respect to the urethra) to the area of the obstruction, a sterile 1:1 solution of isotonic saline (or other physiological solution) and water-based lubricant is injected. Palpation and retrograde manipulation of the stone can be attempted via the rectum, vagina or transabdominal palpation while this lubricating solution is being injected. In anticipation of flushing the catheter with physiological solution, an assistant applies digital pressure in appropriate sized patients via the rectum or vagina to the urethra, either distal to the obstruction (with respect to the urethra) to prevent backflow and promote urethral dilation or proximal to the obstruction to dilate the segment of the urethra with the obstruction and when pressure is released abruptly, carry the stone or plug to the bladder. The urethral opening at the penis may be occluded around the catheter in males. A Foley catheter with the balloon inflated may substitute for or complement digital occlusion [4]. The author has found that 1 cc syringes generate the pressure needed to relieve obstructions due to plugs in male cats when larger syringes have failed. Once the obstruction is relieved, a new indwelling catheter may be considered if urethral catheterization is warranted.

Indwelling Catheter Care

If a catheter is to be left in place, a closed collection system is utilized. Closed collection systems are commercially available and contain a sampling port and distal emptying spigot or one can be constructed from a collection bag, tubing, three-way stopcock, injection caps and adapters, all ideally sterile. Cable ties and the associated

“gun” are available at home improvement stores to secure connections in either case.

It has been suggested that a used IV catheter bag that contained dextrose-free solutions can be used as the collection bag if it is capped with a sterile plug and stored for <7 days in a cabinet. However, this requires that the closed collections system be “broken” for emptying of the bag. This “open” system had a slightly higher incidence of CAUTI compared with a closed collection system in one study, but the difference was not significant. Limitations included an average catheterization time of 2 days, none longer than 7 days, and a relatively small sample size [20]. Regardless of the system used, contamination of any spigot or connection should be prevented; this means keeping the bag off the floor (e.g. laying it in a clean plastic container), but always lower than the patient to prevent retrograde flow [1,2].

If a Foley catheter is placed, the catheter is advanced to insure the balloon is in the bladder, then the balloon is inflated with sterile water using the volume indicated on the balloon port of the catheter. Gentle caudal traction

is applied until resistance is met, insuring the catheter is seated appropriately. Non-Foley catheters are secured using two skin sutures placed into the vulva or prepuce apposed 180° utilizing a commercially available or tape-made “butterfly” encompassing the catheter. Care should be taken to ensure that the collection system is not placing tension on the urethral catheter by bandaging the collection tubing to a leg or tail. If the tail is used, distal anchoring is recommended to minimize fecal contamination.

Emergent patients with indwelling urethral catheters should undergo regular catheter care every 8 hours or when gross contamination occurs, consisting of hand washing, examination glove usage, cleaning the catheter and area with chlorhexidine scrub (and rinse) and gentle chlorhexidine flushing similar to preplacement. Once an indwelling catheter is no longer needed, it should be removed [18]. Case transfer from emergency care should include information on the indication for the catheter, catheter type, placement and care, and removal contingencies to avoid excessive time of catheterization.

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Mechanical Ventilation in the Emergency Room

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Introduction

Intermittent positive pressure ventilation (IPPV) may be considered in dogs and cats that present to the emergency room in respiratory distress/failure or rapidly developing failure (Box 188.1). Additionally, IPPV may be considered in dogs and cats with toxicity (e.g. baclofen or ivermectin in dogs), with severe hypoventilation or for support following successful CPR. The ER efforts are unique in providing ventilation for these patients, as early initiation of ventilation (prior to CPR) may be associated with a better outcome.

Supplies Required

Ventilation may be simply provided with an Ambu bag or anesthesia machine; in fact, this is almost certainly the first line of therapy in most pets ventilated in the ER. Non-invasive ventilation, which is more commonly used in people, is poorly tolerated in conscious dogs and cats. Hi-flow oxygen therapy (see Chapter 181) may represent an additional approach to treating hypoxemia that is refractory to conventional therapy. Anesthesia ventilators are able to provide more short-term support to ventilated cases, although most frequently these are only able to provide 100% oxygen support. More long-term ventilation may be accomplished with dedicated critical

care ventilators. Many ERs are associated with 24-hour ICU services as well, and in some cases it may be prudent to move a patient to the ICU before initiating long-term ventilation. In emergency hospitals not associated with 24-hour hospitals, efforts to stabilize the patient in the ER before transport to a 24-hour hospital are advised if possible.

Personnel

Most ventilated patients need at least one person dedicated to them full time, although some toxicities/hypoventilating cases are more tolerant of less intensive monitoring. Adequate staff should be available if ventilation is offered for more than a short time.

Transport

If 24-hour ventilatory support is not available and it seems likely that the patient may require more support, it may be necessary to transport the patient to a critical care hospital (Figure 188.1). This may be accomplished in a few urban areas with “animal ambulances” but in general, this is challenging unless the transport distance is short. Animals with hypoventilation may be more easily moved while being ventilated than those dogs or cats with severe hypoxemia. Small oxygen tanks may be used for transport, and in some cases, a veterinarian or veterinary technician may accompany the patient and will provide assisted ventilation during transport. The feasibility of transport should be carefully considered prior to moving a patient, and every effort should be made to avoid transport if possible. However, if the patient is declining or there is no option for ongoing support, transport should be pursued.

Box 188.1 Goals of ventilation in the ER.

- Decrease or eliminate hypoxemia and/or hypercarbia
- Reduce fear and anxiety
- Permit diagnostic tests to evaluate the underlying cause of the respiratory distress, if needed
- Initiate therapy specific for the patient's condition



Figure 188.1 A dog being transported from an emergency hospital to a 24-hour hospital for ventilation following a coral snake attack. Source: Photo courtesy of Alex Lynch BVSc (Hons), DACVECC, University of Florida.

Owner Communication

The decision to provide a pet with IPPV is an important one; it should be based upon a strong assessment of the potential benefits and risks to that patient, as well as a discussion of the emotional and financial implications of IPPV. In some cases, ventilation will clearly be short term (e.g. some toxicities) and in other cases, the outcome will be clear quite quickly so 12–24 hours of support may be warranted and more easily undertaken. In other cases, the decision to pursue IPPV will accompany a significant medical or surgical undertaking (e.g. MRI and ventral slot) and the owner should be advised that ventilation is only a small part of the treatment and hopeful recovery of the patient.

Respiratory Distress (Hypoxemia)

Respiratory distress is common in ER patients; most animals will respond to efforts to stabilize them with oxygen, thoracocentesis, and/or medications. However, in some cases progressive respiratory failure appears imminent and in those cases, consideration should be given to providing IPPV. After a patient is anesthetized and intubated for support, additional diagnostic testing, such as diagnostic imaging or sample collection, may be more safely accomplished. Ventilation is additionally a humane option as it removes anxiety and fear associated with hypoxemia.

Recently, a small study by Edwards et al. evaluated the outcome surrounding ventilation associated with congestive heart failure (CHF) and identified 10 dogs and six cats that were supported with IPPV [1]. Overall survival to discharge was 62.5%, with a mean onset to ventilation from admission of 5.9 ± 6.4 hours, suggesting that IPPV may have a role in the emergency stabilization of animals with CHF.

In dogs with pulmonary contusions (see Chapter 49), in 2000 Campbell and King evaluated 10 dogs that were supported with IPPV and found that 30% of dogs survived [2]. Interestingly, due to the changing approach to fluid therapy, with the pendulum shifting to more conservative fluids in the last 15 years, it may be that IPPV would more successful in dogs and cats treated today following initial resuscitation.

Intoxications/Envenomation

In some parts of the world (e.g. Australia), ventilation for exposure to ticks and snakes results in frequent need for short-term ventilatory support, with a good outcome [3]. Ingestion of sedative drugs, avermectins or tremorgenic toxins may result in the development of respiratory depression or decreased respirations may accompany the anesthetic agents required to control excessive muscle activity or tremors. In these cases, IPPV is very useful to support the patient as the intoxication is directly treated or is metabolized. Some intoxicants (e.g. baclofen) are amenable to hemodialysis and lipid therapy may also be used to shorten the duration of some toxicities (see Chapter 129) [4].

Post Cardiopulmonary Resuscitation

Following successful return of spontaneous circulation (ROSC), IPPV may be pursued to better support the patient during recovery from the arrest. Recurrent CPA is common in survivors of CPR (see Chapter 150), and hypoventilation or apnea can be avoided with support. IPPV may negatively impact cardiac output, so close attention should be paid to monitoring cardiac function and urine output.

Tetraparesis

Tetraparesis may result from a compressive cervical lesion; while normally cervical intervertebral disk disease (IVDD) does not result in hypoventilation, in severe cases it may do so. Dogs that are ventilated for IVDD have a fair to good prognosis with surgery [5]. In the emergency setting, dogs with tetraparesis should be evaluated for hypoventilation. Pulse oximetry values of $>95\%$ while breathing

room air practically exclude hypoventilation [6] but with lower values, an arterial blood gas should be obtained. Care should be taken to not provide supplemental oxygen to a patient with hypoxemia, without excluding hypoventilation, as while the PaO_2 will improve, the PaCO_2 may be rapidly worsened (Table 188.1). End-tidal CO_2 analysis is not helpful when assessing hypoventilation as ETCO_2 may only assess expired air from the anatomical deadspace. In animals with hypoxemia/hypoventilation from lower motor neuron disease (see Chapter 27), the prognosis is much more grave [7].

Ventilation

As in all cases of IPPV, care should be taken to ensure adequate sedation/analgesia, not only for patient comfort but also to decrease work of breathing and limit patient–ventilator asynchrony (see Chapter 191). Ventilatory settings should be as conservative as possible, with efforts aimed at prevention of worsening lung injury and iatrogenic complications. Tolerance of moderate amounts of hypoxemia (e.g. SpO_2 89–90%) may limit the inspiratory pressures or volumes required, which can help avoid complications.

Conclusion

Emergent mechanical ventilation can be life-preserving, allowing for support of respiration in cases of imminent

Table 188.1 Arterial blood gases from a Doberman pinscher with tetraparesis and respiratory failure associated with wobbler's syndrome. The dog was given oxygen therapy to treat the hypoxemia, without appropriate recognition of the respiratory failure. Note the effect of supplemental oxygen on PCO_2 and pH.

	On admission	After oxygen therapy
pH	7.237	7.021
PCO_2	51.3 mmHg	91.5 mmHg
PO_2	59.7 mmHg	371.4 mmHg
HCO_3	22 mmol/L	27 mmHg
BE	−2 mEq/L	+3 mEq/L
SPO_2	89% (pulse oximeter)	100% (pulse oximeter)

BE, base excess.

respiratory failure. The ER should be fully prepared to rapidly sedate and intubate these patients and, initially, manually provide positive pressure ventilation. If prolonged assisted ventilation is required, the patient can be transferred to a critical ventilator for further support within the ER or an ICU. Rapid sedation, intubation, and assisted ventilation can allow the ER veterinarian to more fully assess the patient, and educate the owners on underlying disease and prognosis. In addition, with some diseases, positive pressure ventilation, in conjunction with therapeutic medications, will provide support while the underlying insult resolves.

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Damage Control Surgery

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Introduction

Damage control surgery (DCS) is a set of surgical techniques and principles utilized to care for critically ill patients in the emergency room setting. There is a subset of patients, etiologies, and situations that require immediate surgical intervention without the benefit of a surgeon being present or immediately accessible. The decision to switch from definitive treatment to damage control should be made early, ideally prior to entering the operative suite, as this has been associated with improved mortality [1–4].

In humans, the leading cause of death among trauma patients remains uncontrolled hemorrhage which accounts for approximately 30–40% of trauma-related deaths [1,2].

The implementation of DCS in humans emphasizes preventing the lethal triad of metabolic acidosis, hypothermia, and coagulopathy, rather than providing definitive surgical intervention and correction of the distorted anatomy.

The life-saving methodology of DCS has resulted in a significant decrease in morbidity and mortality of critically ill patients; however, it is important to remember that complications associated with DCS being undertaken by an undertrained or unprepared team will lead to fatal consequences. In human trauma patients, the procedure is generally indicated when a severe injury occurs that induces severe hemorrhage that leads to the lethal triad as a sequela [3]. The surgical approach, performed in the emergency room, would provide a limited surgical intervention in order to control both hemorrhage and contamination. This allows for the emergency clinician to focus on reversing the physiological insult and stabilizing the patient prior to definitive surgical intervention. While the temptation to perform a definitive procedure may exist, it is avoided in this situation because of the secondary deleterious effects on patients.

In small animal trauma patients, DCS can and should be employed in similar circumstances as described in the human literature, attempting to avoid and correct persistent hypothermia, metabolic acidosis, and progressive coagulopathy.

In animals with severe, acute, abdominal trauma, DCS is divided into three stages.

1. Initial laparotomy
2. Intensive care unit or postoperative resuscitation and stabilization
3. Definitive repair

Each of these three stages has to be well timed and meet specific objectives to assure a successful outcome.

Damage Control Surgery Stage 1: Initial Laparotomy

The first goal of stage 1 is controlling hemorrhage. Current human recommendations are to keep the operative time to 90 minutes or less to avoid death [2]. Control of ongoing contamination, packing of the abdomen or compartment, and placement of a closed suction drainage device are all part of stage 1. One of the most important factors in determining the outcome of a stage 1 DCS patient is to minimize the length of time spent in this phase. The ultimate outcome associated with stage 1 DCS is directly related to the ability to mobilize appropriate personnel, equipment, and the particular resources required to treat the patient. Establishing and maintaining control over hemorrhage is the most important step in this phase. The packing off of all four abdominal quadrants with radiopaque laparotomy sponges usually will allow the clinician to establish initial hemorrhagic control. Depending on the source of hemorrhage, a number of different techniques and methods are utilized.

While the patient is being prepared for anesthesia and surgery, all potential required supplies are identified and made available to the surgical team. This would include, but is not limited to, surgical packs with a variety of instrument sizes, straight and curved hemostats, Satinsky forceps, suction devices and multiple suction canisters, cell saver device or similar supplies needed for autotransfusion, abdominal retractors, a variety of suture sizes and materials, large radiopaque laparotomy pads, and radiopaque gauze squares. Topical hemostatic agents can also be used to control hemorrhage in certain situations [5]. Fibrin and thrombin topical sprays and gels, cyanoacrylate tissue glue, topical collagen, gelatin sponges, oxidized cellulose and VETIGEL (Suneris, Brooklyn, NY), a novel, rapid-acting, plant polymer topical hemostatic agent, are currently available products.

Electrosurgery is indispensable for rapid and efficient control of hemorrhage. Both monopolar and bipolar electrosurgery are indispensable when performing DCS. Attempting to control hemorrhage at any level in any tissue without electrosurgery in an unstable and potentially hypothermic and coagulopathic patient will lead to significant prolongation of anesthesia and surgery times and ultimately to the patient's demise. Electrosurgery has to be used judiciously; indiscriminate and inappropriate use will lead to thermal damage, ischemia, and delayed healing.

It is necessary to have a good light source available and often, the lighting in an emergency room is not adequate for exploration of the abdomen. A head-mounted halogen, xenon, or LED light source is recommended.

The fur of the ventral abdomen is clipped with the animal in lateral recumbency, ideally prior to providing general anesthesia. All loose and clipped fur is removed from the patient and from the surgical table with a vacuum prior to applying the surgical scrub. Once the patient is intubated and secured in dorsal recumbency, the animal is draped and the skin incision is made from the xiphoid to the pubis. One of the most common and costly mistakes in early DCS is limited exposure of the peritoneal cavity. If the skin incision is not long enough, the linea incision will be limited and so will the ability of the surgeon to identify the source of hemorrhage and control it. The linea should be incised from the xiphoid to the level of the umbilicus.

At this point, the peritoneum is still intact and blood will not be able to rapidly leave the abdominal cavity. A Poole suction tip is used to penetrate the falciform fat and peritoneum at the most caudal extent of the linea incision. The suction tip is aimed to the right and caudal in the abdomen to avoid the spleen and omentum. This technique allows for a controlled evacuation of blood from the abdomen. The blood can be immediately processed for autotransfusion (see Chapter 176). Once most

of the blood has been removed from the abdomen, the linea incision is expanded to the level of the pubis.

The most efficient method to identify the source of the hemorrhage is to have a consistent and repeatable plan for exploration that starts with evaluation of the most common sites of hemorrhage. The most common sources of hemorrhage are the spleen, liver, and retroperitoneum. If these locations do not provide the source of hemorrhage, a routine systematic abdominal exploratory is performed. Less common sites of severe hemorrhage include mesenteric vessels, the portal vein, and direct damage to the caudal vena cava or iliac veins, or the aorta and its major branches. Temporary occlusion of the aorta, caudal vena cava, or portal vein may be required. Solid organ injury should be dealt with by complete or partial resection, if possible. The spleen is rapidly evaluated for hemorrhage. If it is the source of hemorrhage, a rapid splenectomy technique is performed or the splenic hilar vessels can be clamped with hemostats or Carmalt forceps. The liver is evaluated next and exploration of all liver lobes on all surfaces is facilitated by linea incision that is extended from the xiphoid to the pubis. The liver can be retracted caudally by placing laparotomy sponges between the diaphragm and the concave cranialmost surface of the liver. This technique may also partially tamponade the hepatic veins as they leave the liver parenchyma cranially to enter the caudal vena cava. If the liver is the source of hemorrhage, it is possible to temporarily slow or cease the flow of blood to the liver. The Pringle maneuver is performed by identifying the portal vein and the hepatic artery within the hepatoduodenal ligament [5]. The hepatoduodenal ligament is the portion of the lesser omentum that attaches the liver to the descending duodenum and forms the ventral border of the epiploic foramen.

Compressing the hepatoduodenal ligament with the portal vein and hepatic artery with a vascular clamp will cease all blood flow to the liver. This technique also inadvertently occludes the bile duct. The technique can be performed intermittently as needed to identify the source of liver hemorrhage and control it. If the portion of the bleeding liver lobe can be rapidly removed with a guillotine suture technique or surgical stapling device (thoracoabdominal stapler), this can be performed at the time of DCS. If the hemorrhage cannot be immediately stopped, an encircling loop of 2-0 to 0 PDS suture is tied and secured proximal to the site of hemorrhage. This technique is unlikely to yield a permanent solution to the hemorrhage but the compression of the liver parenchyma around the intrahepatic vessels will decrease the amount of active bleeding. Laparotomy sponges are lightly moistened and packed in the cranial abdomen to assist in the tamponade of the source of the liver hemorrhage. The sponges are retained in the cranial abdomen

and the incision is closed, stabilization continues, and definitive sponge removal and surgical intervention are performed at another time in the near future.

The portal vein and hepatic artery cannot be clamped for a long period of time. The abdomen should not be closed with the hepatoduodenal ligament compressed. Intermittent use of the Pringle maneuver is well tolerated intraoperatively but prolonged compression is damaging to the intestines and pancreas and rapidly induces severe portal hypertension so its use must be limited to the DCS event.

Common sources of severe retroperitoneal hemorrhage include the kidneys and their blood supply, the phrenicoabdominal veins, and the deep circumflex iliac arteries leaving the aorta at the level of the lumbar vertebral bodies. These vessels may need to be ligated and the patient closed prior to definitive repair being performed. In cases of severe renal trauma with significant hemorrhage, the renal artery and vein can be clamped or ligated and the kidney and ureter definitively removed once the patient is more stable. Other arteries and veins directly associated with the caudal vena cava or abdominal aorta may be able to be ligated but attempts to spare the celiac and cranial mesenteric artery must be performed.

Acute ligation of the caudal vena cava distal to the renal veins can be performed but will induce significant venous obstruction to the pelvic limbs and a decrease in cardiac preload. Ligation of the cava proximal to the renal veins will lead to renal azotemia, a massive decrease in preload, and ultimate failure of the kidneys. Temporary caudal caval occlusion can be performed during DCS to identify the source of hemorrhage and repair it. The use of a Satinsky clamp is ideal to isolate a tear in the caudal vena cava. The clamp is applied parallel to the long axis of the vessel so that the damaged region is isolated but blood can still flow through the non-clamped portion of the vessel.

If the abdominal aorta or any of its major tributaries are the source of the hemorrhage, they can be clamped during DCS stage 1 for up to 30 minutes without permanent damage to the viscera.

Once hemorrhage control is achieved, one should quickly proceed to controlling intra-abdominal contamination from hollow-viscous organs. Although it may be tempting to perform an intestinal resection and anastomosis during DCS, this should not be done. The goal of DCS is to prevent continued intra-abdominal contamination without restoring normal luminal flow of the bowel. This can be undertaken with the utilization of a TA stapler to come across the bowel, or primary suture closure. Once this is complete, the abdomen should be packed. Many of these patients become coagulopathic and can develop diffuse oozing (see Chapter 163). It is important to pack not only areas of injury but also areas

of surgical dissection. There are various methods that can be utilized to pack the abdomen. Packing with radiopaque laparotomy pads allows the benefit of being able to detect them via x-ray prior to definitive closure. As a rule, definitive closure should not take place until there has been radiological confirmation that no retained objects are present in the abdomen.

Damage Control Surgery Stage 2: ICU Resuscitation

Upon completion of the initial phase of damage control, the key is to reverse the physiological insult that has taken place. The second stage of DCL is resuscitation focused on correction of physiological derangements, acidosis, oxygen debt, coagulopathy, and hypothermia which is covered elsewhere in this book (see Section 4).

Prophylactic antibiotics should be administered preoperatively when possible as infection rates increase if given intra- or post-operatively only, and duration should be no longer than 24 hours, unless soft tissue wounds are present or if there is concurrent trauma to the abdominal viscera with secondary spillage of gastrointestinal, biliary tract, or urogenital tract contents (see Chapter 200).

Damage Control Surgery Stage 3: Definitive Reconstruction

Definitive surgical intervention and reconstruction occurs once the patient is stable and improving. This is usually within 24–48 hours after presenting to the hospital. In veterinary medicine, DCS is often performed at the primary veterinary clinic or within the emergency department of a specialty hospital. Stage 3 of DCS in small animals often involves the transportation of the patient to a referral facility for definitive surgical intervention. The patient must be stable enough to tolerate transportation without significant decompensation, impeding stage 3 DCS. In human trauma patients, stage 3 will only occur after the resolution of acidosis, hypothermia, and coagulopathy has occurred. All tamponade materials used to pack the abdomen are gently removed. If radiopaque laparotomy pads or gauze squares were used for abdominal packing, they may induce a debridement effect when removed, causing serosal damage and hemorrhage. To prevent this and to facilitate safe removal, sterile saline is used as an abdominal lavage to loosen the adhesive interaction between the packing material and the serosal surface of the viscera prior to its removal.

Immediately after removal of the packing material, a complete and thorough abdominal exploratory is

performed. The goal of the re-exploratory is to identify any injuries missed during the initial laparotomy and re-evaluate the known injuries. If hemorrhage has ceased completely, no further intervention may be necessary. Once the previous source of hemorrhage is identified, evaluated, and addressed, attention is then turned to performing the necessary bowel anastomosis or other definitive repair. In many cases, the abdomen will be lavaged with 200–600 mL/kg of warm sterile saline and a closed suction drain placed and maintained for 24–48 hours.

Although there are no data supporting the use of DCS in dogs and cats, anecdotal data do exist enabling the translation of the human literature to the practice of DCS in emergency trauma small animal patients. Utilizing the lethal triad of metabolic acidosis, hypothermia, and coagulopathy in small animal trauma patients as a justification to elect DCS is reasonable. However, other factors such as financial implications, co-morbidities, and availability of emergency doctors and support staff that are comfortable with DCS stages 1 and 2 may preclude the implementation of such interventions.

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Section 7

Anesthesia and Analgesia for the Emergency Room Patient

Anesthesia and Analgesia in the Emergency Room: An Overview

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Introduction

Pain is the most common presenting complaint in human emergency departments (EDs), yet treatment is consistently delayed and underdelivered. Only 20–50% of human patients presenting to the ED with acute pain receive analgesia, and the time to delivery increases with severity of illness, age, trauma, overcrowding, triage category, time of arrival, and gender [1,2]. In an Australian survey, general surgery and trauma patients were most likely to receive delayed analgesia [3].

Veterinary ED patients also encounter “oligoanalgesia,” or lack of timely and adequate analgesia, with similar contributing factors. Patient pain tolerance and clinician and nurse identification and quantification (i.e. scoring) of pain are variable. Compared to anesthesiologists, veterinary students assigned lower pain scores for painful dogs, and many (58.8%) French veterinarians indicated an inadequate ability to quantify pain [4,5].

There is also a scarcity of reliable, sensitive, species-specific pain scoring systems. Most currently used scoring systems (e.g. Visual Analogue Score, Glasgow Composite-Measure Pain Scale, Simple Descriptive Scale (SDS), University of Melbourne Pain Scale) were developed and evaluated in patients already diagnosed with pain or following surgery, using an observer’s interpretation of the patient’s behavior and interaction with the environment to assign a score.

Beyond published pain scales, physiological responses and pain-mediated sympathetic stimulation (e.g. tachycardia, tachypnea, hypertension) are used for diagnosis of pain, but are inconsistent and neither sensitive nor specific markers [4,6,7].

While data are limited, a study conducted in a veterinary intensive care unit (ICU) found an overall 22% prevalence of pain in hospitalized dogs. Dogs on the orthopedic or neurosurgical service were more likely to

be characterized as painful, using an SDS [8]. In one veterinary ED, the prevalence of pain was estimated to be approximately 56% [9]. Unstable and under-resuscitated patients may be more susceptible to the cardiovascular and respiratory depressant side-effects of analgesic and anesthetic drugs, and in both humans and animals, clinicians are reluctant to administer pain medications to emergency patients for this reason and for concerns of masking changes in clinical condition (i.e. progression of neurological disease) [4,9–13].

Reconciling these challenges to rapidly identify and score pain in the emergent patient will allow the astute clinician to formulate and administer safe and effective analgesic or anesthetic protocol incorporating pharmacological and non-pharmacological therapies.

Origins and Sequelae of Pain

Pain sensation arises from a series of neural and electrochemical events following noxious mechanical, thermal, or chemical stimuli. These stimuli result in a release of ions, cytokines, and other substances (e.g. PGE₂) that sensitize or directly stimulate peripheral nociceptive receptors. In the periphery, this chemical stimulus is transduced to an electrochemical event that is then transmitted to the dorsal horn of the spinal cord, where it is modulated prior to its projection along the spinothalamic tracts to the brain, where it is perceived as pain.

Pain initiates a series of neuroendocrine events leading to hypothalamic-pituitary-adrenal gland axis activation with subsequent release of proinflammatory cytokines and catecholamines, resulting in altered immune function as well as cardiorespiratory changes. Pain also decreases subcutaneous oxygen tension, and may impair wound healing [14].

If nociceptor stimulation persists unmitigated, it may lead to increased responsiveness of dorsal horn neurons and promote central sensitization (“wind-up”) or hyperalgesia. This may decrease the efficacy of analgesic drugs, and require the administration of higher doses of medications that may result in more pronounced side-effects.

General Approach to the Painful Patient

Triage examination to gauge cardiorespiratory, neurological, and urological stability should be performed initially (see Chapter 2), followed by appropriate volume repletion and evaluation of acid–base status and electrolyte concentrations. This can ideally occur prior to the administration of analgesic or sedative medication, but in some animals with extreme pain, analgesia should be administered along with resuscitation. Frequent monitoring of heart rate (HR), blood pressure (BP) and pulse quality, mucous membrane color, capillary refill time, rectal and distal extremity temperature, respiratory rate (RR) and effort, and mentation should be performed both initially and following resuscitation.

When assessing pain in emergency patients, the signalment of the patient, as well as evaluation of the location and type of pain (e.g. visceral, orthopedic), should be taken into consideration. The cause, duration, and severity of the pain should also be determined. Behavioral indications of pain include vocalization or protective behaviors, especially following palpation of the affected area. Serial monitoring to evaluate trends in the physiological response to pain, which is typically characterized by increased HR, BP, and RR, may be more sensitive in assessing pain and effectiveness of analgesia than focusing on single measurements of these variables alone. However, in states of high catecholamine release, patients will display a decrease in HR variability, which further reinforces the need to consider the many factors affecting pain rather than relying on only physiological parameters [15].

In Muir’s study of pain in the ED, painful dogs were significantly older and heavier, and the majority had acute pain of mild-to-moderate severity that was somatic in origin (with skin and orthopedic injuries predominant). Painful cats were also significantly older, though their pain was more chronic in duration, and was visceral in origin, with pancreatitis, colitis, or obstruction (urethral or constipation) most common [16].

The implementation of triage pain protocols in the human ED has resulted in decreases in the time to analgesia administration, and increases in the number of patients receiving analgesia [17]. The incorporation of pain scores results in more consistent and timely delivery of opioid analgesia in this population [18].

Treating the Painful Emergent Patient

For the emergent patient, limited knowledge about disease and organ function promotes the selection of analgesics that are reversible and titratable, with minimal cardiorespiratory side-effects. Adverse side-effects can also be minimized by selecting synergistic combinations of analgesics that can result in adequate analgesia using lower total doses of each drug. These combinations are encompassed within the concept of multimodal analgesia, which also incorporates the use of local or regional analgesia to further decrease systemic drug side-effects. The use of local anesthetics (e.g. lidocaine) either locally or epidurally is another example of a multimodal approach that can result in significantly lower systemic drug requirements. For example, the use of a coccygeal epidural with lidocaine may allow better relaxation for urinary catheterization in cats with urethral obstruction, and require less systemic anesthesia [19].

The pharmacokinetics and pharmacodynamics of analgesic drugs, as well as the mechanism of action and associated side-effects, require careful consideration in emergency patients. Side-effects such as myocardial depression, decreased vasomotor tone, depressed mentation, impaired ventilation and respiratory drive, and prolonged duration of action (due to slower elimination because of metabolic dysfunction or organ hypoperfusion) are all possible in the critically ill patient. In addition, highly protein-bound drugs may have altered pharmacokinetics in patients with hypoalbuminemia. Hypothermic patients are more sensitive to the sedative and respiratory depressant effects of opioids and alpha-2 agonists [20]. The drugs of choice for the critically ill patient have predictable bioavailability, are reversible and titratable, and can be administered as a constant-rate infusion (CRI).

Analgesic Agents and Tranquilizers

(Figure 190.1)

Opioids are ideal analgesics for the critically ill patient; they are potent analgesics, are reversible (with the antagonist naloxone), provide variable duration of action (depending on the specific drug), and can be delivered as a CRI, facilitating fine-tuning of the medication dosage to achieve effective, individualized pain relief. Opioids have few cardiovascular side-effects, other than a vagally mediated bradycardia, which is most pronounced with the more potent opioids (e.g. fentanyl, remifentanyl). Although respiratory depression is a major side-effect in human patients, gastrointestinal ileus and dysphoria are more common in veterinary species. Meperidine and morphine are associated with histamine release, which may cause decreased vasomotor tone. Some opioids

Respiratory Depression	CV Depression			
	Drug	Dose/CRI	Reversal	Analgesia Sedation
	Opioid		Naloxone (0.02–0.04 mg/kg IV)	
	Fentanyl	3–5 µg/kg IV; 2–6 µg/kg/h		++++ ++
	Hydromorphone/ Oxymorphone	0.05–0.1 mg/kg IV/IM; 0.0125 – 0.05 mg/kg/h		+++ ++
	Buprenorphine	0.01–0.03 µg/kg IV/IM; 1–4 µg/kg/h		++ +
	Methadone	0.1 –0.4 mg/kg IV; 2–6 µg/kg/h		++ ++
	Morphine	0.2 –0.5 mg/kg IV/IM; 0.1 – 0.3 mg/kg/h		++ ++
	Butorphanol	0.1 – 0.4 mg/kg IV/IM; 0.025 – 0.3 mg/kg/h		+ +++
	<hr/>			
	Benzodiazepines*+		Flumazenil (0.01–0.02 mg/kg IV)	
	Midazolam/ Diazepam**	0.25–0.5 mg/kg IV, IM; 0.25 –0.5 mg/kg/h		0 ++
	Propofol***		None	0 +++++
	<hr/>			
	Phenothiazines⁺		None	
	Acepromazine	0.005 – 0.02 mg/kg IV/IM/SC		0 +++
	<hr/>			
	Alpha-2 agonists⁺		Atipamezole (0.1 mg/kg IM)	
	Dexmedetomidine	1–5 µg/kg IV/IM; 0.5 – 2 µg/kg/h		+ +++

Figure 190.1 This chart demonstrates the relative sedative and analgesic qualities of various analgesic and anesthetic medications available for use in the ED. +Synergistic sedative effects when combined with an opioid. *Can cause CNS excitation if given alone. **Oral diazepam is associated with hepatic necrosis in cats, parenteral solution is hyperosmolar precluding long-term peripheral CRI infusion. ***Heinz body anemia can develop in cats after prolonged usage. CRI, constant-rate infusion; IM, intramuscular; IV, intravenous; SC, subcutaneous.

may cause emesis in dogs, and this should be taken into account in animals that present to the ED with ocular or head trauma, or with a history of vomiting. A CRI administration of fentanyl generally does not result in emesis, and is preferred in critically ill animals, as it may be easily titrated to an appropriate level of analgesia to minimize side-effects. Morphine may also be administered as a CRI. Morphine and butorphanol seem to have the most sedative effects of the opioids in dogs, and some clinicians prefer oxymorphone or methadone in cats because they may result in less excitement.

Benzodiazepines (e.g. diazepam, midazolam) are tranquilizers without analgesic properties that are used for anxiolysis and adjunctive sedation. Synergistic effects are achieved when these drugs are used in combination with opioids (neuroleptanalgesia). When given alone, these drugs can lead to unpredictable sedation or excitation. In the critical and emergent patient, benzodiazepines are

relatively safe with little cardiovascular and respiratory depression, are reversible (using flumazenil), and can be titrated and delivered as a CRI. Benzodiazepines are the drugs of choice for initial stabilization of patients with seizures (see Chapter 21 for additional information on seizure treatments).

Alpha-2 agonists (e.g. dexmedetomidine, xylazine) are tranquilizers that are generally avoided in patients with any cardiovascular instability, history of trauma, or other condition in which reduced tissue perfusion should be avoided. These drugs cause initial peripheral vasoconstriction and reflex bradycardia, which decrease cardiac output [21]. Alpha-2 agonists also increase urine output, and are relatively contraindicated in animals with urinary obstruction. These drugs do provide potent analgesia and are reversible (using atipamezole or yohimbine), but their use is restricted to cardiovascularly stable, otherwise healthy patients.

Phenothiazines (e.g. acepromazine, chlorpromazine) should be avoided in animals with cardiovascular instability, as they are irreversible smooth muscle vasodilators (via α -1 antagonism) and can result in hypotension. Combined with opioids, acepromazine provides potent sedation, and this combination may be useful for sedation and anxiolysis of animals with upper airway obstruction or for sedation during short procedures.

The neuroleptic combination of an opioid and a tranquilizer is extremely important in the ED. Neuroleptanalgesia can provide sedation for brief procedures (e.g. radiography), premedication prior to anesthetic induction, and synergistic analgesia for treatment of painful conditions. The authors prefer a combination of opioid and benzodiazepine for this purpose, as they have minimal cardiorespiratory depression, and both are reversible. For more stable patients, the combination of an opioid and α -2 agonist provides potent sedation and analgesia that may be adequate to permit more painful procedures (e.g. splinting of fractured limbs, minor laceration repair). Hypoventilation may be more frequent using a combination of opioid and α -2 agonists.

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, possesses moderate analgesic qualities. In addition, NMDA antagonists modulate pain at the level of the spinal cord, reducing central sensitization and wind-up. Analgesic and sedative effects are best achieved through combination with an opioid and/or benzodiazepine. Ketamine has dose-dependent sympathomimetic activity, so caution should be exercised and dose reduced in patients with cardiac disease or hypertension. Ketamine increases cerebral metabolic rate and is not recommended in patients who are or may be at risk of elevated intracranial pressure (e.g. traumatic brain injury). Ketamine causes a mild increase in intraocular pressure, which may become clinically significant in patients with ocular trauma or glaucoma [22]. Ketamine is also excreted unchanged in the urine in cats, and in situations such as a urinary blockage or urinary bladder rupture, prolonged sedation may be seen until the urine is removed from the body. The combination of low-dose ketamine in a CRI with a morphine and lidocaine has been described for both intraoperative and postoperative analgesia [23].

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclo-oxygenase enzyme, which produces prostaglandins from cell membrane arachidonic acid (AA) [24]. There are two main isoforms of cyclo-oxygenase (COX-1 and COX-2), producing prostaglandins for homeostasis (e.g. renal perfusion, mucosal blood flow; generally COX-1) and pain and inflammation (generally COX-2). NSAIDs can be non-specific or can have

a more selective inhibition of the COX-2 enzyme. The COX-1 sparing NSAIDs, including carprofen, deracoxib, firocoxib, and meloxicam, inhibit some COX-1 activity, especially at high doses. NSAID side-effects can result in gastric ulceration, acute kidney injury, and platelet dysfunction. NSAIDs are contraindicated in dehydrated or hypovolemic patients, those with other organ dysfunction or co-morbidity, or those receiving other medications that can potentiate these effects (e.g. diuretics, nephrotoxic drugs, corticosteroids, other NSAIDs).

Induction Agents (see Figure 190.1)

Emergent intubation is frequently necessary in the ED. Induction drugs are generally given intravenously, resulting in rapid unconsciousness and allowing endotracheal intubation. With the exception of combinations involving ketamine or tiletamine, induction drugs are potent respiratory depressants and can result in hypotension from vasodilation. Although most induction agents provide rapid onset of anesthesia, they are not analgesic agents and should not be used as single agents for painful procedures. The combination of induction agents with neuroleptanalgesia can significantly decrease the necessary dose of induction agent for intubation, and thus decrease side-effects. This approach is recommended when intubation is necessary in unstable animals. Regardless of induction protocol, preoxygenation is recommended prior to drug administration.

Propofol is a short-acting intravenous drug that may be used for the induction and maintenance of anesthesia. In addition, it can be used as an adjunctive sedative agent in animals where a neuroleptic combination is not effective alone. Propofol administered as an IV bolus has more potent respiratory depressant and vasodilatory effects compared to its administration as a CRI. Propofol as a CRI may be used to control seizures in patients that are refractory to other therapies (see Chapter 21), and lower doses (e.g. 50–100 μ g/kg/min) can be used to maintain sedation in some patients. Repeated administration of propofol can cause Heinz body anemia in cats, so prolonged usage should be avoided in this species. The benefits of anesthesia with propofol are that patients experience a rapid, smooth recovery; even those receiving long-term infusions of propofol recover relatively rapidly.

Alfaxalone is a synthetic neuroactive steroid that provides anesthesia and muscle relaxation and works in a similar manner to propofol for IV induction and maintenance of anesthesia. Alfaxalone may also be administered by an IM route. Combined with other medications, IM alfaxalone can induce anesthesia in dogs and cats [25,26].

Inhalant Anesthetics (see Figure 190.1)

In general, induction of anesthesia using inhaled agents (e.g. isoflurane, sevoflurane) is not recommended. The high doses required to induce anesthesia can result in significant hypotension and hypoventilation. In addition, the slower induction process may cause emesis during a period when the patient is unable to protect its airway, and may result in aspiration of gastrointestinal contents. In rare circumstances, very aggressive animals that must be anesthetized while breathing 100% oxygen may be induced with inhalant anesthetics. In practice, animals are placed in a plexiglass container that will allow observation during induction and into which gas and inhalant can be introduced and removed. Removal of the animal from the container will release a large amount of anesthetic into the room, and exposure of personnel should be minimized during this process. The use of a tight-fitting mask to induce anesthesia may cause stress to the animal, and carries with it the same risks of an unprotected airway, although it may be used in more tractable or sedated animals. Additional strategies for the aggressive ED patient are discussed in Chapter 199.

Conclusion

In the emergency patient, pain results from multiple pathologies, including trauma, illness, and surgery and, if left untreated, may exacerbate these same etiologies. Effective pre-emptive analgesia may mitigate central sensitization and the development of chronic pain. In humans, prompt delivery of appropriate opioid therapy to the acutely painful patient is a clinical indicator of the quality of emergency care [1,27].

Effective anesthesia and analgesia in the emergent patient relies on anticipation and prompt recognition with early and serial evaluation of pain. The use of scoring systems may make quantification of pain more practical. Analgesia should be tailored to the suspected etiology, duration, and severity of pain, taking into account the patient's overall status, history, and co-morbidities [28]. The use of neuroleptanalgesia can provide both synergistic analgesia and sedation for emergency procedures, and this and other multimodal therapeutic approaches should be employed in emergency patients.

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Anesthetic Concerns and Protocols for Common Conditions

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Introduction

Prior to placing a patient under anesthesia, the clinician should obtain a minimum database that ideally consists of a packed cell volume (PCV), total protein, blood glucose, creatinine, electrolytes, lactate, and urine specific gravity. An ECG and blood pressure reading should also be obtained if indicated [1].

Before induction of anesthesia, it is highly recommended to have immediate vascular access via one or more peripheral venous catheters [1] (see Chapter 178). A laryngoscope and a range of appropriately sized endotracheal tubes should also be readily available. Many emergency patients present with a full stomach and are at risk of aspiration if they vomit or regurgitate and their airway is not adequately protected [1]. See Table 191.1 for an overview of recommendations for specific conditions.

Dystocia/Cesarean Section

(see Chapter 118)

Anesthetic protocols for cesarean section must take both the dam and neonates into consideration. Maternal lethargy and decreased neonatal vitality during the immediate postoperative period can result in decreased colostrum intake and increased neonatal mortality. Ideal protocols utilize drugs with minimal respiratory, cardiovascular, and central nervous system depression [2].

Anesthetic Concerns

Dam

- Animals that have been in active labor for a prolonged period of time may suffer from hypoglycemia and/or hypocalcemia and may require supplementation prior to anesthesia [3].

- Pregnant animals are at increased risk for regurgitation and aspiration due to a progesterone-induced decrease in lower esophageal sphincter tone and prolonged gastric emptying times [4].
- High levels of progesterone result in a 16–40% decrease in the minimum alveolar concentration (MAC) of inhalant anesthetics [3].
- The gravid uterus reduces the dam's functional residual capacity (FRC) and oxygen reserve within the lungs. This, combined with an increase in oxygen consumption associated with pregnancy, can result in hypoxemia during even short periods of apnea [3].
- Ventilation and venous return may be impeded when the dam is placed in dorsal recumbency.

Neonate

- All anesthetic drugs including inhalants cross the placental barrier, resulting in a variable amount of neonatal depression [2].
- Fetal blood flow is entirely dependent on maternal cardiac output. Anything that decreases uterine arterial flow will decrease fetal oxygen and nutrient delivery [3].
- Respiratory depression is of extreme concern in the neonate as even small changes in tidal volume and respiratory rate can result in hypoxemia [3].

Protocols

A primary goal of anesthesia for cesarean section is to minimize fetal concentrations of anesthetic drugs with respiratory, cardiovascular or central nervous system depression. Drugs that can be antagonized are ideal choices because they can be reversed in neonates after delivery [3].

Most animals undergo cesarean section without premedication, as most sedatives and tranquilizers have cardiovascular and respiratory side-effects that have been shown to increase fetal mortality. Alpha-2 agonists,

Table 191.1 Anesthetic protocols for common emergencies. Doses reflect those commonly used at Cummings School of Veterinary Medicine.

Anesthetic emergency	Premedication	Induction	Maintenance	Postoperative
Dystocia/ C-section Cat and dog	None	Propofol 6 mg/kg IV to effect Alfaxalone 1.5 mg/kg (dog), 3 mg/kg (cat) IV to effect	Isoflurane or sevoflurane Incisional block with lidocaine (1 mg/kg) and bupivacaine (1 mg/kg) Buprenorphine (0.01 mg/kg) IV after delivery	Cat Meloxicam 0.1 mg/kg SC once Dog Carprofen 2.2 mg/kg SC once Or Meloxicam 0.1 mg/kg SC once
Enucleation Cat and dog	Opioid: fentanyl (3–5 µg/kg), hydromorphone (0.1 mg/kg), methadone (0.3–0.5 mg), IM or IV Phenothiazine (otherwise healthy): acepromazine (0.01–0.05 mg/kg) IM/IV Benzodiazepine (sick/debilitated): midazolam (0.1–0.2 mg/kg) IV/IM, diazepam (0.1–0.2 mg/ kg) IV Anticholinergic: atropine (0.02 mg/kg) or glycopyrrolate (0.01 mg/kg) IM/IV	Propofol 4 mg/kg IV to effect Alfaxalone 1.5 mg/kg (dog), 3 mg/kg (cat) IV to effect	Isoflurane or sevoflurane Lidocaine CRI (50 µg/kg/min, dogs only) Ketamine CRI (0.6 mg/kg/h)	Cat Buprenorphine (0.01 mg/kg) IV Meloxicam 0.1 mg/kg SC once Dog Buprenorphine (0.01 mg/kg) IV Carprofen 2.2 mg/kg SC Or Meloxicam 0.1 mg/kg SQ
Foreign body Cat and dog	Opioid: fentanyl (3–5 µg/kg), hydromorphone (0.1 mg/kg), methadone (0.3–0.5 mg), IM or IV Phenothiazine (otherwise healthy): acepromazine (0.01–0.05 mg/kg) IM/IV Benzodiazepine (sick/debilitated): midazolam (0.1–0.2 mg/kg) IV/IM, diazepam (0.1–0.2 mg/ kg) IV	Ketamine (5.5 mg/kg) IV with diazepam or midazolam (0.28 mg/kg) IV to effect Propofol 4 mg/kg IV to effect Alfaxalone 1.5 mg/kg (dog), 3 mg/kg (cat) IV to effect	Isoflurane or sevoflurane +/- fentanyl CRI (0.1–0.5 µg/kg/ min) Lidocaine CRI (50 µg/kg/min, dogs only) Ketamine CRI (0.6 mg/kg/h)	Continue pure mu-agonist opioid intermittently or fentanyl CRI (1–3 µg/kg/h) IV
Gastric dilation- volvulus Dog	Opioid: fentanyl (3–5 µg/kg), hydromorphone (0.1 mg/kg), methadone (0.3–0.5 mg), IM or IV +/- Benzodiazepine midazolam (0.1–0.2 mg/ kg) IV/IM, diazepam (0.1–0.2 mg/kg) IV	Ketamine (5.5 mg/kg) IV with diazepam or midazolam (0.28 mg/kg) IV to effect Recumbent/ debilitated: Fentanyl (3 µg/kg) IV Midazolam (0.1 mg/kg) IV Ketamine (2 mg/kg) IV	Isoflurane or sevoflurane Fentanyl CRI (0.1–0.5 µg/kg/min) IV Lidocaine CRI (50 µg/kg/min, dogs only) IV Ketamine CRI (0.6 mg/kg/h) IV	Continue pure mu-agonist opioid intermittently or fentanyl CRI (1–3 µg/kg/h) IV

Hemoabdomen

Dog

Opioid: fentanyl (3–5 µg/kg), hydromorphone (0.1 mg/kg), methadone (0.3–0.5 mg), IM or IV
+ /– **Benzodiazepine** midazolam (0.1–0.2 mg/kg) IV/IM, diazepam (0.1–0.2 mg/kg) IV

Ketamine (5.5 mg/kg) IV
with diazepam *or* midazolam
(0.28 mg/kg) IV to effect

Recurrent/

debilitated:

Fentanyl (3 µg/kg) IV

Midazolam (0.1 mg/kg) IV

Ketamine (2 mg/kg) IV

Isoflurane or sevoflurane

Fentanyl CRI (0.1–0.5 µg/kg/min) IV
Lidocaine CRI (50 µg/kg/min, dogs
only) IV

Ketamine CRI (0.6 mg/kg/h) IV

Continue pure mu-agonist opioid
intermittently *or* fentanyl CRI
(1–3 µg/kg/h) IV

Major wounds

Cat and dog

Opioid: fentanyl (3–5 µg/kg), hydromorphone (0.1 mg/kg), methadone (0.3–0.5 mg), IM or IV

Otherwise healthy: acepromazine (0.01–0.05 mg/kg) IM/IV

or
Dexmedetomidine (1–5 µg/kg) IM or IV

Sick/debilitated: midazolam (0.1–0.2 mg/kg) IV
or IM, diazepam (0.1–0.2 mg/kg) IV

Isoflurane or sevoflurane

Lidocaine CRI (50 µg/kg/min, dogs
only) IV

Ketamine CRI (0.6 mg/kg/h) IV

Cat

Continue pure mu-agonist opioid
intermittently

Meloxicam 0.1 mg/kg SC once *or*
Robenacoxib (1 mg/kg) PO for
3 days

Dog

Continue pure mu-agonist opioid
intermittently

Carprofen 2.2 mg/kg SC *or*
Meloxicam 0.1 mg/kg SC

Pacemaker

Dog

Opioid: fentanyl (3–5 µg/kg), hydromorphone (0.1 mg/kg), methadone (0.3–0.5 mg), IM or IV

+ /– **Benzodiazepine** midazolam (0.1–0.2 mg/kg) IV/IM, diazepam (0.1–0.2 mg/kg) IV

**Significant heart disease/
failure:**

Diazepam (0.1 mg/kg) IV
followed by Etomidate
(1 mg/kg) IV to effect

Minimal heart disease:

Propofol 4 mg/kg IV to effect
Alfaxalone 1.5 mg/kg (dog)
IV to effect

Isoflurane or sevoflurane

Buprenorphine (0.01 mg/kg) IV

Urethral obstruction

Dog

Opioid: fentanyl (3–5 µg/kg), hydromorphone (0.1 mg/kg), methadone (0.3–0.5 mg), IM or IV

+ /– **Benzodiazepine** midazolam (0.1–0.2 mg/kg) IV/IM, diazepam (0.1–0.2 mg/kg) IV

Propofol 4 mg/kg IV to effect

Alfaxalone 1.5 mg/kg (dog)
IV to effect

Isoflurane or sevoflurane

Buprenorphine (0.01 mg/kg) IV
Carprofen 2.2 mg/kg SC *or*
Meloxicam 0.1 mg/kg SC

CRI, constant-rate infusion; IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

particularly xylazine, should be avoided due to their association with decreased fetal survival [4]. In calm patients, intravenous catheter placement, as well as the initial clip and surgical prep, should take place prior to administration of anesthetic medications.

Due to the increased risk for regurgitation and aspiration, patients should be induced in sternal recumbency with their head elevated. Propofol and alfaxalone are ideal induction agents due to their short half-life and rapid metabolism. An incisional line block with lidocaine and bupivacaine prior to surgery can decrease response to surgical stimulation, as well as providing some intra- and postoperative analgesia [4].

It is important to avoid excessive concentrations of inhalants to minimize neonatal apnea. Inhalant anesthetics readily cross the placenta, but are rapidly cleared as long as the neonate is breathing shortly after delivery.

Buprenorphine can be administered IV or IM to the dam for pain control following delivery. Buprenorphine is selected over other opioids due to its long duration of action and minimal cardiovascular and respiratory side-effects [3]. As long as preoperative laboratory testing is normal, and mean arterial blood pressures remain greater than 60 mmHg during surgery, a single dose of carprofen or meloxicam will provide additional analgesia for the dam [4]. This opioid and postoperative NSAID combination typically provides adequate analgesia for the dam, and has minimal likelihood of interfering with her ability to care for the newborns.

Enucleation/Proptosis

Proptosis and other ocular conditions prompting emergent enucleation are typically caused by trauma. As a result, the patient should be thoroughly assessed for concurrent life-threatening injuries prior to being placed under anesthesia and an appropriate minimum database should be obtained [4].

Anesthetic Concerns

- Pressure or manipulation of the globe during surgery may elicit the oculocardiac reflex. This reflex is mediated by the trigeminal and vagus nerves, and can result in the development of dysrhythmias such as bradycardia, ventricular ectopy or asystole [3].
- Most anesthetic drugs do not affect or even decrease intraocular pressure (IOP) but common side-effects, such as vomiting, can result in a transient increase in IOP.
- Stimulation of the larynx and pharynx during intubation can transiently increase IOP [3].
- Enucleation is a painful procedure and appropriate analgesics should be administered.

Protocols

Patients with ocular trauma should be handled carefully, as even routine physical restraint or inadvertent pressure on the jugular veins can increase IOP. Intravenous catheter placement in a hindlimb may be less stressful on the patient and will also provide easier access for drug administration during the procedure.

Premedication should include an opioid in combination with a benzodiazepine or phenothiazine administered IV or IM. An anticholinergic (i.e. glycopyrrolate or atropine) can also be included in the premedication to reduce the risk of the oculocardiac reflex during surgery [4]. Induction with propofol or alfaxalone will allow for a smooth, rapid intubation. Maintenance of anesthesia can be achieved with an inhalant gas such as isoflurane or sevoflurane.

Heart rate should be monitored closely during the procedure. If there is any concern for initiation of the oculocardiac reflex, the surgeon should be asked to stop the procedure and atropine should be administered IV immediately.

Following surgery, any animal that is dysphoric can be given low-dose acepromazine or dexmedetomidine. This will provide mild sedation and help reduce the possibility of trauma to the surgical site [4]. Postoperative analgesia consists of an opioid and an NSAID to reduce swelling and pain at the surgical site [4].

Foreign Body (Esophageal, Gastric, Intestinal)

Patients with gastrointestinal foreign bodies often present with a history of vomiting, anorexia, and abdominal discomfort. These animals are typically dehydrated due to frequent vomiting and decreased fluid intake.

Preoperative laboratory testing should include a chemistry panel and complete blood count (CBC), as gastrointestinal disease often results in electrolyte and acid-base disturbances. The most common abnormalities seen include a hypochloremic metabolic alkalosis with low serum potassium values, due to loss of gastric contents secondary to vomiting (see Chapter 74). Additional laboratory testing may show evidence of dehydration, with elevated PCV, total protein, BUN, and creatinine concentrations [3].

Fluid deficits and electrolyte abnormalities should ideally be corrected with intravenous administration of balanced electrolyte solutions prior to the induction of anesthesia but with severe obstructions, chloride abnormalities cannot be resolved until the obstruction is removed (see Chapter 167). Because hypokalemia can result in muscle weakness, decreased GI motility

and cardiac arrhythmias, severe cases should be corrected with the intravenous administration of potassium chloride at a rate no greater than 0.5 mEq/kg/hr [3] (see Chapter 109).

Anesthetic Concerns

- Patients with gastrointestinal foreign bodies should be assumed to have a full stomach, making rapid airway capture a priority at induction in order to prevent aspiration of stomach contents.
- Body heat is rapidly lost from exposed viscera during abdominal surgery which may result in hypothermia and decreased inhalant requirements.
- For endoscopy, opioids and atropine may increase pyloric sphincter tone, making it difficult to pass the endoscope into the proximal duodenum [3].
- Overinsufflation of the stomach during endoscopy can result in decreased venous return, as well as vasovagal stimulation and bradycardia [3].

Protocols

Animals presenting for exploratory laparotomy should be premedicated with a pure mu-agonist opioid for its analgesic and MAC-sparing properties. A preanesthetic sedative may also be administered, depending on the attitude of the patient. Debilitated patients can be given a benzodiazepine and opioid combination prior to induction. More stable patients can be given low-dose acepromazine in combination with an opioid. Acepromazine is an excellent anxiolytic with central antiemetic properties, but should not be administered to dehydrated or hypovolemic patients [3].

Ketamine in combination with a benzodiazepine is an excellent induction agent for exploratory laparotomies, especially in hemodynamically compromised patients [3]. Ketamine acts as a sympathomimetic, providing cardiovascular support as well as somatic analgesia. In hemodynamically stable patients, propofol or alfaxalone are suitable alternatives, keeping in mind that neither drug provides additional analgesia.

Maintenance of anesthesia can be achieved via inhalant anesthetics such as isoflurane or sevoflurane. Nitrous oxide is contraindicated because it rapidly diffuses into gas-filled compartments, resulting in an increased volume of air trapped in the viscera [3]. For hemodynamically compromised patients, inhalant concentrations should be kept as low as possible with the use of multimodal techniques such as lidocaine, ketamine, and/or fentanyl continuous rate infusions.

Postoperative pain can be managed with intermittent dosing of a pure mu-agonist opioid or a constant-rate infusion (CRI) of an opioid. NSAIDs are contraindicated

for analgesia in patients with gastrointestinal disease due to their effects on intestinal blood flow and association with gastric ulceration [3].

Gastric Dilation-Volvulus (see Chapter 82)

Gastric dilation-volvulus (GDV) is an acute, life-threatening disorder caused by distension of the stomach accompanied by a 90–360° rotation on its mesenteric axis, resulting in complete gastric outflow obstruction. Dogs with GDV often present with acute onset of abdominal distension accompanied with abdominal pain and non-productive retching. These cases can present in multiple types of shock, including obstructive, hypovolemic, and distributive [1] (see Chapter 152).

Anesthetic Concerns

- Extreme gastric distension and increased intra-abdominal pressure can compress the caudal vena cava, portal vein, and splanchnic vasculature, resulting in significant impairment of venous return to the heart [3].
- Gastric distension also prevents caudal displacement of the diaphragm, resulting in decreased pulmonary compliance and functional residual capacity [3].
- Cardiac arrhythmias are common and can include sinus tachycardia, and ventricular tachycardia [3].
- Splenomegaly can occur secondary to displacement by the rotated stomach.
- Hemoabdomen and accompanying anemia may occur as a result of tearing of the short gastric vessels [3].
- GDV is considered a painful condition and analgesics should be administered as part of the initial therapy.

Protocols

Patients with GDV require aggressive fluid resuscitation, the details of which are beyond the scope of this chapter and are discussed elsewhere (see Chapter 153). At least two large-bore catheters should be placed in both cephalic veins, or one cephalic vein and a jugular vein. Gastric decompression by trocarization or orogastric tube placement should be performed prior to induction in order to optimize cardiac output.

A pure mu-opioid, alone or in combination with a benzodiazepine, can be used as a premedication or to facilitate gastric decompression. Full mu-agonists are the drug of choice because of their MAC-sparing effects and minimal cardiovascular effects. Fentanyl, methadone, hydromorphone or oxymorphone administered IV may be less likely to cause nausea compared to other mu-agonists such as morphine [1].

Ketamine in combination with a benzodiazepine is recommended for induction in patients without significant arrhythmias or cardiovascular disease. Depressed or recumbent patients may be induced with a combination of fentanyl-midazolam-ketamine. Propofol is a less ideal induction agent in this patient population due to the potential for significant hypotension following IV administration.

Maintenance of anesthesia can be achieved via inhalant anesthetics such as isoflurane or sevoflurane. Nitrous oxide is contraindicated prior to gastric decompression because it rapidly diffuses into gas-filled compartments, resulting in organ distension and increasing intragastric volume [3]. Because inhalant anesthetics cause dose-dependent vasodilation and myocardial depression, their maintenance concentrations during surgery should be decreased as much as possible by the use of multimodal anesthetic techniques. A CRI of fentanyl or morphine may be used intraoperatively for their inhalant-sparing effects as well as additional analgesia. Lidocaine plus ketamine CRIs will provide multimodal analgesia, as well as further reducing the amount of inhalant anesthetic required. Lidocaine has the additional benefit of preventing or reducing the severity of ventricular arrhythmias [3].

An attempt should be made to place an arterial catheter in the dorsal pedal artery for invasive blood pressure monitoring, as many dogs with GDV are hypotensive (see Chapter 178). However, this attempt should not delay surgery. Fluid therapy during anesthesia should be continuously reassessed and modified on the basis of parameters such as blood pressure, PCV, total protein concentrations, heart rate, and lactate concentrations. Hypertonic saline, colloids, and blood products should be available in case hypotension refractory to isotonic crystalloid therapy occurs, or excessive bleeding and coagulopathy develop [3] (see Section 5). If necessary, inotropic drugs such as dopamine and dobutamine can be administered to maintain mean arterial pressures above 60 mmHg. In patients with hypotension refractory to fluid therapy and inotropic support, administration of vasopressor drugs such as norepinephrine, phenylephrine or vasopressin may be necessary [3].

Hemoabdomen (see Chapter 84)

Patients with a hemoabdomen often present in hypovolemic shock. Prior to undergoing anesthesia, these animals should be stabilized with administration of intravenous crystalloid solutions, hypertonic saline, and/or colloids (see Chapter 153). Resuscitation goals should include a heart rate below 150 bpm, systolic blood

pressure greater than 90 mmHg, and PCV/TS of 20% and 4g/dL, respectively, in conjunction with a decreasing lactate [4]. If blood loss exceeds 20% of the patient's estimated blood volume, or if the PCV is less than 20%, whole blood or packed RBC should be administered [4] (see Chapters 176 and 177).

Anesthetic Concerns

- The combination of pre-existing hypovolemia and administration of anesthetic agents that cause vasodilation can result in a profound hypotension.
- Cardiac arrhythmias are common and can include sinus tachycardia, and ventricular tachycardia (see Chapter 53).
- Until the source of bleeding is controlled, ongoing blood loss can occur.

Protocols

The same anesthetic protocols outlined for GDV patients apply.

Major Wounds (see Chapter 166)

Wounds that require repair under general anesthesia in the emergency room are typically the result of trauma. These patients may have severe tissue injury, inflammation, and potentially hemorrhage. Trauma patients may present in a state of shock, and stabilization prior to undergoing anesthesia is essential. Diagnostic imaging should also be performed to look for communication of wounds with the abdomen or thorax, or concurrent conditions such as pneumothorax or intracavitary effusion [3].

Anesthetic Concerns

- Pain associated with trauma is complex and can have effects on the cardiovascular and neuroendocrine systems as well as wound healing.

Protocols

Animals presenting for wound repair should be premedicated with a pure mu-agonist opioid for its analgesic and MAC-sparing properties. A preanesthetic sedative may also be administered depending on the attitude of the patient. Debilitated patients can be given a benzodiazepine and opioid combination prior to induction. More stable patients can be administered acepromazine or an alpha-2 agonist in combination with an opioid.

Ketamine in combination with a benzodiazepine is an excellent induction agent for wound repairs, as ketamine provides analgesia to the skin and muscular tissue. Propofol or alfaxalone are suitable alternatives, although neither drug provides additional analgesia to the patient.

Maintenance of anesthesia can be achieved via inhalant anesthetics such as isoflurane or sevoflurane. Whenever possible, regional anesthetic techniques with lidocaine or bupivacaine should be used to provide analgesia and reduce the amount of inhalant required [3]. Postoperative pain can be managed with the combination of an opioid and an NSAID to reduce swelling and pain at the surgical site [4].

Pacemaker

The most common reason patients present for emergency pacemaker placement is for bradyarrhythmias such as AV block (see Chapter 53). AV block is defined as the prolongation or intermittent failure of transmission of atrial depolarization through the AV node to the ventricles. First-degree AV block involves slowed conduction of depolarization through the AV node, visible as a prolongation of the P-R interval on the ECG. Second-degree AV block is characterized by intermittent failure of atrial depolarization to be conducted through the AV node, visible as one or more isolated P-waves that are not followed by a QRS complex [3].

Third-degree AV block is complete failure of AV nodal conduction and subsequent dissociation of the atria and ventricles. This is visible on an ECG as regular P-wave generation at normal sinus rate, and a ventricular escape rhythm (30–50 bpm in dogs, 60–80 bpm in cats) that has no association with the P-waves [3]. Typically, only “high-grade” second-degree and third-degree AV blocks require placement of a permanent ventricular pacemaker.

Anesthetic Concerns

- Patients with AV block already have reduced cardiac output, increasing their risk of hypotension under anesthesia.
- Introduction of the catheter and pacemaker into the heart may trigger arrhythmias.

Protocols

Animals presenting for placement of a permanent ventricular pacemaker should have temporary transthoracic pacing pads applied prior to premedication, in case drug administration results in a more severe bradycardia.

Pacemaker patients should be premedicated with a pure mu-agonist opioid for its analgesic and MAC-sparing properties. A benzodiazepine may be administered along with the opioid, depending on the temperament of the patient, and for additional MAC-sparing effects.

If there is concern for significant heart disease and/or heart failure, etomidate in combination with a benzodiazepine is the induction agent of choice. If there is no evidence of significant heart disease, propofol or alfaxalone are suitable alternatives for induction. Maintenance of anesthesia can be achieved via inhalant anesthetics such as isoflurane or sevoflurane. Arrhythmias associated with introduction of transvenous catheters or the pacemaker itself can be treated with an IV bolus of lidocaine (2 mg/kg). However, it is important that the ventricular escape beats not be confused for arrhythmias, as their suppression can result in cardiac arrest. If necessary, inotropic drugs such as dopamine or dobutamine can be administered to maintain mean arterial pressures above 60 mmHg. Postoperative pain can be managed with an opioid such as buprenorphine.

Urethral Obstruction (Canine)

Dogs presenting for urethral obstruction typically require general anesthesia for placement of a urinary catheter, since blockage usually occurs from cystic or urethral calculi. Prior to anesthesia, the patient's hydration status and electrolyte values (particularly potassium) should be assessed and abnormalities treated with IV fluids if necessary [4] (see Chapter 109).

For significant hyperkalemia (potassium > 7.5 mEq/L), calcium gluconate and dextrose (+/– regular insulin) should be administered for patient stabilization. Calcium gluconate does not directly influence serum potassium levels but stabilizes cell membranes and helps minimize cardiotoxic effects of hyperkalemia. Dextrose induces the endogenous release of insulin, which aids in the translocation of potassium out of the bloodstream and into cells. Regular insulin may also be administered in conjunction with dextrose, but requires close monitoring of the patient's blood glucose for signs of hypoglycemia [4]. Other treatment options indicated for persistent life-threatening hyperkalemia include sodium bicarbonate and beta-2 agonists.

Anesthetic Concerns

- Hyperkalemia influences the electrical excitability of the heart, and can result in bradyarrhythmias and ultimately cardiac arrest.
- Elevated serum potassium levels can be exacerbated with hypoventilation and respiratory acidosis [4].

Protocols

Dogs with urethral obstruction should be premedicated with a mu-agonist opioid for its analgesic and MAC-sparing properties. A short-acting induction agent such as propofol or alfaxalone is recommended, given that urethral catheterization should not take long once the patient is anesthetized. Maintenance of anesthesia

can be achieved via inhalant anesthetics such as isoflurane or sevoflurane. Intermittent positive pressure ventilation to normocapnia (PaCO_2 35–45 mmHg) should be implemented in order to prevent exacerbation of hyperkalemia by respiratory acidosis [4]. In dogs without evidence of acute or chronic kidney disease, NSAIDs can be administered postoperatively for pain management and to decrease urethral inflammation [4].

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Sedation for the Emergency Room Patient

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Introduction

Emergency room clinicians commonly examine and treat animals presenting with injuries or underlying conditions requiring sedation. These animals may be painful, anxious or aggressive and may have underlying co-morbidities, making the choice of drugs used important. Unfortunately, sedation in the ER is not a one-size-fits-all scenario as one drug may be safe for one patient but may cause severe cardiovascular compromise in another. For this reason, it is important that clinicians be familiar with the pharmacology of the commonly used analgesics and sedatives and aware of the indications and contraindications for each drug.

In addition to understanding the pharmacology of the sedatives, it is important that the patient be appropriately monitored, oxygen be provided, and the patient's airway be protected when indicated. When using heavy sedation, one should always be prepared to intubate and have all necessary equipment ready, including a laryngoscope, induction agent, endotracheal tubes, and means to supply positive pressure ventilation. Monitoring during sedation procedures should include all standard monitors including end-tidal carbon dioxide (if intubated), pulse oximeter, ECG, and blood pressure. Pulse oximetry provides valuable information such as pulse rate and oxygenation, as well as an idea of whether the cardiac rhythm is normal. If at any time the oxygenation decreases or hypoventilation occurs, the patient should be intubated immediately.

Healthy Dog/Cat Emergencies

Examples of patients presenting as systemically healthy emergencies include simple laceration repairs, fractures/luxations, fractious cat examination, urinary tract issues, or patients presenting for diagnostic imaging such as radiographs or ultrasound. These patients are

physiologically normal but need sedation to either diagnose or treat the presenting disease/injury.

Several different drug protocols may be chosen and used in healthy dogs and cats and should be designed based on the amount of pain expected from the procedure, the length of procedure, and the degree of sedation required. The attending clinician should evaluate the need for presedation bloodwork and treat any suspected underlying issues or electrolyte abnormalities prior to sedation.

Dog: Fast, Non-Painful Procedure (Radiographs, Blood Draws, Small Laceration Repair)

- Option 1: Butorphanol (0.2–0.4 mg/kg) + with dexmedetomidine (3–7 µg/kg) +/– midazolam (0.2–0.3 mg/kg) or ketamine (2–3 mg/kg) IM
- Option 2: Butorphanol with either acepromazine (0.02–0.05 mg/kg) +/– ketamine (3–5 mg/kg) IM
- Option 3: Butorphanol + midazolam + alfaxalone (1–2 mg/kg) IM

Cat: Fast, Non-Painful Procedure (Fractious Cat Exam, Radiographs, Blood Draws)

- Option 1: Butorphanol (0.3–0.4 mg/kg) with dexmedetomidine (5–7 µg/kg) +/– midazolam (0.3 mg/kg) or ketamine (3–5 mg/kg) IM
- Option 2: Butorphanol with either midazolam (0.2–0.3 mg/kg) or dexmedetomidine (3–5 µg/kg) + alfaxalone (1–2 mg/kg) IM

Healthy Dog: Painful Procedure (e.g. Aural Hematoma, Laceration Repair, Fracture Stabilization, Closed Hip Reduction)

- Option 1: Full µ-opioid + dexmedetomidine +/– midazolam OR ketamine IM
- Option 2: Full µ-opioid + acepromazine +/– ketamine IM

- Option 3: Full mu-opioid + midazolam +/- alfaxalone IM
- Option 4: Any of the above combinations + propofol sedation

Healthy Cat: Painful Procedure (Laceration Repair, Fracture Stabilization, Closed Hip Reduction)

- Option 1: Full mu-opioid with dexmedetomidine (5–10 µg/kg) +/- midazolam (0.3 mg/kg) or ketamine (3–5 mg/kg) IM
- Option 2: Full mu-opioid with either midazolam (0.2–0.3 mg/kg) or dexmedetomidine (3–5 µg/kg) + alfaxalone (1–2 mg/kg) IM
- Option 3: Buprenorphine (0.015–0.02 mg/kg) + dexmedetomidine (5–10 µg/kg) +/- ketamine (3–5 mg/kg) IM
- Option 4: Any of the above combinations + alfaxalone OR propofol sedation

Rapid Sedation For Upper Airway Obstruction/Respiratory Compromise

Intubation and oxygen supplementation must be provided.

- Option 1: Butorphanol (0.2–0.3 mg/kg) + midazolam (0.2–0.3 mg/kg) +/- alfaxalone (1 mg/kg) IM
- Option 2: Butorphanol (0.1–0.2 mg/kg) + propofol (2–4 mg/kg) IV
- Option 3: Butorphanol + mixture of 2 mg/kg ketamine and 2 mg/kg propofol (“ketafol”) IV

Sedation Protocols for Brachycephalic Dogs

Brachycephalics are at increased risk for upper airway obstruction, regurgitation, and aspiration pneumonia than their dolichocephalic counterparts. It is for this reason that *intubation is recommended* to provide airway protection and oxygen supplementation.

Non-Painful Procedures

Intubation highly recommended.

- Option 1: Butorphanol (0.2–0.3 mg/kg) + dexmedetomidine (3–5 µg/kg) IM OR acepromazine (0.02–0.03 mg/kg) IM + propofol (2–4 mg/kg) IV to effect
- Option 2: Substitute alfaxalone (1–2 mg/kg) for propofol in above combinations

Painful Procedures

Intubation highly recommended.

- Option 1: Methadone (0.2–0.3 mg/kg) + dexmedetomidine (3–5 µg/kg) OR acepromazine (0.02–0.03 mg/kg) IM + propofol to effect or ketafol to effect

Table 192.1 Full mu-opioid doses.

Drug	Dose range (mg/kg)
Hydromorphone	0.1 IM; 0.05 IV
Oxymorphone	0.1 IM; 0.05 IV
Methadone	0.3–0.5 IM; 0.1–0.2 IV
Morphine	0.5 IM
Fentanyl	3–5 µg/kg IV

- Option 2: Oxymorphone (0.1 mg/kg) + dexmedetomidine OR acepromazine IM + propofol OR ketafol to effect
- Option 3: Substitute alfaxalone for propofol OR ketafol in above combinations

Geriatric, Debilitated, or Hemodynamically Unstable Cat or Dog Emergencies

It is common for sick, weak, debilitated, hemodynamically unstable patients to present to the ER in need of diagnostics to aid in the proper recognition and treatment of their disease. Common presenting signs include uncontrolled hemorrhage, respiratory distress, pericardial effusion, traumatic injury, seizure activity, arrhythmias, etc. These patients need sedation protocols that will not depress their cardiac output, worsen bleeding, depress respiratory drive, or worsen seizure activity. One should always be prepared to emergently intubate these patients and reversal agents should be easily accessible.

The following protocols can be used for these patients.

- Option 1: Butorphanol (0.1–0.15 mg/kg) + midazolam (0.1–0.3 mg/kg) IV
- Option 2: Full mu-opioid (Table 192.1) + midazolam (0.1–0.3 mg/kg) IV
- Option 3: Butorphanol (0.2–0.3 mg/kg) + midazolam (0.2 mg/kg) + alfaxalone (1–2 mg/kg) IM if unable to place intravenous catheter

Sedation Agents

Opioids

Butorphanol is a mu-opioid receptor antagonist and a kappa-opioid receptor agonist used in non-painful procedures or to achieve sedation [1,2]. It is often used in animals with cardiac disease due to its lack of significant cardiovascular depression, wide therapeutic window, and short duration of action [3]. Butorphanol should not be used in painful procedures as it has been shown in several studies to be a poor analgesic drug [1,4,5].

Buprenorphine is a partial mu-opioid agonist used to provide analgesia in moderate-to-severe pain. It is commonly used in cats as it provides good analgesia with less dysphoria and hyperthermia than full mu-opioid agonists [1,6].

Full mu-opioid agonists include oxymorphone, hydromorphone, fentanyl, methadone, and morphine. These drugs are agonists at both mu-opioid and kappa-opioid receptors and exert maximal clinical response when bound to these receptors. All full mu-agonists cause centrally mediated, vagally induced bradycardia, although drugs such as methadone may do so to a greater degree than others such as morphine [7,8]. Other side-effects of full mu-agonists in dogs include panting, dysphoria, ileus, vomiting, sedation, hypothermia, miosis, respiratory depression and reduced response to carbon dioxide, and defecation [9–11]. Side-effects are similar in cats but often include central nervous system excitation instead of sedation, mydriasis, hyperthermia, and, less often defecation [9,12,13]. Hydromorphone can be used in cats but is associated with dysphoria and hyperthermia [14,15].

Methadone differs from the other full mu-opioid agonists in that it also has NMDA antagonist properties [7,16]. Owing to its unique NMDA antagonism, methadone may be useful in patients experiencing hyperalgesia or chronic pain, such as dogs presenting with cervical or thoracolumbar pain.

Full mu-opioids are useful in the ER setting because of their excellent analgesic and sedative properties.

Antagonists

Naloxone is the mu-opioid and kappa-opioid receptor antagonist and can be used to reverse all opioids [17]. Butorphanol can also be given at low doses (0.05 mg/kg IV to effect) to reverse unwanted side-effects of full mu-opioids, such as sedation, while sparing some of the analgesic effects. These agents are useful in the ER setting, as many patients need to be awake enough after procedures to be discharged quickly.

Alpha-2 Agonists

Alpha-2 agonists cause dose-dependent cardiovascular responses, including initial vasoconstriction followed by baroreceptor-mediated bradycardia and subsequent disruption of centrally mediated sympathetic outflow and an indirect reduction in cardiac output [10,18]. Alpha-2 receptors are abundant in the body and are found in the dorsal horn of the spinal cord, brain, and the periphery. They play a significant role in modulating the pain signals descending from the brain thereby reducing hyperalgesia.

Dexmedetomidine is an alpha-2 agonist commonly used in the emergency department due to its sedative

and analgesic properties. Patients in which to avoid the use of dexmedetomidine include those with degenerative valvular disease or systolic dysfunction, patients with reduced cardiac output and oxygen delivery, critically ill patients, and those with bradyarrhythmias such as sick sinus syndrome or third degree AV block. The use of dexmedetomidine is controversial in cats with hypertrophic cardiomyopathy (HCM) although it has been shown to be of benefit in those with left ventricular outflow tract obstruction [19]. Adding an opioid and possibly another sedative such as midazolam or alfaxalone to the protocol will reduce the doses of dexmedetomidine needed in cats with known HCM. Patients sedated with dexmedetomidine remain noise and light sensitive and can be aroused, even under seemingly heavy sedation.

Supplemental oxygen should always be supplied to the patient to improve oxygen delivery to all tissues (see Chapter 181).

Acepromazine

Acepromazine is a phenothiazine used to provide long-lasting sedation in both cats and dogs. It must be used in conjunction with an opioid due to its lack of analgesic effects. In addition to providing sedation, acepromazine is also an antiemetic, antiarrhythmic, antihistaminic agent. Its cardiovascular side-effects include vasodilation and tachycardia. Acepromazine can be used in the ER in patients with seizures as it has not been shown to affect the seizure threshold [20,21]. It may be useful in animals in which an increase in afterload must be avoided, such as those with degenerative valvular disease or pulmonic stenosis.

Benzodiazepines

Benzodiazepines are commonly used to provide sedation and muscle relaxation and are often chosen for their lack of negative cardiorespiratory effects. The two benzodiazepines used in the ER are midazolam and diazepam, which have very similar pharmacological profiles and are often used interchangeably. Midazolam differs from diazepam in that it is water soluble and can be administered IM and has a shorter half-life, making its effects shorter lived [22]. Diazepam contains propylene glycol and should not be given IM as it will have erratic and poor absorption and can cause tissue irritation. Benzodiazepines are safe to use in patients with cardiac, respiratory, renal, or neurological disease as they cause minimal cardiorespiratory depression, maintain cardiac output and renal perfusion, and suppress seizure activity.

The use of benzodiazepines is controversial in patients with hepatic disease due to their dependence on phase I hepatic metabolism. Since the effects of benzodiazepines

can be fully reversed by the antagonist flumazenil, many clinicians choose to use these drugs in animals with hepatic disease [23]. Although these drugs are often used to sedate a patient in the ER, it is not uncommon to note dysphoria and excitement in both dogs and cats [24,25].

Induction Agents Used for Sedation

Propofol

Propofol is a short-acting sedative hypnotic agent commonly used to provide procedural sedation in humans in the ER [26,27]. Propofol has a rapid onset and offset with a smooth recovery profile. Side-effects are dose dependent and include vasodilation, respiratory depression, and reduced cardiac output [27–29]. In cats and dogs, propofol is not often used as a sedative but more commonly as an induction agent into anesthesia. If propofol is used carefully and titrated to effect, it can be given in small amounts to allow enough sedation in order to complete many procedures in a timely manner. It should always be used with adequate premedication and analgesia and not as a sole sedation agent. When using propofol as a sedative, it is imperative that supplies be in place to perform a rapid intubation if necessary. It is also mandatory that oxygen supplementation be provided and that the patient's vital signs be monitored (see Chapter 181).

Alfaxalone

Alfaxalone is a neurosteroid that enhances the actions of GABA_A to produce muscle relaxation, sedation, and anesthesia. Alfaxalone comes as a clear, colorless, non-irritating, aqueous formulation and is marketed

for intravenous use only, although it can be used off-label and administered IM as part of a sedation protocol. Alfaxalone has a similar pharmacodynamic profile to propofol in the dog and cat, although it may cause less vasodilation and less reduction in cardiac output [30–32]. When used as part of a sedation protocol in dogs or cats, alfaxalone can be added to an opioid and a benzodiazepine or dexmedetomidine; both combinations have been shown to provide adequate muscle relaxation and sedation to perform minor procedures [33,34]. Alfaxalone is particularly helpful in sedating aggressive animals in the ER whose underlying cardiac status is unknown [35].

Ketamine

Ketamine is a rapid-acting dissociative anesthetic used in dogs and cats to induce sedation without significant respiratory depression [36]. In addition to providing sedation, it is also used as an induction agent and as part of analgesic protocols. Ketamine is becoming more commonly used as part of procedural sedation in pediatric emergency rooms owing to its rapid effects, lack of cardiorespiratory depression, and analgesic profile [37]. Side-effects of ketamine sedation include myoclonus, dysphoria, increased intracranial pressure, and possible pain on injection. Ketamine should be avoided in patients in whom an increase in contractility and heart rate may be detrimental, such as cats with HCM or those with tachyarrhythmias and suspected or confirmed intracranial disease. Ketamine is commonly combined with an opioid and a sedative to provide sedation in the ER. Recently, ketamine and propofol have been combined (in same syringe) and used as a rapid-acting induction agent with analgesic properties.

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Pain Management in Critical Patients

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Pain in the Emergency Patient: Concerns and Goals

Pain has the potential to be a source of distress to the patient, the owner and caregivers, but it is also a cause of ileus and ventilatory impairment, inhibits cough and appetite, and may lead to self-injury, hypertension, and arrhythmias. Unrelieved moderate-to-severe pain is a stressor and excessive stress negatively affects health and recovery. The goal is to reduce pain to a level where the patient can cope physiologically and emotionally, not to remove all pain. Most analgesic regimens do not completely alleviate pain of tissue injury. Single-agent analgesia (e.g. fentanyl infusion) in complex pain states may not provide sufficient relief.

How Much Pain and How to Approach It

The degree and type of tissue injury, severity and extent of the inflammatory process should guide analgesia. Observation of the individual patient's response to analgesia is the only way to accurately gauge treatment success. Situational influences can greatly influence pain tolerance – fearful or anxious animals often display enhanced responses to manipulations. It can be difficult to distinguish anxiety from pain but the two have very different treatment strategies.

Pain assessment is beyond the scope of this chapter. Suffice it to say that the patient who is able to recline in a relaxed manner, is oriented and who will alert to nearby individuals, who will move with little inhibition and is easily handled is probably adequately treated for pain, and that patients who are dull, or aggressive, stiff, grunting, and poorly able to focus on things outside their own bodies are in significant amount of distress; whether from pain or some other cause is the challenge of the

veterinarian. It is more difficult to evaluate very critical patients whose behavior is inhibited by weakness, immobility or CNS depression. Continuous vocalization is, in the author's experience, less indicative of pain and more indicative of psychological abnormality; in an alert and oriented patient, it can be attributed mainly to anxiety but if there is delirium, then medication side-effects or neurological impairment are more likely to blame.

Pain can be complicated by iatrogenic damage resulting from environmental conditions, positioning, and restraint. Anesthetized or immobilized patients cannot support unstable joints or avoid positions that endanger nerves, muscle or other vulnerable structures. Thus critical patients must be handled thoughtfully and meticulously with neutral positioning. More robust patients with undertreated pain may become aggressive, struggle and resist treatment.

Drug Interactions

Adverse drug–drug interaction concerns include the following.

- *Combinations of sedative analgesics* which promote excessive central nervous system depression or inability to protect the airway.
- *Drugs which increase the risk of serotonin syndrome:* serotonin syndrome resulting from routine doses of anxiolytics and opioids is not generally thought to be a problem in veterinary medicine, but cautious prescribing is advisable.
- *Potentiation of inhalant or intravenous anesthetic action by analgesics:* when opioids, local anesthetics, ketamine, or alpha-2 agonists are used prior to or during general anesthesia, inhalant anesthetic requirements are significantly lessened. If not taken into account by minimizing anesthetic doses, extreme depression of

respiration and cardiac output and decreased elimination of drugs (e.g. intravenous lidocaine) may occur, risking morbidity or death. Decreased renal blood flow when NSAIDs are used risks nephrotoxicity.

- *Use of two drugs in succession with similar toxicities:* switching from a non-selective to COX-2-selective NSAID is thought to pose a significant GI ulceration risk.

Dose Titration, Timing, and Duration

Doses are increased when pain control requires it for opioids, alpha-2 agonists, and gabapentin. Increasing doses of NSAIDs may increase risk of organ toxicity. “Loading” doses of NSAIDs are cited for both Metacam and Deramaxx. This author recommends against use of loading doses of NSAIDs due to the potential for toxicity, accidental failure to reduce to maintenance dosing, and because the current evidence in humans is that increasing the dose of NSAID tends to increase duration rather than magnitude of effect [1].

The speed of onset of analgesia varies with the type of drug and route of administration. Approximate onset times and duration (of intermittent dosing) are listed under individual drug classes but duration generally depends on the dose. Constant-rate infusions of pure agonist opioids, alpha-2 agonists, and ketamine are preferable to intermittent injection of drug because “peaks and valleys” of effect can be avoided and the rate can be adjusted to suit the patient.

When anesthesia is planned for injured patients, ideally patients awaken from anesthesia smoothly with little discomfort; analgesia should be adequate at the time of recovery. Fear and panic, lack of orientation to surroundings, extended anesthesia time, and hypothermia lead to rough, struggling recoveries. The presence of pain potentiates fear and panic.

Pain should be expected to increase as the postinjury inflammatory response proceeds. Most humans report that pain after strenuous activity becomes evident within 12–24 hours. Thereafter, pain tends to subside over time, depending on the severity of the injury, speed of tissue repair, complicating factors, and the effectiveness of the analgesic therapy. If specific anti-inflammatory drugs (NSAIDs or corticosteroids) are contraindicated, intravenous lidocaine (dogs only) may provide anti-inflammatory effects.

Breakthrough and Unexpected Pain

Pain may episodically become more severe, especially upon or just after procedures, and is preferably pretreated with increments of additional analgesia. When

pain is of greater magnitude or duration than expected despite attempts to treat it, there is reason to suspect one of several complications. These include wound infection or dehiscence, nerve impingement, fracture, ischemia, bandage or splint pain, gastric or esophageal ulceration, urinary retention, delayed gastric emptying, and pancreatitis. Trauma patients frequently suffer distressing levels of GI stasis influenced by immobility, pain, and opioid therapy. A thorough physical exam is mandatory. The author reminds practitioners that it is very difficult to bandage even your own limbs comfortably, so bandages are common significant contributions to pain.

Pharmacological Methods for Treating Acute Pain

Opioids

Advantages of opioids include safety, good evidence for dosing, rapid onset, and reversibility. While side-effects are rarely lethal, there is an increasing trend towards “opioid sparing” in medical care – using other strategies to reduce reliance on the opioid. In small animal medicine, nausea, vomiting, inappetence, ileus, and urinary retention may occur with use of opioids acting at the mu-receptor. Respiratory depression is of concern with moderate-to-severe pulmonary dysfunction, high intracranial pressure, and acidosis. Opioids are potent cough suppressants; in patients with airway compromise or vomiting/regurgitation, suppressing a cough reflex may lead to significant morbidity. Dogs receiving mu-agonist opioids have altered thermoregulatory set points, leading to what is generally a non-clinically significant hypothermia of the order of 98°F; efforts to warm dogs who are otherwise alert and stable just risks making them feel worse. In cats, hyperthermia may occur, and hydromorphone is particularly implicated [2]. When cats appear distressed, temperature monitoring and partial reversal or a switch to buprenorphine and active cooling may be necessary.

Opioids can cause behavioral changes, including sedation, euphoria, and dysphoria. Dysphoria is a specific opioid-related syndrome (particularly with pure agonist opioids). Patients appear to be very vocal, confused and agitated, and poorly responsive to human contact; this is often mistaken for pain or anxiety [3]. The addition of tranquilizers or sedatives does not permanently resolve the condition. A dramatic response is seen following slow IV reversal of the opioid with 0.01 mg/kg naloxone or 0.1 mg/kg butorphanol. Generally within minutes, the patient becomes oriented to surroundings with more normal behavior, and does not experience more pain

[4,5]. “Weaker” opioids and adjunctive analgesics may be used to treat pain from then on.

Injectable opioids take effect within approximately 10–40 minutes (depending on the drug) when given by the intravenous or intramuscular route. Subcutaneous administration of opioids is not recommended as it produces erratic and poor analgesia [6].

Extensively studied in cats, buprenorphine is recommended to be given by the IV route when possible, and the commonly used 0.01 mg/kg dose is not thought to produce reliable analgesia as a sole analgesic. Buprenorphine has a high affinity for the mu-receptor, and is difficult to antagonize. If buprenorphine has been given prior to switching to a full mu-agonist opioid, there may be some dampening of the effect at the mu-receptor. This has led to a tendency to “withhold” morning doses of buprenorphine prior to surgery, but unfortunately this leads to a gap in analgesia coverage. As unbound mu-receptors are likely to be available, it does not represent a major limitation to continue the buprenorphine until the time that the full mu-agonist is given.

In dogs and cats, methadone does not generally cause vomiting and is also generally felt to cause less dysphoria and sedation than other common pure mu-agonists. Methadone at low doses (<0.3 mg/kg) is less suitable as an anesthetic premed as it does not spare inhalant levels as effectively as pure mu-agonists. Butorphanol is not regarded as having sufficient analgesic efficacy to treat moderate-to-severe pain.

NSAIDs

Non-steroidal anti-inflammatory drugs are extremely reliable and valuable analgesics but are insufficient as sole analgesics for moderate-to-severe pain. The impact of NSAIDs on tissue repair (COX-2 mediated) makes them unsuitable in critical situations (e.g. compromised gastric mucosal integrity), and prostaglandin inhibition is contraindicated in states of volume depletion, poor cardiac output, or with pre-existing renal compromise as the kidney relies on prostaglandins to improve renal blood flow. NSAIDs may take up to several hours for onset, regardless of route of administration. From a GI ulceration perspective, washout times of 5–7 days between administration of different NSAIDs, with the exception of aspirin (>7 days recommended), and avoiding any close overlap of corticosteroids and NSAIDs is prudent [7]. Dogs admitted to the hospital with chronic osteoarthritis or cancer pain that has been adequately treated with NSAIDs may experience disabling pain upon discontinuation; alternative methods to provide analgesia (opioids, IV lidocaine, IV microdose ketamine) must be substituted.

Local Anesthetics

Local anesthetics are very effective for acute pain control; beyond analgesia, they also have broad anti-inflammatory and antimicrobial effects [8,9]. Regional and epidural techniques require expertise to perform, and the duration of “single-shot” bupivacaine injections is limited to approximately 6–8 hours. Intravenous lidocaine (IVL) is beneficial for pain of soft tissue surgery in humans, with effects lasting beyond the duration of the infusion, leading to extrapolation of its use in veterinary patients [10]. Non-surgical pain (e.g. major trauma, burns, pancreatitis) may also benefit from IVL use. Onset of analgesia from IVL in humans with long-standing neuropathic pain began at approximately 15 minutes and was complete at 45 minutes [11]. In horses and in humans, IVL reduces the duration of post-surgical ileus [12,13]. It should be used with caution and possibly lower doses in dogs with reduced serum albumin or poor cardiac output due to increased risk of toxicity. IVL use in cats is not recommended because of poor ability to metabolize the drug [14].

Ketamine

Subanesthetic or so-called “low-dose” or “micro-dose” ketamine (0.6 mg/kg/h) is demonstrated to improve opioid sparing, prevent opioid tolerance, and reduce acute somatic and visceral pain [15–21]. Low-dose ketamine infusions are now widely used as an analgesic adjunct in dogs and cats for acute pain. Ketamine also has the potential to reduce production of proinflammatory cytokines and this may prove to be beneficial in critically ill veterinary patients, although more research is needed [22,23]. In a study of chronic (human) neuropathic pain patients, a mean 55% reduction in reported pain occurred during a 40-minute infusion, but this reduction did not persist after discontinuation of the infusion [24]. In the author’s experience, when low-dose ketamine is given to anesthetized patients, the reduction in responsiveness to painful manipulation and ability to reduce the vaporizer setting occurs within 10 minutes but the onset of analgesia with administration of low-dose ketamine in dogs and cats has yet to be determined.

Dexmedetomidine

Dexmedetomidine produces sedation and, at higher doses, analgesia. As a sole agent, its analgesic effects may only occur above a dose rate of 5 µg/kg/h but when used with lidocaine and ketamine infusions, profound inhalant anesthetic-sparing effects and a level of analgesia equivalent to that of fentanyl are seen [25–27]. A major disadvantage is that it causes decreased cardiac index (CI).

At the higher doses used to facilitate minor procedures, and also at microdoses of >1 mg/kg/h, CI is reduced by 30–50%. One study suggests that at 0.5 – 1 μ g/kg/h, CI is not appreciably depressed [28]. Above that dose range, its use is therefore recommended only in patients who would not be vulnerable to cardiovascular depression [29]. Another major advantage is that the sedative effects can be reversed, although this also reverses any analgesic effect.

Gabapentin

Gabapentin acts to reduce neuronal hyperexcitability, and has been used in humans for alleviation of neuropathic and other pain states. Recent meta-analyses have found limited support for perioperative reduction in pain or morphine requirements in humans, but there is encouraging evidence that perioperative administration of gabapentin reduces the incidence of chronic postsurgical pain [30]. Studies in dogs both support and fail to support its efficacy in reducing postoperative pain [31–33]. Several case reports supporting efficacy of gabapentin in both dogs and cats with complex chronic pain states have been published [34–36]. Gabapentin has sedative and anxiolytic properties, which the author finds useful in hospitalized patients, and may be additive with

other analgesics and anesthetics. Currently, gabapentin is only available in an oral formulation.

In the dog and cat, gabapentin is relatively non-toxic even at high doses, and has been used even in critically ill or systemically impaired animals. Dose reductions in situations of hepatic or renal insufficiency should be considered. The empirically advocated doses of gabapentin in the small animal patient with acute pain are 5 – 20 mg/kg every 8 – 12 hours [37]. Gabapentin can be combined with all other analgesics and may be a useful option for sustained analgesic therapy in dogs and cats with acute pain.

Cryotherapy

Cryotherapy is typically used after recent injury or during active inflammation and is easily applicable in dogs. Cats do not tolerate cryotherapy unless they are very sedated. Cryotherapy is performed using crushed ice, frozen gel packs, or frozen alcohol/water slushes. Animals may initially find it aversive but after a few minutes the analgesic effects begin to be appreciated. Excessive cooling of skin may risk injury, and so it is to be avoided in animals with poor circulation or thin skin, and in those animals too sedated to signal severe discomfort.

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194

Opioids

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Introduction

Opioids are classified based on the specific receptor(s) they bind to, their affinity for the receptor(s), and the action at the receptor(s). All opioids fall into one of the following categories.

- **Full agonist:** defined as a drug which when bound to its receptor activates the receptor to its maximal response.
- **Partial agonist:** defined as a drug which when bound to its receptor activates the receptor to a level below the maximal response. Increasing the dose of a partial agonist over the maximal therapeutic dose does not result in greater analgesia or more severe side-effects (ceiling effect).
- **Agonist/antagonist:** defined as a drug that acts simultaneously on different receptor subtypes, functioning as an agonist at one or more receptor subtypes and an antagonist at other one or more subtypes. Like partial agonists, this group of opioids also has a ceiling effect and will not induce extreme respiratory depression or bradycardia with increasing doses. Neither will they induce maximal analgesia and are not as effective at treating intense pain as are full-agonist opioids. Due to their antagonist effects, they are useful at reversing the effects of full-agonist opioids while still providing some analgesia. They are also preferred analgesics in patients where opioid side-effects can deter use.
- **Antagonist:** defined as a drug which when bound to its receptor fails to produce any stimulation of the receptor.

Opioids are also classified based in their potency and efficacy. Potency is a description of the amount of drug required to produce an effect. The potency of opioids is ranked by comparison to morphine. Morphine is given a relative potency of 1 and all other opioids are classified based on the equivalent dose required to create the same analgesia as that due to a specific dose of morphine.

Potency simply reflects a comparable mg dose and does not reflect the maximal response that an opioid can induce (efficacy). Hence, the partial agonist buprenorphine has a greater potency than morphine but is unable to effect the same maximal level of analgesia (less efficacy). As a result, it is not recommended as an effective treatment for extremely painful patients, which are best treated with a full-opioid agonist.

The efficacy of opioids is the maximal pharmacological effect that the drug can induce. It is unrelated to potency. It is determined by the intrinsic activity of a drug at its receptor. The efficacy of full agonists is greater than that due to partial agonists or agonist/antagonists. Side-effects of some full-agonist opioids, such as codeine, are severe at higher doses, thereby limiting their efficacy.

Mechanism of Action

Opioids act at specific receptors in the brain and spinal cord. In the brain, these receptors are in highest concentration in the thalamus, where they dull chronic and poorly localized pain. Opioid receptors in the limbic system, amygdala, corpus striatum, and hypothalamus, parts of the brain that modulate the emotional response to pain, are involved in euphoric responses to opioid administration. In the spinal cord, opioid receptors have been identified in the substantia gelatinosa. Here, they are found on synaptic membranes where they regulate the transmission of information from primary sensory pain afferents. Opioids also block the release of substance P, an important neurotransmitter of painful stimuli, in the dorsal horn of the spinal cord.

Based on the structure of opioid receptors and known agonists and antagonists, three different opioid receptors have been identified: kappa, mu, and delta. Kappa- (primarily located in the spinal cord and peripheral tissues), mu- (primarily located in the CNS but also present in

peripheral tissues), and delta-receptors (associated with the mu-receptor) have been shown to be associated with opioid-induced analgesia.

Opioid receptors are in the G-protein-coupled family of receptors and affect ion channels in pre- and postsynaptic nerves. Binding of an agonist to opioid receptors causes a decrease in intracellular cAMP, which results in an increase in potassium movement out of cells and a reduction in calcium movement into cells. Neurons become hyperpolarized, leading to postsynaptic neuronal inhibition and a decrease in transmission of information to the cerebral cortex. It also inhibits presynaptic neurotransmitter release. With nerve damage, opioid receptors may be lost, causing the presynaptic effect of opioids to be diminished.

Duration of Action and Administration Techniques

The duration of action of an opioid is determined by its affinity at the receptor, its rate of redistribution out of blood, its metabolic pathway (and concurrent administration of other drugs that rely on or inhibit enzymes in that pathway), and elimination from the body. Buprenorphine has a relatively high affinity for the mu-receptor and spends a greater amount of time bound to the receptor. It diffuses away from the receptor more slowly, thus prolonging its duration of action. In contrast, fentanyl is very lipophilic and has a high volume of distribution so it diffuses quickly away from receptors, thus shortening its duration of action. These drugs have similar metabolic and elimination pathways despite very different durations of action.

The route of administration may also significantly influence opioid duration of action, especially if the drug

is administered in a location that delays its exposure to normal metabolic pathways. Morphine administered parenterally has a duration of action of 3–4 hours but when it is administered epidurally, even at a significantly lower dose, its duration of action is increased to 12–24 hours. This is not only due to the site of administration but to its low lipid solubility as can be demonstrated by comparison to fentanyl, an opioid as described above with high lipid solubility. Fentanyl is administered at the same dose and has the same duration of action whether given via the parenteral (IM or IV) or epidural route.

Intravenous and Epidural Administration Techniques

Intravenous (IV) administration of opioids offers the most predictable bioavailability of any possible route of administration. An opioid can be titrated to effect and then administered at regular intervals or at a constant rate of infusion (CRI) to maintain blood levels within the therapeutic range and reduce the risk of side-effects. A table listing IV and CRI doses of commonly used opioids is provided (Table 194.1).

Epidural administration can be used when the patient has pain that can be localized to the caudal half of the body. Epidural opioids do not cause motor paralysis and can be administered as a single shot or after placement of an epidural catheter. They can be administered alone or with a local anesthetic or alpha-2 agonist as part of a multimodal analgesia technique. Epidural administration of a single dose of morphine minimizes the drug's side-effects and lengthens its duration of action. Epidural administration is performed at the lumbosacral junction in the dog and cat using sterile technique and preservative-free morphine at a dose of 0.1–0.2 mg/kg (1/10th of the parenteral dose required). Other opioids such as fentanyl and oxymorphone can be administered

Table 194.1 Opioid drugs, their doses and mechanisms action.

Drug Name	Action	Opioid Receptor	IV (mg/kg) and CRI (mg/kg/hr) doses	
			Canine	Feline
Buprenorphine	Partial agonist	μ	0.005–0.02	0.01–0.02
Butorphanol	Agonist/antagonist	κ/μ	0.1–0.4	0.1–0.4
Fentanyl	Agonist	μ	0.002–0.005 CRI: 0.001–0.006	0.002–0.005 CRI: 0.001–0.006
Hydromorphone	Agonist	μ	0.05–0.1	0.05–0.1
Methadone*	Agonist	μ	0.1–0.5	0.1–0.3
Morphine	Agonist	μ, δ	0.3–0.5	0.3–0.5
Naloxone	Antagonist	μ, κ	0.005–0.02	0.005–0.02
Oxymorphone	Agonist	μ	0.05–0.1	0.03–0.1
Remifentanyl	Agonist	μ	CRI: 0.001–0.003	CRI: 0.001–0.003

*also has reported antagonist activity at the NMDA receptor and agonist activity at the Alpha 2 adrenergic receptor.

via this route but have a shorter duration of action (similar to IM administration) and require doses essentially the same as those required for parenteral administration. Epidural fentanyl is best administered as a CRI through an epidural catheter to maintain therapeutic levels for more than 1–2 hours.

Alternative Routes of Administration

Per os (PO), oral transmucosal (OTM), subcutaneous (SC), intramuscular (IM), and transdermal routes of administration are not typically used in a critical care setting. This is because this patient population often presents challenges in predicting uptake from the GI and peripheral tissues due to underlying diseases. External heating devices such as circulating water blankets and forced air warmers are often employed in these patients to maintain body temperature in the physiological range, also making uptake from transdermal patches unpredictable. However, in an emergency setting where patients may present for minor ailments, these routes of administration are advantageous, particularly when treating healthy, painful patients.

Transmucosal (oral and nasal) administration of opioids allows uptake of drug without first-pass metabolism. Drug absorption is relatively rapid (comparable to IM administration) and can be dosed similar to that administered parenterally. This route has been established as an effective and safe technique for administering buprenorphine to cats but requires the cat to have a normal (alkaline) oral pH [1]. Significant dental disease can lower the oral pH and may reduce the bioavailability of buprenorphine administered by this route. Buprenorphine is also not as bioavailable when administered transmucosally to dogs and higher doses are required to reach therapeutic levels [2].

In the US, fentanyl is the only opioid currently marketed in a transdermal formulation by veterinary distributors; however, buprenorphine patches are available in the US. Several European studies looking at the effectiveness of buprenorphine patches in cats and dogs have not shown a tremendous advantage to their use and until more favorable data are available, buprenorphine patch use in animals is not recommended. Patches must be placed in an area inaccessible to patient disruption or consumption. Hair should be clipped and the skin oil removed with minimal damage or irritation to the tissue. Fentanyl patches are dosed at 2–3 µg/kg for dogs and 12–25 µg per cat. The duration of action of these patches on dogs has been shown to be up to 72 hours whereas a fentanyl patch on a cat has been shown to maintain therapeutic drug blood levels in excess of 4 days. Owners must bring the patient to the veterinarian for patch placement.

Advantages and Side-Effects

There are many advantages to using opioids to treat pain in an intensive care setting. Opioids provide excellent analgesia with minimal cardiovascular alterations and can be antagonized in situations where they cause significant undesirable effects. The older opioids are quite reasonably priced and there are many different drugs and delivery mechanisms, allowing the veterinarian to select an analgesic that closely matches the needs of both the patient and the clinic or client. They cause sedation, which can be helpful when a patient is experiencing stress from hospitalization, can be titrated to effect and in most situations are the most innocuous and effective analgesics that can be administered, particularly when compared to non-steroidal anti-inflammatory drugs (NSAIDs) and alpha-2 agonists.

However, there are side-effects associated with their use that must be considered when making the decision to include opioids in the patient's treatment plan. Side-effects relevant to patients in a critical care setting are described below.

In most cases, reducing the dose of the opioid is an effective way to reduce the side-effects. In some situations, using an agonist/antagonist or partial agonist, which has a ceiling on the effects it causes, is an effective way to reduce side-effects but critical patients may have a profound response to these drugs and they should also be titrated to effect if used in a critical care setting. This is particularly problematic in the case of buprenorphine, which is difficult to titrate to effect due to the relatively long time (15–30 min) it takes to reach peak effect after IV administration, and its high affinity for the mu-receptor, which makes it very difficult to reverse. Because of this, the author strongly recommends buprenorphine not be used in a critical care setting until the patient has been well stabilized and is able to tolerate the effect of other opioids at standard doses.

Respiratory Effects

Opioids depress the respiratory center's responsiveness to CO₂. Patients have a dose-dependent increase in PaCO₂ due to a decrease in minute volume that is typically manifest as a decrease in respiratory rate although the tidal volume may also decrease. Respiratory depression is well tolerated in animals with no respiratory disease but in animals with upper airway or lung disease, the respiratory depression can cause significant hypoxemia and potentially death. Respiratory depression can also be potentially fatal in patients with pre-existing elevations in intracranial pressure (ICP) such as is associated with head trauma or brain tumors, since the rise in PaCO₂ will further increase ICP, potentially leading to brain herniation, coma, and death. Elevations in PaCO₂

will also worsen acidosis when patients have underlying metabolic disease and in patients with hyperkalemia due to renal disease, worsening acidosis further increases blood potassium levels, potentially resulting in cardiac arrhythmias and death.

In all of these groups of patients, reversible opioids can be safely administered in the presence of pre-existing pain, at low-to-moderate doses and only if proper care is taken to assure the patient is frequently assessed for complications described above. If problems are observed, opioids should be reversed with naloxone given slowly, over 2–3 minutes, IV to effect.

Administration of opioids to pregnant animals will cause both maternal and fetal respiratory depression since opioids readily cross the placenta. Although relatively well tolerated by the mother, oxygen should be concurrently supplemented to ensure that oxygen delivery to the fetus is not compromised. Neonates delivered after maternal administration of opioids should be treated with naloxone, administered either orally or IV in the umbilical vein to reverse the drug-induced respiratory depression and stimulate ventilation (see Chapter 118).

Antitussive Effects

Opioid agonists, partial agonists, and agonists/antagonists suppress the cough reflex. This effect is mediated by opioid receptors on A delta fibers that are located in or beneath the respiratory epithelium and is independent of their action on the respiratory center [3]. Opioids should be avoided in animals that are at risk for regurgitation and aspiration, particularly brachycephalic breeds with pre-existing evidence of aspiration pneumonia and/or dyspnea. Opioids should also be avoided in dogs that have undergone an arytenoidectomy or laryngeal tieback surgery because they are more likely to aspirate food or regurgitated material that enters their oral cavity.

Effects on Body Temperature

In dogs, opioids reset the thermoregulatory center in the brain, causing the patient to actively cool themselves by panting or moving away from external heat sources. Once the body temperature drops, dogs will not shiver to maintain normothermia. Hypothermic patients are more likely to be bradycardic and show signs of excessive sedation (see Chapter 148). In cats, opioid agonists, especially at higher doses, can cause elevations in body temperature. Drugs such as morphine and hydromorphone have been shown to cause hyperthermia. The SC buprenorphine formulation Simbadol, which is dosed at a higher dose than that used for IM/IV/OTM, has also been associated with hyperthermia.

All patients receiving opioids should have their body temperature regularly assessed and efforts should be made to keep their temperatures within a normal physiological range.

Opioid-Induced Hyperalgesia (OIH)

Opioids can cause hyperalgesia in patients after one or more doses due to somewhat complex cellular and molecular processes that result in the development of this condition. The most consistent finding that leads to a diagnosis of OIH is a worsening of pain in response to increasing doses of opioids. The following options have been shown to be helpful in resolving OIH: reduce the dose of opioid or rotate opioid used. Methadone is an antagonist at NMDA receptors and may be beneficial in improving analgesia due to its multimodal mechanism of action. NMDA receptor antagonists such as ketamine (0.1–0.6 mg/kg/h) or amantadine, or a low dose infusion of an alpha-2agonist (e.g. dexmedetomidine at 0.025–1 µg/kg/h) will help reduce the dose of opioid needed. A systemic infusion of lidocaine at 1–3 mg/kg/h may also reduce opioid requirements and resolve OIH.

Urine Retention

Opioids that are agonists at the mu-receptor have been reported to cause dose-related urinary retention (inability to urinate with a full bladder). Studies have demonstrated that fentanyl, buprenorphine, and, to a lesser extent, morphine alter bladder sensations and increase the residual volume in the bladder after voiding for several hours after administration. This occurs because opioids inhibit the sacral parasympathetic outflow, especially after epidural administration and after large IV doses, resulting in an increased maximal bladder capacity and detrusor muscle relaxation. Animals being treated with opioid agonists should have their urine output and bladder size assessed regularly and a urinary catheter should be placed if the bladder cannot be expressed.

Other Effects

Dysphoria

Animals may vocalize, pace, and appear anxious after opioid administration. The patient should be assessed to identify and resolve any underlying conditions such as a full bladder or a need to defecate. If none is identified, a low dose of a tranquilizer such as acepromazine or a benzodiazepine can be administered or the prescribed opioid changed to an agonist/antagonist, fentanyl or methadone, all of which are less likely to be associated with dysphoria.

Bradycardia

Central stimulation of vagal input caused by opioids may result in bradycardia. This effect is more severe in hypothermic patients.

Vomiting, Nausea, and Defecation

In opioid-naïve animals, opioid administration frequently results in GI stimulation manifested as nausea, vomiting, and defecation early after the drug is administered IV, IM or SC. This usually only occurs with the first dose of an opioid. Full-agonist opioids both stimulate the chemoreceptor trigger zone (CRTZ), which causes vomiting, and depress the vomiting center which blocks input from the CRTZ. Opioids quickly reach the CRTZ but their lipid solubility determines how fast they cross the blood–brain barrier (BBB) to reach the vomiting center.

Vomiting occurs more frequently with morphine sulfate administration and less commonly with oxymorphone and fentanyl administration. This is because morphine is more water soluble than oxymorphone so crosses the BBB more slowly, allowing time for CRTZ activation to stimulate the vomiting center. Vomiting occurs rarely after administration of partial agonists and agonists/antagonists although these drugs do induce other GI effects typical of opioid administration, including delayed GI motility and increased sphincter tone.

Prior to administering opioids to any patient, it is important to ensure that the animal can open its mouth, is alert enough to position itself appropriately to avoid aspiration and is not limited by muzzles or other devices, and the oral and pharyngeal cavities are not obstructed by disease conditions (e.g. large oral foreign bodies or tumors). Avoid vomiting by administering an antiemetic such as maropitant prior to opioid dosing.

Histamine Release

Morphine and meperidine can induce histamine release when administered rapidly intravenously. To prevent or minimize this response, these two opioids should ideally not be administered intravenously. If an analgesic is immediately required, the drugs may be slowly administered intravenously (over 2–3 min) while the patient is

monitored for signs of hypotension, shock or cutaneous manifestations of histamine release.

Immunosuppression

Opioids have immunomodulatory effects *in vitro* and in animal models, which are generally believed to increase the risk of infection. However, the clinical significance of opioid-induced immune suppression remains controversial, even in the critical care setting. Like other opioid-induced actions, the immune effects are reversible with administration of an opioid receptor antagonist.

Patient Management Recommendations

Opioids remain the safest and most effective analgesics for treating pain. The practitioner should follow simple guidelines to avoid using them in patients unable to tolerate the side-effects and patients receiving opioids should be monitored for significant adverse events as indicated below.

- Do not administer full agonists to any patient with an obstructed oral cavity or evidence of elevated ICP.
- Opioids may be used in patients with respiratory compromise only to facilitate correction of the problem. During this time, oxygen should be supplemented. If the problem cannot be corrected, the opioid should be reversed with naloxone, administered slowly IV, over 2–5 minutes to effect.
- Sick and debilitated patients should only receive reversible opioids.
- Monitor urine output and defecation in patients receiving opioids and take action (e.g. bladder catheterization, stool softener) if indicated.
- Giving an agonist/antagonist opioid (i.e. butorphanol) to an animal that has received a full agonist (i.e. hydromorphone, oxymorphone or fentanyl) will reverse the effects of the full agonist. This can make awake animals more painful (*bad*) or reduce side-effects in an unarousable patient showing excessive sedation after opioid administration (*good*).

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Alpha-2 Adrenergic Agonists

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Introduction

The alpha-2 agonists cause dose-dependent sedation, anxiolysis, and analgesia via action at alpha-2 receptors in the CNS and peripheral tissues. Three alpha-2 receptor subtypes have been identified: alpha-2A, alpha-2B, and alpha-2C, all of which are G-protein-coupled receptors [1–3]. Important consequences of alpha-2A receptor binding include supraspinal analgesia, sympatholytic effects, and sedation with primary localization of this receptor in the CNS (cerebral cortex and locus ceruleus) [2,3]. Alpha-2B receptors are located in the spinal cord and vascular endothelium; therefore, receptor binding at this location causes the initial vasoconstriction observed with alpha-2 agonist administration, but also allows for spinal analgesia [2,3]. The alpha-2C receptor is responsible for mediating hypothermia [2].

Alpha-2 agonists used historically in small animal patients include xylazine, medetomidine, and dexmedetomidine. Medetomidine is a racemic mixture of levo- and dex-medetomidine with the L-isomer exhibiting significantly less activity than the D-isomer [1–3]. Receptor selectivity ratios (alpha-2:alpha-1) indicate that medetomidine and dexmedetomidine have higher specificity (1620:1) for the alpha-2 receptor than xylazine (160:1) [1–3].

For the purposes of this chapter, dexmedetomidine will be the drug of focus given its more widespread use in small animal patients and the limited commercial availability of medetomidine. The duration of action of dexmedetomidine in dogs and cats is approximately 1–2 hours, and the action of the drug can be effectively reversed with atipamezole.

Alpha-2 agonists should be used cautiously in emergent and critically ill patients, mainly due to their profound cardiovascular side-effects at the

manufacturer's recommended dose. In patients presenting with any degree of hemodynamic instability, dexmedetomidine should be avoided, as other drug options are available with minimal to no effects on cardiovascular function.

The main physiological alterations that follow alpha-2 agonist administration include an initial increase in systemic vascular resistance and bradycardia [1–5]. The combination of these peripheral effects can reduce cardiac output up to 30–50% in dogs and cats, depending on the dosage of alpha-2 agonist administered [1–6]. A delayed central phase follows with decreased sympathetic output, causing continued bradycardia and hypotension [2,3,5]. Anticholinergics can be administered concurrently to offset dexmedetomidine-induced bradyarrhythmias; however, myocardial work and oxygen demands increase significantly so their use should be reserved for the delayed central phase only (~45–60 minutes after initial administration).

The administration of dexmedetomidine is contraindicated in patients with pre-existing heart disease, such as dilated cardiomyopathy, valvular disease, and pulmonic stenosis, as any increase in afterload and myocardial work would be detrimental [2,5] to the cardiovascular function of the patient. Similarly, patients with underlying arrhythmias should not be given alpha-2 agonists. While one study observed a positive benefit to alpha-2 agonist administration in cats with hypertrophic cardiomyopathy and left ventricular outflow tract obstruction [7], their use remains controversial; therefore, reaching for dexmedetomidine when treating the critical cat with suspected or known heart disease should be avoided [6,8,9] or the dose reduced considerably.

The presence of other underlying disease(s) also influences a patient's ability to tolerate the effects associated with alpha-2 agonist administration.

Dexmedetomidine interferes with antidiuretic hormone action at the level of the renal tubules and collecting ducts [2,3], resulting in diuresis. If administered to a patient with urinary tract obstruction, catheterization must be performed rapidly or an alternative sedative should be chosen. Furthermore, in blocked patients with pre-existing bradycardia, dehydration, and significant electrolyte abnormalities, dexmedetomidine should be avoided [10,11]. The majority of cats and some dogs will vomit following dexmedetomidine administration. Consider avoiding dexmedetomidine or administering an anti-emetic in patients with underlying ocular disease in which vomiting will result in an increase in intraocular pressure. Finally, dose-dependent and transient hypoinsulinemia and hyperglycemia can occur due to drug effect on pancreatic beta-cells.

While there are several true contraindications for alpha-2 agonist use in critically ill patients, incorporating dexmedetomidine into pain management strategies and sedation protocols in this subset of patients can be extremely beneficial. In order to optimize the positive effects and minimize the adverse effects associated with dexmedetomidine administration, a significantly *lower* dose must be administered (Table 195.1), and when possible, the drug should be administered concurrently with low doses of other sedative and analgesic drugs. Incorporating dexmedetomidine into sedation protocols in mechanically ventilated dogs and cats with adequate cardiovascular stability is prudent as administration often causes minimal to no alterations in arterial blood gas values such as pH and PaCO₂ [2,3]. Use of dexmedetomidine constant-rate infusion (CRI) has proven an equivalent if not superior alternative to benzodiazepines in mechanically ventilated human patients, with fewer behavioral alterations and reduced ventilator times [12].

An additional factor that can be both challenging to recognize and manage in the emergency and ICU patients is pain. Relying on multimodal pain management allows for improved patient comfort and outcome while minimizing side-effects of higher doses of single analgesic agents. This is particularly important in post-operative abdominal, thoracic, and polytrauma cases in which patient pain is multifactorial. Dexmedetomidine bolus and CRI administration has been shown to be effective in both dogs and cats given the antinociceptive properties alpha-2 agonists demonstrate at both central and peripheral levels [1–3,13–16]. Dosing strategies for dexmedetomidine will differ for dogs and cats based on the desired drug effect and route of administration (see Table 195.1).

A unique analgesic application is the use of alpha-2 agonists alongside a local anesthetic to prolong and

Table 195.1 Dexmedetomidine and atipamezole dosing strategies for critical care patients.

Indication	Dosage	Route of administration
Sedation	1–10 µg/kg (dogs)	IM*
	5–15 µg/kg (cats)	IM*
	1–3 µg/kg	IV
Pain management and postoperative sedation	1 µg/kg loading dose, then 0.25–3 µg/kg/h (dogs)	IV**
	0.5–1 µg/kg loading dose, then 0.25–2 µg/kg/h (cats)	IV**
Antisedan (drug reversal, atipamezole)	100 µg/kg	IM, IV

*The IM route of administration should be avoided in emergent and critical care patients since significant underlying disease might influence muscle perfusion and drug uptake. If combining dexmedetomidine with another sedative (e.g. opioid) for IM administration, the dose should be reduced by at least 50%.

**It is recommended to maintain constant-rate infusions in critical patients at the lowest effective dose and titrate the dose up only if needed to improve pain management and provide more adequate anxiolysis.

intensify peripheral nerve blockade [2,17,18]. While this technique requires more specialized skill and equipment (e.g. nerve stimulator, ultrasound guidance), systemic side-effects of dexmedetomidine are blunted and longer lasting analgesia is provided to the patient.

The final two positive benefits of alpha-2 agonists in the emergency room and ICU settings are immunomodulatory properties and drug reversibility. Many studies demonstrate the anti-inflammatory potential of alpha-2 agonists [19–21], which may ultimately improve patient outcome in critically ill dogs and cats.

Lastly, when any drug is administered to a critically ill patient, the ability to rapidly and completely reverse the action of that drug becomes particularly important. Once the reversal agent atipamezole has been given and taken effect, heart rate, blood pressure, and temperature will normalize [1–3,15]. The sedative and analgesic effects are also reversed by atipamezole and alternative analgesia should be provided to the patient with persisting pain. When the effects of dexmedetomidine are not life threatening, drug reversal should be carried out via the intramuscular route as rapid intravenous administration can result in hypotension. In the emergent scenario, however, intravenous administration is recommended.

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Non-Steroidal Anti-Inflammatory Drugs

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used class of analgesics in veterinary medicine [1]. Additionally, they possess anti-inflammatory and antipyretic properties. Several agents are currently approved by the United States Food and Drug Administration (FDA) for use in dogs (meloxicam, carprofen, firoxicib, deracoxib, galliprant) and cats (meloxicam, robenacoxib) and are available in a wide variety of formulations including oral, injectable, and transmucosal spray. Several other NSAIDs including mavacoxib, cimicoxib, and vedaprofen are available outside the United States. Off-label usage of NSAIDs in other companion animal species such as birds, rabbits, ferrets, and pocket pets is common. While NSAIDs are the cornerstones in the treatment of osteoarthritis (OA) and other chronic painful conditions, they are generally safe and useful in many emergency room and acute pain settings as well.

Mechanisms of Action

Upon tissue injury, arachidonic acid is released from cell membrane phospholipids by the action of phospholipase A₂, resulting in a chain of events known as the arachidonic acid cascade. Two biologically and clinically important pathways are established, including 5-lipoxygenase (LOX), which metabolizes arachidonic acid into various leukotrienes, and cyclo-oxygenase (COX), which metabolizes arachidonic acid into prostaglandins, prostacyclin, and thromboxanes [2]. NSAIDs exert their clinical effect predominantly by the inhibition of COX [3].

Cyclo-oxygenase is present in most tissues and two primary forms of COX have been identified: COX-1 and COX-2 [3]. Initially, COX-1 was recognized as a constitutive isoform whereas COX-2 was identified as an inducible isoform, but further studies have elucidated

that both isoforms are constitutive as well as inducible [4–6]. A third isoform (COX-3), identified primarily in the canine cerebral cortex with minimal amounts found peripherally, is selectively inhibited by analgesics such as acetaminophen and metamizol (dypyrone) [7].

Cyclo-oxygenase-1 produces prostaglandin (PG) E₂ and thromboxane A₂ [3]. PGE₂ produces numerous physiological responses, including vasodilation and nociceptor sensitization, leading to both peripheral and central sensitization. PGE₂ plays a crucial role in gastrointestinal (GI) tract functioning, including generation of mucus production, increasing secretion of bicarbonate in the duodenum, decreasing gastric acid secretion, and increasing the rate of turnover of mucosal cells. The function of thromboxane A₂ results in increased platelet aggregation and vasoconstriction, leading to enhanced coagulation and blood clot formation. COX-1 is constitutively expressed in the cerebral cortex where its inhibition may contribute to the central analgesic and antipyretic effects of NSAIDs [8].

Cyclo-oxygenase-2 produces PGE₂, prostacyclin (PGI₂) and 15-epi-lipoxin A₄, also known as aspirin-triggered lipoxin (ATL) [3]. PGE₂ produced by COX-2 or COX-1 results in the same physiological effects as discussed previously. PGI₂ is produced in endothelial cells and results in inhibition of platelet aggregation and vasodilation, leading to an antagonistic effect to thromboxane A₂ [3]. PGI₂ has also been identified in inflamed tissues and in the GI tract where it produces similar gastroprotective effects as PGE₂ [3].

Cyclo-oxygenase-2 is constitutively expressed in the dorsal horn of the spinal cord and contributes to the propagation of nociceptive stimuli. Inhibition of COX-2 with NSAIDs can also produce central analgesic effects [9,10]. COX-2 is increased in damaged tissue as well, producing PGE₂ and PGI₂, resulting in sensitization of peripheral nociceptors just as with COX-1 [3]. COX-2 is upregulated in endothelial cells within the hippocampus

during fever, which is a proposed mechanism of action for the antipyretic effect of some NSAIDs.

Beyond nociception, GI, and hemostatic functions, PGE₂ and PGI₂ alter renal physiology. They increase sodium excretion, inhibit sodium reabsorption, and alter chloride transport [3]. They also stimulate renin release and can profoundly alter total renal blood flow and regional blood flow within the kidneys of dogs [3,11].

Recently, galliprant became FDA approved for dogs as a non-COX-inhibiting NSAID. This drug uniquely targets the PGE₂ receptor EP4 with the goal of achieving anti-inflammatory and analgesic action while theoretically minimizing adverse side-effects. Clinical experience with galliprant remains in its infancy and time will tell whether or not its side-effect profile will truly differ from that of other NSAIDs.

Pharmacokinetics

Non-steroidal anti-inflammatory drugs are well absorbed after oral and injectable administration, with the exception of the licensed formulation of firocoxib which has a low oral bioavailability [12,13]. Deracoxib is best absorbed with food, but efficacy still occurs when administered to fasted dogs [14]. Most NSAIDs are highly bound to plasma proteins, but clinical implications of high protein binding are limited.

The liver is the primary organ of NSAID biotransformation, including biliary secretion, conjugation reactions, and the cytochrome P450 system [12]. Disease leading to decreased hepatic function and ability to biotransform drugs may decrease the rate of elimination and increase the terminal half-life and “area under the curve” which may lead to more total drug exposure and increase adverse effects. Some renal elimination of NSAIDs occurs and urinary alkalization resulting in ion trapping of the weak acids may increase this elimination. A thorough review of the pharmacokinetics is available elsewhere for further reading [12].

Adverse Effects

Adverse effects of NSAIDs localize to the GI tract, kidneys, liver, and to hemostatic function.

Hemostatic Function

With the exception of aspirin, NSAIDs themselves do not appear to induce clinically significant bleeding disorders and therefore will not be a focus of this section [15–20]. The use of NSAIDs in animal patients with known bleeding disorders has not been fully investigated and

therefore they should be avoided or used with caution at this time. The effect of COX inhibition and the potential for thromboembolic occurrence have not been well studied in dogs and cats.

Gastrointestinal Effects

Gastrointestinal adverse effects are the most commonly reported adverse effect of NSAIDs [21]. Inhibition of the COX enzymes by NSAIDs leads to potential adverse effects such as delayed gastric healing, vomiting, diarrhea, lethargy, anorexia, gastroenteritis, ulceration, GI perforation, and potentially death [3,4,22–27]. NSAIDs are weak acids and can also directly irritate the GI mucosa when administered orally or following secretion in bile regardless of the route of administration [28]. GI ulcers are most commonly reported in the proximal duodenum and pylorus of dogs [27,29]. It is important to understand that when considering the most recently approved NSAIDs (carprofen, meloxicam, deracoxib, firocoxib, robenacoxib), there is no specific evidence-based literature, using controlled clinical trials, demonstrating that one drug produces a lower frequency of GI adverse effect than another.

Renal Effects

Healthy patients given approved doses of NSAIDs are at low risk for renal adverse events. However, as discussed in previous sections, PGE₂ and PGI₂ have a profound effect on the kidney. In dogs, COX-1 and COX-2 are both constitutively expressed and COX-2 is upregulated in times of renal ischemia and hypotension [30,31]. In response to volume depletion, hypotension, or hyponatremia, PGE₂ production is increased by COX-2 in dogs, resulting in alteration of renal blood flow by decreasing vascular resistance [30,32,33]. Therefore, renal injury secondary to NSAID administration may occur as a result of the inhibition of prostaglandin synthesis.

The effect of label doses of veterinary-approved NSAIDs on canine and feline renal blood flow and the distribution of blood flow within the renal cortex has not been investigated extensively. Reported cases of NSAID-induced nephropathy in dogs and cats are most commonly associated with high doses of NSAIDs or other complicating factors, including sodium depletion, dehydration, hypovolemia, poorly managed perioperative hypotension, shock, and pre-existing renal disease [32–36]. Perianesthetic hypotension should not be an unexpected risk for NSAID renal toxicity as isoflurane and sevoflurane cause a dose-dependent decrease in renal blood flow in dogs [37,38]. It should be expected that any animal undergoing anesthesia has the potential for decreased renal perfusion which may increase the

risk of NSAID-induced renal toxicity. In humans, the use of NSAIDs during concurrent congestive heart failure is an additional risk factor for acute kidney injury.

The reported effect of NSAIDs on the renal function of dogs and cats with underlying chronic renal disease is unclear. It has been hypothesized that dogs with underlying renal disease have increased COX-2 expression in the renal vasculature as a compensatory mechanism and NSAID administration could lead to exacerbation of renal disease [3,39]. However, some more recent work has failed to show a detrimental effect of short- and long-term NSAIDs when given to dogs and cats in a setting of chronic kidney disease [40–43]. It is important, however, to consider that patients in these studies underwent regular monitoring and that the NSAID doses used in these studies were often lower than labeled drug doses and that some of these studies were retrospective in nature. Further research on the subject is indicated before strong conclusions can be drawn.

Hepatic Effects

Hepatic toxicity is uncommon but can occur with any pet breed or with any NSAID, and is either a dose-dependent toxicity or an idiosyncratic, dose-independent toxicity. The intrinsic, dose-dependent toxicity is typically due to massive overdosing of NSAIDs [44].

Few data describe the use of NSAIDs in animals with underlying hepatic disease and no data indicate that animals with hepatic disease are at increased risk of NSAID hepatic toxicity. However, the biotransformation and elimination of NSAIDs in these animals may be altered. It is unclear if the dose of an NSAID needs to be decreased for an animal with pre-existing hepatic disease or whether NSAIDs should be avoided all together. The precise dose adjustments in animals with hepatic disease has not been determined and, therefore, any use in animals with hepatic disease should be undertaken with caution and owner consent. Additionally, patients with liver disease may be more prone to GI ulceration and NSAID use in these cases may increase this complication [45].

Drug–Drug Interactions

Non-steroidal anti-inflammatory drugs are highly protein bound and drug displacement of other drugs from albumin can occur, although the clinical occurrence of these interactions is uncommon and low [46].

Administration of NSAIDs with corticosteroids significantly increases the risk of GI toxicity, including ulceration and perforation, and may also result in adverse effects on the kidney and with platelet function [47–50]. The concurrent administration of different NSAIDs may increase the risk for GI adverse effects [48,51]. Based

on the information available, the concurrent use of two NSAIDs or an NSAID with a corticosteroid is viewed as contraindicated.

Furosemide's effect on sodium depletion may increase the risk for renal adverse effects of NSAIDs [36]. Patients receiving aminoglycosides or other potentially nephrotoxic agents may also be at higher risk for renal adverse effects. NSAIDs may affect the management of hypertension and have been shown to decrease the blood pressure-lowering effect of angiotensin converting enzyme (ACE) inhibitors and beta-blockers in humans [52,53]. Other work has suggested that the co-administration of ACE inhibitors and NSAIDs may increase the risk of renal injury in patients with impaired function [54].

Clinical Usage

Non-steroidal anti-inflammatory drugs are effective analgesic, anti-inflammatory, and antipyretic agents that are a benefit to the diverse emergency room patient population. There is little evidence to support differences in effectiveness for pain treatment when comparing all NSAIDs. NSAIDs are useful as stand-alone agents or in combination with other drugs for multimodal analgesia. When used at or below their recommended dosage, their benefits often outweigh their risks.

Prior to instituting NSAID therapy, a complete physical examination should be performed. The need for bloodwork and urinalysis should be assessed on an individual patient basis. In addition, information on recent medications, previous drug adverse reactions, and any medical conditions should be reviewed.

Non-steroidal anti-inflammatory drugs should not be administered to patients that are currently dehydrated, experiencing hypotension or systemic hypoperfusion, or have GI disease (including vomiting and diarrhea). Once these issues are resolved, an NSAID can be considered. Due to evidence in humans suggesting an increase in risk of leakage following gastrointestinal surgery, non-steroidal anti-inflammatory drugs should be avoided in dogs and cats following gastrotomy, enterotomy, or anastomosis. It is generally recommended to avoid NSAIDs in patients that are anorexic, although this practice has come into question in humans [55]. NSAIDs should be avoided or used with caution in patients with renal insufficiency, significant hyponatremia, or hepatopathy. They are strictly contraindicated in patients that recently received or are currently on NSAIDs or corticosteroids. It is the author's opinion that NSAID administration is best withheld until the postanesthetic period to avoid concurrent administration during unexpected perianesthetic hypotension. NSAIDs are not known teratogens in people but they are typically avoided late in gestation and beyond a single dose in the nursing mother

to avoid developmental changes to the fetal and newborn kidney.

Drugs such as misoprostol, famotidine, and omeprazole have been recommended for patients with increased risk of GI adverse effects or when NSAIDs are prescribed for long-term use. However, these recommendations lack comprehensive studies with strong evidence to support

their use in dogs and cats at this time. Routine hematological and biochemical analysis is recommended for patients that continue on to long-term NSAID therapy. Appropriate client education and patient selection are paramount to maximize the benefits of NSAIDs in the emergency room while reducing their risk for adverse effects.

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Regional Anesthesia Techniques

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Introduction

Regional anesthesia has been extensively used to manage intraoperative and postoperative pain. It is commonly used as part of a multimodal approach to pain management and helps reduce the use of systemic opioids and their associated side-effects. Regional anesthetic techniques provide effective and site-specific analgesia with relatively minimal adverse effects and can be a useful tool to provide analgesia and facilitate procedures in the emergency room [1–4].

Increased familiarity with the use of ultrasound as a diagnostic tool for focused assessments in human emergency rooms has facilitated the expansion of regional anesthesia in that setting, and the same is likely to happen in veterinary medicine. While regional anesthetic techniques are routinely used in veterinary anesthesia, their use in emergency medicine is still limited. Training of emergency clinicians in regional anesthesia techniques as well as clinical studies evaluating their feasibility, effectiveness, and potential benefits in the veterinary emergency room are needed to further expand the use of regional anesthesia.

Selected Regional Anesthetic Techniques

This section provides an overview of regional anesthesia techniques (Table 197.1). Selected procedures of particular interest for the emergency clinician are described in the text. For the interested reader, more specific information and excellent in-depth technique descriptions can be found in dedicated sources [5]. Please note that to perform the majority of the techniques discussed here, sedation or brief anesthesia may be required to prevent patient movement. The choice of sedation and/or anesthetic protocols should be made according to the temperament and health status of each individual patient.

Intercostal Nerve Blocks

Intercostal nerve blocks can be used to provide anesthesia and analgesia for fractured ribs, flail chest, intercostal thoracotomies, thoracocentesis, chest tube placement or any other procedure involving the thoracic wall (see Chapters 49 and 184). This technique is easy to perform. The ribs are identified by manual palpation and ideally the block should be performed as dorsal as possible in order to maximize the desensitized area. Intercostal nerves and the associated artery and vein are located just caudal to each rib. The needle is typically directed into the lateral aspect of the rib and then walked off its caudal border and advanced slightly medial. After careful aspiration (blood or air would indicate that the needle tip was unintentionally placed in a vessel or within the pleural space), local anesthetic is injected [6].

Due to the distribution of the innervation, it is generally recommended that at least two intercostal spaces be blocked cranially and caudally to the intercostal space one wishes to desensitize. The use of electrolocation has been suggested to increase the safety of this technique in overweight patients when palpation of the ribs is difficult [5,6].

Interpleural Block

Interpleural blockade is usually used to provide analgesia for postoperative thoracotomies and other painful procedures involving the chest wall. Analgesia to the cranial abdomen (pancreas and liver) is also reported in people [7]. This technique is typically used when a chest tube is in place (a catheter could be placed in the pleural space for this purpose). It involves the blockade of intercostal nerves by the diffusion of local anesthetic administered within the interpleural space via the chest tube or catheter.

After local anesthetic injection, the animal should be placed with the side to be desensitized down (or in sternal

Table 197.1 Brief overview of selected regional anesthetic techniques, categorized by region of anatomical location.

	Desensitized area	Indications	Notes of interest	References
Head				
Maxillary block	Alveolar bone, teeth and surrounding soft tissue Hard and soft palates Upper lip Nose	Maxillary fractures Teeth extractions Upper lip lacerations Foreign body removal Rhinoscopy Biopsies	This block provides desensitization ipsilateral to the nerve blocked. A bilateral block is needed for procedures involving the entire nose, palate, and incisors. This block does not desensitize the nasal septal mucosa and additional analgesia may be required	[8,29,30]
Mandibular (inferior alveolar) block	Alveolar bone, teeth and surrounding soft tissue Lower lip/chin	Mandible fractures Teeth extractions Lower lip laceration Biopsies	This block provides desensitization ipsilateral to the nerve blocked	[8,29,30]
Auriculotemporal, great auricular, and internal auricular nerve block	Internal and external ear	Ear canal ablation Deep ear cleaning Foreign body removal Aural hematomas Laceration repair	This block has shown benefit for deep ear canal debridement but further studies are needed to verify its efficacy for other procedures of the ear	[31,32]
Thoracic limb				
Brachial plexus block	From scapula to digits (cervical paravertebral approach) From mid-humerus to digits (axillary approach)	Procedures of distal humerus, at or below the elbow, including: Fracture repair Arthroscopy Arthrodesis Wound debridement Laceration repair	The cervical paravertebral approach is difficult to perform (especially in muscular or obese dogs) and has been associated with low success rates and relatively high incidence of complications	[33–38]
Radial, ulnar, median, and musculocutaneous (RUMM) nerve block	Forelimb, distal to the elbow	Procedures distal of the elbow, including: Fracture repair Arthrodesis Wound debridement Lacerations	While the blind technique was associated with low efficacy, the use of electrolocation and ultrasound provided successful analgesia	[39,40–42]
Pelvic limb				
Combined psoas compartment block and parasacral block	The entire pelvic limb (including hemipelvis and coxofemoral joint)	Surgical procedures of the proximal pelvic limb, involving the hemipelvis and coxofemoral joint: Femur fracture repair Amputation	The techniques described to provide such proximal blocks are technically more challenging and carry a higher risk of complication. An epidural would be an alternative technique for most procedures performed under these blocks	[37,43–46]
Combined femoral and sciatic nerve blocks	From mid-femur to digits (inguinal approach for femoral and distal to the ischiatic tuberosity for sciatic nerve)	Procedures distal to mid-femur: Tibial and distal fracture repair Correction of femorotibial joint instability (TPLO, MPL, etc.)	Desensitization of the tarsal joint and distal structures can be achieved with just a sciatic nerve block (except for the first digit and the skin over the dorsomedial aspect of the tarsus, which are innervated by the femoral nerve)	[46]

MPL, medial patellar luxation; TPLO, tibial plateau leveling osteotomy.

recumbency in case of a sternotomy) for 10–20 minutes, to allow the local anesthetic to spread over the targeted area. Local anesthetics are rapidly absorbed from the pleural space into systemic circulation, and may yield high plasma concentrations [8]. Therefore, it is important to use appropriate doses of local anesthetics to avoid potential systemic toxicity. In small patients, dilution of the local anesthetic may be needed to provide enough volume without excessive dosage, but excessive dilution of local anesthetic concentration may affect the block's efficacy. Bupivacaine 0.25–0.5% (1.5 mg/kg) is typically used and can be repeated every 8–12 hours [6]. Potential complications associated with this technique include systemic local anesthetic toxicity, pneumothorax, and impaired diaphragmatic function (more severe with bilateral blockade) [9]. Caution is recommended when using this technique in patients with compromised respiratory function.

Epidural Anesthesia

Epidural anesthesia provides bilateral sensory (and often motor) blockade of caudal abdomen, pelvis, pelvic limbs, and tail. The technique relies on palpation of anatomical landmarks (dorsal spinous processes of L7 and S1) to identify the location of the lumbosacral intervertebral space and is typically performed with the dog positioned in sternal or lateral recumbency.

The spinal needle is introduced at the dorsal midline (between L7 and S1), perpendicular to the skin, and advanced through skin, subcutaneous tissues, supraspinous and intraspinal ligaments, and ligamentum flavum (Figure 197.1). As the needle goes through the ligamentum flavum, a “pop” or loss of resistance

can be felt, indicating that the tip of the needle has reached the epidural space [5,10]. Presence of blood or CSF at the hub of the needle indicates intra-vascular or subarachnoid needle placement, respectively. Local anesthetic should not be injected if blood is present, and the dose of local anesthetic should be significantly reduced if a subarachnoid injection is performed. Particular attention should be paid to cats, as the spinal cord typically extends beyond the lumbosacral space in this species, increasing the risk of potential spinal injection. Careful aspiration should always be performed prior to injecting local anesthetic.

A sacral-coccygeal/coccygeal approach (caudal epidural) can also be used to provide anesthesia and analgesia to the area of the perineum and tail (while sparing the pelvic limbs). This technique has been described to provide pain management and facilitate catheterization in cats with urethral obstruction [11]. Needle insertion site is determined by locating the first movable intervertebral space caudal to the sacrum.

Duration of blockade will depend on the type of local anesthetic used (short- or longer-acting) and concentration, among other factors [10]. Preservative-free morphine (with or without local anesthetics) may also be used to provide long-lasting analgesia. Epidural catheters are recommended to provide analgesia for extended periods of time and allow for easy redosing (Figures 197.2 and 197.3).

Epidurals are contraindicated in patients with coagulopathies, sepsis, hypovolemia (untreated), neurological deficits, and skin infection at the site of needle insertion. Potential complications include hypotension, prolonged motor blockade, urinary retention, infection, and slow hair growth [12].



Figure 197.1 Epidural needle placement in a dog in sternal recumbency. The operator inserts the spinal needle on the dorsal midline, between L7 and S1, perpendicular to the skin. Reproduced with permission of Pedro Boscan.

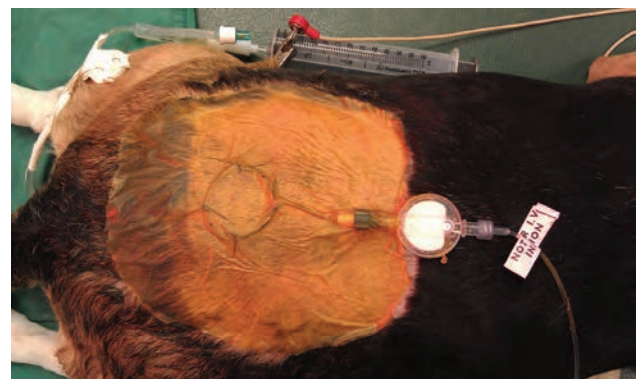


Figure 197.2 An epidural catheter secured in place with sutures and adhesive sterile drape. An in-line filter can be seen attached to the catheter port. Epidural catheters can allow for intermittent or continuous drug infusion. Reproduced with permission of Pedro Boscan.



Figure 197.3 A lateral radiograph of the lumbar spinal region of a dog showing an indwelling epidural catheter. Reproduced with permission of Pedro Boscan.

Potential Complications

Systemic Toxicity

Systemic toxicity, from accidental intravascular injection or excessive dosing of local anesthetics, is likely the most severe and life-threatening complication from regional anesthesia. The importance of careful aspiration prior to injecting local anesthetics cannot be overstated. Excessively high plasma concentrations of local anesthetics can cause central nerve system (CNS) and cardiovascular (CV) depression, which may be fatal.

Typically, CNS signs occur first and include agitation, muscle twitching, and seizures, and may progress to loss of consciousness, coma, and respiratory arrest. As plasma levels continue to rise, cardiovascular symptoms become apparent and include hypotension and cardiac arrhythmias (bradycardia, wide QRS complex, ventricular premature contractions, ventricular tachycardia, ventricular fibrillation, and asystole). In people, a retrospective review of local anesthetic toxicity indicated that while most cases follow this pattern (60%), in some cases cardiovascular depression occurred without CNS signs [13]. It should be noted that the CNS symptoms might not be apparent in sedated or anesthetized patients, which is the case for most veterinary patients.

Longer-acting (more lipophilic) local anesthetics such as bupivacaine (and to a lesser degree levobupivacaine and ropivacaine) have significant cardiotoxic potential. Bupivacaine differs from most other short-acting local anesthetics (e.g. lidocaine) in that CV depression occurs simultaneously with or before CNS symptoms and seems to be more severe and difficult to reverse [14–16]. Levobupivacaine and ropivacaine have similar potency and

clinical profile to bupivacaine, and can also cause severe cardiotoxicity, but it seems to occur at higher doses, indicating a reduced toxic potential [17,18]. In addition, cardiovascular collapse caused by ropivacaine overdose was easier to reverse compared to bupivacaine and levobupivacaine (mortality rates of 10%, 50%, and 30%, respectively) [19].

While intravascular injection and overdosing are the most common causes for systemic toxicity, other conditions may increase the potential for higher plasma concentration than anticipated: increased systemic absorption in highly vascularized areas (intercostal muscles, epidural space), hypoproteinemic states (local anesthetics are highly protein bound), impaired metabolism and elimination (renal and hepatic disease, hypotension, and heart failure), among others [20]. Acidosis, hypoxemia, and hypercarbia have also been shown to potentiate cardiovascular toxicity in sheep and additional caution should be exercised when using local anesthetics in patients presenting with those physiological abnormalities [21].

Treatment of local anesthetic cardiotoxicity should include circulatory and respiratory support, with early cardiopulmonary resuscitation. Strong evidence supports the use of intravenous 20% lipid emulsion (Intralipid 20%) to reverse bupivacaine, levobupivacaine, and ropivacaine toxicity and its use is recommended by the American Society of Regional Anesthesia and Pain Medicine [20,22,23] (see Chapter 128). In one experimental study, all dogs were successfully resuscitated from bupivacaine-induced cardiovascular collapse after intravenous administration of 20% lipid emulsion (4 mL/kg bolus followed by 0.5 mL/kg/min for 10 min) [23].

Nerve Injury

While the incidence of neurological complications after regional anesthesia is low and permanent nerve damage is rare, care should be taken to avoid nerve injury. Increased resistance to injection is highly suggestive of intraneural injection and neurological deficits resulting from high injection pressures seem to be more severe and longer lasting [24,25]. While not all intraneural injections may cause nerve injury, all efforts should be made to avoid it. If resistance is encountered, injection should be stopped and the needle repositioned. When electrical nerve location is used, it is currently recommended that electrical current be reduced to 0.2 mA after the nerve is located, and termination of motor response ensured prior to anesthetic injection. However, absence of motor response at low currents does not exclude the potential for intraneural injection [26,27]. Ultrasound-guided techniques seem to be more sensitive to identify intraneural injections, even with small-volume injections [26,28]. As local anesthetic

is injected, a circumferential spread of hypoechoic fluid should be seen around the nerve.

Infection

The incidence of infection associated with regional anesthesia is low, but aseptic technique should always

be used. This is particularly important with epidural anesthesia as infection and abscess formation at close proximity of the spinal cord may have serious consequences.

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Go Home Analgesics

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Pain Assessment

Every animal presented to the emergency department should be assessed for evidence of pain using a pain scale that all staff are trained on and the pain score should be documented in the animal's medical record.

Pain assessment in animals is largely interpretation of animal behavior and understanding pain behaviors for dogs and cats [1]. Animals presenting to the emergency department are known to have a high incidence of pain, but detection of pain behaviors can be challenging in traumatized animals [2]. Generally, there is no pre-existing veterinarian–patient relationship that precludes the veterinarian from being able to develop an understanding of normal behaviors or reliable pain behaviors exhibited by this individual. Additionally, traumatized animals may not demonstrate normal pain behaviors due to the neuroendocrine response to trauma, resulting in sympathetic activation and release of endorphins and enkephalins, and endogenous opioids. Environmental factors such as traumatic events and physiological factors such as species, age, body condition, and concurrent disease may influence pain behaviors by either amplifying or tempering pain responses and should be taken into consideration when assessing animals for pain. Alternative means of assessment and an appreciation for conditions that are normally associated with pain are necessary and often an empiric approach to managing pain may be necessary in order to avoid undertreating pain in these animals [3,4].

Various pain assessment scales have been described for use in veterinary medicine, including the visual analogue scale (VAS), a simple descriptive pain scale, the numeric rating scale, and categorical pain scales [1]. Many pain scales are subjective, allow for bias, and are associated with interobserver variability. Categorical pain scales that utilize both physiological and behavior indicators of pain may be the most reliable assessment tools when acute or chronic scoring systems are used [4,5]. More

recently, owner assessment of pain in their pet through the implementation of questionnaires has been used to aid the clinical assessment of pain. Utilization of dog- and cat-specific outcome measure questionnaires introduces another level of consideration of pain assessment by questioning individuals who are most familiar with an animal's behavior [6–10].

Pathophysiology of Pain

Pain can arise from acute, high-intensity stimuli, from tissue injury or inflammation or damage of peripheral nerves. The high-intensity stimuli responsible for acute pain carry a high propensity for actual or potential tissue damage and are associated with aversive, protective behaviors (withdrawal, guarding) that are generally proportional to the intensity of the stimulus. Somatotopic localization of pain origin is usually well defined. Acute pain activates the autonomic nervous system such that these animals generate a measurable sympathetic response proportional to the stimulus intensity. In fact, autonomic responses such as heart rate variability represent a potential objective modality for acute pain assessment [11].

Pain and stress associated with tissue damage play a prominent role in the traumatized patient by triggering a neuroendocrine reaction leading to local inflammation or, if severe and progressive, systemic inflammation [12]. Tissue injury or inflammation alters the response characteristics of small afferent nerve endings that innervate inflamed tissues. Afferent nerve endings that are typically responsive only to high-intensity stimuli are now activated with lower intensity stimuli, an activation of so-called silent nociceptors. There is a disproportionate stimulus–response relationship such that there is an enhanced pain response and an increase in nerve firing given the level of stimulus applied. Characteristic of

the inflammatory pain state, there is activation of local factors and mediators that lead to the altered afferent responses described above. Release of local proinflammatory cytokines and peptides comprise this sensitizing soup [12,13]. Central spinal action of cyclo-oxygenase (COX) also plays a major role in inflammatory pain [14]. Facilitated input from afferent nerves in the setting of inflammation leads to the release of prostaglandins from the second-order neurons which bind prostanoid receptors in nerve terminals and enhance spinal excitability. Excitatory neurotransmitters, including glutamate and substance P, are released from primary afferent neurons in response to tissue injury and inflammation that cause persistent activity in small primary afferent nerves.

Damage to peripheral nerves, a condition that may or may not be associated with tissue damage, exhibits unique characteristics compared to acute or inflammatory pain. Neuropathic pain persists beyond the point at which the stimulus is removed and tissue healing occurs. Pain may be spontaneous or unprovoked and is referred to the peripheral distributions of the injured nerve. Tactile allodynia, non-painful stimuli such as light touch evoking a pain response, is a salient feature of neuropathic pain. Unlike acute pain or pain associated with tissue injury or inflammation, animals with neuropathic pain have an attenuated response to traditionally efficacious analgesics such as opioids.

Go Home Analgesics

Optimal management of pain requires a mechanistic approach to classifying pain, ultimately allowing selection of pain therapeutics targeted at specific components of the pain pathway (Table 198.1). Pain associated with trauma or emergency situations is often multimechanistic in nature, necessitating a multimodal therapeutic approach [15]. In-hospital management of pain in the emergency department is often opioid based, but transitioning to go home analgesics while accounting for all aspects of the pain syndrome often requires non-injectable formulations. Common go home analgesics are usually oral formulations although a number of non-injectable, parenteral formulations of analgesics are now available (Table 198.2).

Opioids

Opioids represent the mainstay for management of acute, physiological pain. Unfortunately, bioavailability of oral formulations is generally poor and metabolism from prodrug to active metabolites is limited in dogs and cats, leading to lack of clinical efficacy [16,17]. A study investigating codeine in dogs demonstrated

Table 198.1 Efficacy of common go home analgesics in the treatment of specific pain syndromes. Drug classes are considered effective (+), ineffective (–), or demonstrated to have questionable efficacy (+/–).

Drug class	Acute, physiological pain	Tissue injury, inflammatory pain	Nerve injury, neuropathic pain
Opioid	+	+	+/–
Non-steroidal anti-inflammatory drug	+	+	+
NMDA antagonist	–	+	+
Anticonvulsant (gabapentin)	–	+	+
Tricyclic antidepressant	–	+	+
Tramadol	+/–	+	+

NMDA, N-methyl-D-aspartate.

analgesic efficacy comparable to tramadol but rescue analgesia was required in a third of animals receiving codeine [18]. Additionally, oral opioids such as codeine, hydrocodone, morphine, oxycodone, and others may be co-formulated with acetaminophen, which poses toxicity potential and represents a significant risk for liability due to the abuse potential by owners and drug diversion.

The limited efficacy of oral opioid formulations has led to the development and utilization of parenteral formulations such as patches, transdermal creams, and injectable forms administered transmucosally. Fentanyl patches have long been utilized as a means for providing multi-day opioid therapy in the home setting despite unpredictable plasma concentrations [19–21].

Buprenorphine is available as a 0.3mg/mL injectable formulation suitable for oral transmucosal administration in cats in the home setting and a 1.8mg/mL solution suitable for once-daily subcutaneous administration lasting 24 hours (not to be dispensed to the owner) for the management of pain in cats [22,23].

Non-Steroidal Anti-Inflammatory Drugs

The therapeutic role NSAIDs play in treating pain associated with hypersensitivity pain states in emergency patients must be balanced with their potential adverse effects. The homeostatic functions of constitutively expressed COX isoforms are related to the adverse effects commonly encountered with this drug class. Platelet dysfunction, renal, hepatic, and gastrointestinal

Table 198.2 Common go home analgesics for dogs and cats.

Drug	Dog	Cat	Comments
Non-steroidal anti-inflammatory drugs			
Carprofen	4.4 mg/kg PO SID 2.2 mg/kg PO BID 4.4 mg/kg SC	4 mg/kg SC once	Off label in cats
Deracoxib	3–4 mg/kg PO SID (postop pain) 1–2 mg/kg PO SID (OA)		
Firocoxib	5 mg/kg PO SID	1.5 mg/kg PO once	Off label in cats
Ketoprofen	0.5–1 mg/kg PO BID	0.5–1 mg/kg PO SID 7–10 days	
Meloxicam	0.2 mg/kg PO once on day 1 then 0.1 mg/kg PO SID	0.3 mg/kg SC once	Black box warning for use in cats, lowest effective dose should be used
Robenacoxib	1 mg/kg PO SID	1–2 mg/kg PO SID up to 3 days	Do not administer with food
Tepoxalin	10–20 mg/kg PO on day 1 then 10 mg/kg SID	5–10 mg/kg	
Grapiprant	2 mg/kg PO SID (dogs)	No dose for cats	
Opioids			
Buprenorphine	–	0.01–0.03 mg/kg oral transmucosal TID	
Buprenorphine (Simbadol)	–	0.24 mg/kg SC SID	Recommend for in-hospital use prior to discharge
Fentanyl			
Transdermal patch (Duragesic)	< 10 kg 25 µg/h 10–20 kg 50 µg/h 20–30 kg 75 µg/h > 30 kg 100 µg/h	25 µg/h	18–24 h to peak effect in dogs 12–18 h to peak effect in cats
Analgesic adjuvants			
Amantadine	2–5 mg/kg PO SID-BID×at least 28 days	2–5 mg/kg PO SID-BID×at least 28 days	
Amitriptyline	1–2 mg/kg PO SID- BID	0.5–1 mg/kg PO SID	Not recommended to co-administer with tramadol or trazadone
Gabapentin	10–20 mg/kg PO BID-QID	10–20 mg/kg PO BID-QID	
Tramadol	2–5 mg/kg PO TID-QID	2–4 mg/kg PO BID	Unpalatable to cats

BID, twice a day (*bis in die*); OA, osteoarthritis; PO, by mouth (*per os*); QID, four times a day (*quater in die*); SC, subcutaneous; SID, once a day (*semel in die*); TID, three times a day (*ter in die*).

adverse effects constitute the primary adverse effects of NSAID therapy [24,25].

The most common side-effects of NSAIDs affect the gastrointestinal tract in dogs although more recently labeled NSAIDs, such as firocoxib, meloxicam, and carprofen, appear to have a lower incidence compared to older drugs such as aspirin, ketoprofen, etodolac, and flunixin meglumine [25–29]. It is possible that better COX-2 selectivity allowing for COX-1-mediated production of gastric prostaglandin E₂ (PGE₂) may account for the safer gastrointestinal profile in newer NSAIDs, but long-term safety studies are needed to definitively prove safety over similar but older drugs

[30]. Measures taken to minimize the risk of gastrointestinal and other side-effects of NSAIDs in dogs include ensuring they are eating and drinking normally throughout the course of therapy. Co-administration of proton pump inhibitors, H₂ receptor antagonists or synthetic prostaglandin analogues such as misoprostol has limited evidence of efficacy.

The trauma patient poses the additional risk that volume depletion or hypovolemia may be present. The use of NSAIDs in volume-depleted or hypovolemic patients should be avoided until a normal circulating volume is re-established due to the risk for hypoperfusion to the gastrointestinal and renal systems [31,32].

Other animals in which NSAIDs should be avoided include pregnant or lactating animals, those with asthma or severe pulmonary disease, acute intervertebral disk herniation due to risk of worsening hemorrhage, coagulopathies, animals currently receiving NSAIDs or corticosteroids, and animals with hepatic or renal disease due to the risk for adverse effects [33].

Renal and gastrointestinal effects are the most common reported adverse effects of NSAIDs in cats. The 2010 Food and Drug Administration's addition of a Black Box Warning to the label for oral and injectable meloxicam for cats, brought about by the increased incidence of renal failure and death associated with this drug, prompted the re-evaluation of the off-label use of NSAIDs in cats. Inhibition of vasodilatory PGE₂ and PGI₂ production leading to vasoconstriction-mediated renal perfusion impairment, renal tubulointerstitial nephritis, and papillary necrosis resulting in renal failure are the primary mechanisms for renal toxicity [34]. Robenacoxib, a newer NSAID labeled for cats, appears to have a better safety and efficacy profile than meloxicam or ketoprofen [35–37]. Long-term studies evaluating safety are limited but do not suggest safety concerns for 9–30 day dosing [37–39].

Grapiprant

The priprant class of drugs act as antagonists at the target receptors for prostaglandins: prostanoid (EP) receptors [40]. The E type prostaglandins, particularly PGE₂, is one of the most widely produced PGs and is responsible for a variety of physiological functions, namely inflammation and pain. The target receptors whereby PGE₂ exerts its effects are the EP1, EP2, EP3 and EP4 receptors [41,42]. Sensory neuron sensitization and pain are primarily mediated through activation of the EP4 receptor.

Grapiprant (Galliprant®), a selective EP4 receptor antagonist, is labeled for use in the United States to treat pain and inflammation associated with osteoarthritis in dogs. Grapiprant has been demonstrated to be effective in reducing owner and veterinarian-assessed pain in dogs with naturally occurring osteoarthritis administered 2 mg/kg orally for 28 days [43]. Most common side-effects, vomiting or diarrhea, are mild, with relatively low incidence rate – 17% and 12% respectively [43]. While not yet labeled for use in cats, early pharmacokinetic data appears similar to dogs [40].

Adjunctive or Alternative Analgesics

Tramadol

Tramadol is not a traditional opioid but has mu-opioid receptor agonist activity as well as serotonin and norepinephrine reuptake inhibition and alpha-2 receptor

agonism. Little parent drug activity at opioid receptors and limited active metabolite formation mean this drug has limited efficacy for acute pain in dogs [44–46]. Cats, however, readily produce the active metabolite responsible for opioid effect, O-desmethytramadol, and therefore have demonstrated analgesic effects in acute pain models [47,48]. Use of tramadol for inflammatory or neuropathic pain states in dogs produces very modest analgesic effects and best utilization of this drug is as an adjunct to other analgesics [49]. Tramadol administered orally is generally well tolerated in dogs but can cause profuse salivation in cats, presumably due to a bitter taste.

Caution is advised when prescribing monodrug therapy or multimodal therapy using drugs that inhibit reuptake of serotonin or have serotonergic effects (tramadol, amitriptyline, trazadone), particularly if animals are on other therapies that have serotonergic effects as the development of serotonin syndrome is possible [50].

Amantadine

Amantadine, an antiviral, is the primary oral N-methyl-D-aspartate (NMDA) antagonist currently used in small animal veterinary medicine. The NMDA receptor is activated with prolonged or significant afferent C-fiber stimulation, which occurs in tissue and/or nerve injury, causing depolarization of second-order neurons in the dorsal horn of the spinal cord. Preventing activation of the NMDA receptor or treating temporally summated C-fiber activity-induced sensitization (wind-up) with an NMDA receptor antagonist will reduce hypersensitivity and may also demonstrate an analgesic-sparing effect. While data for the opioid-sparing effect are conflicting in cats, this may be due to limitations in the model (acute nociception) as opposed to lack of effect that has been demonstrated in a hypersensitivity model [51,52]. In a canine population with osteoarthritis, amantadine was demonstrated to have a NSAID-sparing effect [53] and a single case report demonstrating efficacy with a neuropathic pain condition [54].

Gabapentin

Gabapentin, an antiepileptic medication, has been used in the management of neuropathic pain in humans. While its exact mechanism of action is unknown, gabapentin is known to bind the alpha-2 delta-1 subunit of voltage-gated calcium channels that are present in the superficial laminae of the spinal cord dorsal horn and in the dorsal root ganglia. Data on efficacy of gabapentin in neuropathic pain syndromes are limited. Data in dogs are conflicting but dosing might be insufficient in some studies [55–58].

Cat data are limited to case reports, including trauma cases, and appear more positive although a control population was not available due to the nature of

the information (case reports) [59–62]. Sedation and ataxia are common side-effects that can be minimized by adjusting the dosing schedule (reducing the dose or increasing dosing interval).

Tricyclic Antidepressants

Tricyclic antidepressants such as amitriptyline inhibit reuptake of serotonin and norepinephrine, thereby enhancing neurotransmitter activity in central nerve terminals and producing analgesic effects in neuropathic pain syndromes. Analgesia is also produced by augmentation of bulbospinal tone. Little information is available on analgesic efficacy or dosing in dogs and cats [63,64].

Lidocaine Patches

The transdermal lidocaine patch (Lidoderm) allows administration of lidocaine at local tissue concentrations high enough to produce clinically effective local analgesia without inducing complete sensory block, while producing systemic plasma concentrations far below those capable of producing local anesthetic toxicity [65,66]. Lidocaine patches may be used to provide local analgesia

for skin abrasions, lacerations, and severe local skin irritation and itching (hot spots).

The patches are supplied as a 10×14 cm adhesive patch that, unlike fentanyl patches, may be cut into strips or smaller sizes with a scissors prior to removing the protective liner to adapt to various anatomic uses. Clipping the hair where the patch will be applied is recommended but further skin preparation (application of a depilatory or alcohol) is not recommended as this will alter the pharmacokinetics. While original guidelines recommended not covering incisions or open wounds, recent data suggest that while plasma concentrations are higher when placed over mucosal surfaces, they are still well below toxic levels and local skin irritation was not appreciated [67]. The lidocaine patch can be covered with a dressing or bandage and changes in temperature (e.g. heating pad, forced warm air blanket) are tolerated without affecting drug deposition [68]. Generally, one to two patches trimmed into strips to line an incision is sufficient for most dogs. A single patch trimmed to line an incision is usually sufficient in cats. Patches can be left in place for up to 3 days without causing skin irritation while providing a local anesthetic effect. The patch should be disposed of in a way that prevents unintended human or animal exposure.

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Approach to the Aggressive or Fearful Emergency Room Patient

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Introduction

Dogs and cats are presented to the emergency room (ER) for a wide range of reasons, from traumatic injury and critical illness to lacerations or gastrointestinal upset. The veterinary patient arriving to the ER may be agitated, which can compound fear, anxiety, and pain associated with injury or illness. The combination of these and other patient factors can result in aggression directed towards veterinary clinicians, staff, and even the client. Aggressive behavior in the veterinary patient can be frustrating, dangerous for personnel, and time-consuming, and may ultimately result in delayed therapy for severe or life-threatening illness. Recognizing, anticipating, and mitigating this behavior in the ER patient will reduce stress and the chance of injury to both staff and patient. The utilization of proper restraint techniques can improve the experience for the client, patient, and veterinary personnel.

Patient Fear and Aggression

Dogs and cats can exhibit fearful or aggressive behavior during ER evaluation, regardless of their typical demeanor outside the hospital setting. Patient aggression may be influenced by arousal, excessive stimulation, pain, anxiety, and fear. Fear is an emotional response that spurs an animal to avoid potentially dangerous or harmful situations [1]. Fear is common in veterinary patients, particularly cats, and can be aggravated with forceful restraint (such as scruffing the skin of the neck). The unfamiliar sights and smells of the ER, rapid movements by staff and other animals, and loud noises can compound this fear [2]. Aggression

associated with fear can result in unpredictable behaviors, and may also occur due to pain and discomfort. Additionally, if a pet has previously had negative experiences at veterinary clinics, or has an acute exacerbation of a chronic disease, they can become anxious, anticipating a negative outcome, resulting in fearful or aggressive behavior [3]. Other aspects of the ER visit, such as bright ambient lighting and visual contact with other patients, may contribute to fear [4]. If feasible, the cage or carrier of a fearful animal should be covered to decrease visual stimulation (e.g. using a towel over the opening) and help to calm the animal [4].

Recognizing Fear and Aggression in Dogs and Cats

All veterinary staff should be comfortable with the recognition of fear- or aggression-specific behaviors. From a distance, the animal's posture, eyes, ear, lip, and tail position should be evaluated. Fearful or aggressive behaviors in dogs and cats include cowering in the corner of the room or carrier, trembling, low head carriage with eyes averted, eyes that dart between areas of focus or stare, a tucked tail, or hiding under exam room furniture [3,5,6]. Dogs and cats may pant, or stand or sit with one paw raised [6]. A cat that lashes its tail, or just the tip of the tail, from side to side indicates agitation, annoyance, or arousal [5]. Ears flattened against the head, particularly in the cat, indicate a defensive behavior, which may progress to aggression [2]. In more aggressive and assertive animals, the ears may be positioned forward. Pupil size can correlate to the degree of intensity of the situation, becoming mydriatic with fear. Oblong pupils in the cat can signal aggression [5]. Pain and medications (e.g. opioids) can also affect pupil

size. Aggressive dogs may display threatening behaviors, such as lip lifting, growling, barking, lunging, and biting. Aggressive cats may display hissing, growling, swatting, and biting [7]. However, displacement behavior such as yawning, smacking and licking of the lips in the dog or grooming in the cat can also signal a fear or anxiety-inducing situation [2,7].

If these behaviors are noted, care should be taken to avoid escalation to more aggressive, defensive behavior [7]. Animals that are extremely distressed may void urine, feces, or anal gland secretions, and may frantically try to escape from the situation, while others may freeze and not interact at all [4].

Techniques for Patient Handling and Physical Restraint

The veterinary staff should be comfortable utilizing tools for restraint and handling of aggressive patients. The use of pharmacological restraint techniques may also help to alleviate distress in patients, and if the animal is anticipated to react or does react poorly to physical restraint techniques, pharmacological restraint may be indicated (see below).

Client Communication

If the owner knows that a particular patient may be aggressive at the facility, the owner may be able to safely place a muzzle on the pet immediately prior to presenting for triage examination. If a pet displays severe aggressive behavior, clear communication with the client is necessary to ensure that the pet owner understands the need for manual or pharmacological restraint, as well as the veterinary personnel's genuine concern for the well-being of the pet.

Approaching the Patient

If the animal is in a travel carrier on presentation, opening the door, standing to the side of the open door, and talking softly to the dog or cat may encourage it to walk out of the carrier on its own. Emergency stabilization, however, may necessitate rapid manual removal of the pet from the carrier. Removal of the detachable top of pet carriers can improve access to the pet, and the fearful patient may be more amenable to handling by this route. This approach may also be safer for ER personnel. Any animal that requires assistance to be removed from a car should be muzzled prior to removal; this protects the lifters if the animal is unpredictably painful and bites, but also because the pet

may feel threatened as a stranger enters into a familiar place. If the patient walks into the ER on a leash, avoid confrontation by approaching the pet from the side, without direct eye contact. Avoid backing the pet into a corner or reaching over the head to grab the leash or collar [7]. Slip leashes should be used to control dogs, as the dog's own collar may slip off the neck if the dog resists handling. Talking to the pet in a comforting and soft tone throughout the examination can help reduce stress, fear, and anxiety. Avoid exposing the patient to excessive stimuli or noises (e.g. large numbers of people surrounding the treatment table, clippers, or monitor alarms) during triage evaluation.

Cats are often co-operative enough to be restrained on a table by using one hand or arm to restrain the body and the other hand to restrain the head. Many people will scruff the neck skin to restrain a fractious cat but this can increase fear and spark aggressive behavior [2]. If the cat requires restraint of the head, use the three middle fingers to massage the top of the head (between the ears), and the thumb and pinkie fingers to control the cat's head by firmly gripping it just below the ramus of the mandible [2]. This can allow full restraint of the cat's head while avoiding the stress and arousal associated with scruffing.

Towels are extremely helpful for restraint of fearful or aggressive cats and small dogs. Cats can be restrained by wrapping the body and limbs in a heavy towel in a burrito-like fashion. Once wrapped, limbs may be carefully withdrawn as needed, for procedures such as intravenous catheter placement or blood pressure measurement. A towel rolled length-wise can also be used to aid in restraint of small to medium-sized dogs, as it can be placed around the neck at arm's length and crossed over itself behind the head to facilitate placement of a muzzle. Care should be taken that the towel is not held too tightly around the patient's neck. Towels placed over the head or eyes of fearful animals may also help to calm them, especially in the context of manual restraint [4]. For anxious or fearful animals that are hospitalized, a tight-fitting body wrap or shirt (e.g. Thundershirt, ThunderWorks, Durham, NC) can provide a comforting and calming sensation. In postoperative patients, these wraps also protect surgical wounds.

Muzzles

Muzzles should be available for use in fearful or aggressive patients. They come in a variety of shapes, sizes, and are made of nylon, plastic, or leather. Most muzzles fit snugly over the pet's muzzle and latch or buckle behind the ears. Makeshift muzzles made from

gauze or tape can be configured in the hospital to aid in restraint of the aggressive animal, especially those who might not allow placement of a regular muzzle. Snug-fitting muzzles should not be left on the patient any longer than necessary, as the muzzle closes the mouth and prevents panting, commonly seen in the anxious or fearful patient and necessary for temperature regulation [7]. Muzzles can also interfere with emesis and predispose to aspiration of vomitus. Basket-type muzzles allow the patient to pant effectively and are sometimes easier to place, because they are formed into shape, allowing rapid placement over the face [7]. Muzzles that restrict breathing should be avoided in the emergency patient with respiratory difficulty or in brachycephalic dogs. Cat muzzles cover both the mouth and eyes to aid in handling of the fractious cat. These cone-shaped muzzles may also be used for brachycephalic breeds, as they generally do not obstruct respiration and can also protect the eyes, depending on the size of the dog.

Other Manual Restraint Tools

Nets may assist in handling very aggressive or feral cats. There are also commercially- available nets on a metal clamshell frame (e.g. EZ-Nabber, Campbell Pet Company, Brush Prairie, WA). Once in the net, pharmacological restraint can be administered through the mesh to facilitate further examination. Leather gloves that cover the hands and forearm are available for holding smaller fractious patients and provide protection from bites and scratches; however, they are bulky and limit the dexterity of the handler.

Control poles, or “rabies poles,” are used only with extremely dangerous and aggressive dogs. Restraint of the head with the control pole allows safe administration of intramuscular drugs for sedation. The dog should never be dragged, yanked, pulled, or lifted with the control pole, as this may cause injury. The control pole should be used only when other more humane or less threatening options are not feasible [7].

Pharmacologic Restraint of the Aggressive or Fearful Patient

Delivery of Pharmacological Agents for Restraint

If physical restraint is unsuccessful or dangerous for the veterinary staff or patient, pharmacological restraint may aid with patient handling. If the patient allows placement of an intravenous catheter, IV administration of sedatives results in rapid onset of action.

Intramuscular injection may be more feasible, and can be administered while the animal is muzzled, still inside the travel carrier, or even when distracted while exiting the exam room. For smaller dogs and cats, commercially available squeeze cages can stabilize the animal to allow rapid, accurate IM injections. For larger dogs, an exam room door or large chain-link cage door can make a modified squeeze cage. The dog is walked into a corner where the door meets the wall and the end of the leash is fed through the hinge of the door. The leash is held tight by an assistant on the other side of the door, and the door is swung against the dog, creating a “squeeze cage” between the door and wall. An IM injection can then be given.

Although it is ideal to verify that an IM injection is not accidentally administered IV, this may not be possible in the aggressive animal. Rather, the syringe can be held with the plunger in the palm of the hand so that the needle and medications can be introduced in one firm movement. The authors prefer the epaxial muscles for this type of injection, as there is less danger of accidental injection in the nerves of the hindlimb.

If the handler cannot safely approach the animal to give an injection, commercially available pole syringes can be used to safely administer medications. Anesthetic gas induction chambers can be considered for sedation of aggressive small dogs, cats, non-domestic species and wildlife; however, this methodology results in exposure of personnel to high concentrations of inhalant gas, and the patient cannot be closely monitored during induction [8].

Pharmacological Agents for Use in Aggressive Animals

Various medications can be administered to the fearful or aggressive animal to allow for handling and treatment in the emergency situation (Table 199.1). A neuroleptanalgesic combination of a tranquilizer and an opioid is the safest combination for sedation in patients with unknown cardiovascular status, but may only provide light sedation, rather than heavy sedation or anesthesia. It may be necessary to subsequently place a muzzle and restrain the patient for IV catheter placement. With IV access, additional sedative or anesthetic drugs can be administered to deepen sedation or induce anesthesia. Additional drugs may also be given by the IM route. Opioids given alone may result in emesis, and the practitioner must remain vigilant and rapidly remove tight-fitting muzzles if nausea becomes apparent (i.e. pyalism).

Anesthetic protocols involving dissociative anesthetics (e.g. ketamine or tiletamine) are preferred by the authors for aggressive patients, as the dissociative agent

Table 199.1 Suggested doses of sedative drugs for the fearful or aggressive veterinary patient and special considerations for their use.

Drug	Dose	Effects	Special considerations
Opioids: should be combined with tranquilizer (e.g. benzodiazepine, phenothiazine, alpha-2 agonist) for optimal sedation	Butorphanol 0.2–0.5 mg/kg IV, IM [9]	Good sedative, minimal analgesia	Minimal cardiovascular depression; respiratory depression at higher doses (applies to all opioids) Can partially reverse sedation secondary to administration of pure mu-opioids
	Morphine 0.5–2 mg/kg IM [11]	Very good sedative and analgesia	Can cause histamine release, nausea
	Hydromorphone 0.1–0.2 mg/kg IV, IM, SC [9]	Moderate sedative, good analgesic effects	May cause panting, nausea, and vomiting
	Methadone 0.05–0.6 mg/kg IV; 0.5–1 mg/kg IM [10,11]	Good sedative and analgesic effects	Lower incidence of nausea and vomiting relative to other opioids [11] May cause mild peripheral and pulmonary vasoconstriction [10]
Benzodiazepines: must be combined with opioid or dissociative agent for sedation of aggressive patients	Midazolam 0.1–0.5 mg/kg IV, IM [9]	Centrally acting muscle relaxant, anxiolytic, mild tranquilizer	Minimal cardiovascular and respiratory depression [12]
	Diazepam 0.1–0.5 mg/kg, IV [9]	Some amnesic effects	Can see paradoxical excitement and agitation after administration [9] May see more aggressive behavior after administration due to disinhibition of fear response [13] Do not use alone in aggressive animals
Phenothiazines: must be combined with opioid or dissociative agent for sedation of aggressive patients	Acepromazine 0.005–0.05 mg/kg IV, IM [9]	Good tranquilizer and sedative	May take up to 40 min for full effect
	Can give up to 0.1 mg/kg in single dose (not to exceed 3 mg total in dogs) [9]		May cause hypotension, particularly in hypovolemic patients [9] Good for sedation in patients with respiratory distress; minimal respiratory depression
Alpha-2 agonists	Dexmedetomidine 0.5–20 µg/kg (0.0005–0.0020 mg/kg) IV, IM, PO [11]	Good sedation, muscle relaxation, and analgesia	Need higher doses of dexmedetomidine in highly agitated animals; response may be variable or animal may appear refractory to effects of the drug
	Medetomidine 1.0–20 µg/kg (0.001–0.0020 mg/kg) IV, IM, PO		Do not use as sole agent in aggressive animals
	Xylazine 0.5–1 mg/kg IV; 2.2 mg/kg IM [9]		Significant cardiovascular depression: decreases cardiac output, bradycardia, peripheral vasoconstriction May cause vomiting in cats
Dissociative anesthetics	Ketamine 5–10 mg/kg IV, IM [9,11]	Excellent tranquilization and sedation	Recommended to use ketamine in combination with a tranquilizer (e.g. benzodiazepine, alpha-2 agonist) to provide good muscle relaxation
	Tiletamine/ zolazepam 5–15 mg/kg IM [11]	Useful adjunct to analgesia	Ketamine alone or combined with an alpha-2 agonist may be sprayed directly into an aggressive cat's mouth [11] May note erratic behavior during recovery and muscle twitching, leading to increased body temperature Use lower doses (0.5–2 mg/kg) in patients with suspected heart disease or cardiovascular dysfunction Increases intracranial and intraocular pressure Dose-dependent respiratory depression

(Continued)

Table 199.1 (Continued)

Drug	Dose	Effects	Special considerations
General anesthetic	Alfaxalone 5 mg/kg IV, IM (cats) and 5–10 mg/kg IV, IM (dogs) [14,15]	Excellent sedation and muscle relaxation Minimal cardiorespiratory depression	May cause dysphoria or ataxia in cats [14] May cause transient muscular tremors and staggering gait in dogs Dose-dependent hypoxemia and hypoventilation at higher doses [15] Can cause hypotension May cause apnea if administered rapidly IV

IM, intramuscular; IV, intravenous; PO, by mouth (*per os*); SC, subcutaneous.

impairs the animal's ability to act on aggressive influences. Dissociative anesthetics have minimal effect on cardiorespiratory function.

Alpha-2 agonist drugs should not be used alone for sedation of aggressive patients. They are associated with unpredictable sedation and unanticipated arousal. They also result in significant alterations in vascular tone and heart rate, which may not be tolerated in patients with known or unknown cardiovascular disease. Alpha-2 agonists increase urine output, and should not be used in patients who are unable to void urine. In patients where alpha-2 agonists are anticipated to be safe, their combination with opioid or dissociative anesthetics will result in a safer and more reliable immobilization. In patients that present an open mouth (e.g. a hissing cat), the combination of dexmedetomidine and ketamine may be squirted into the mouth for excellent sedation by transmucosal absorption.

Benzodiazepines should never be given alone to aggressive animals, as disinhibition may worsen the animal's aggressive tendencies. Combined with opioid or dissociative drugs, however, benzodiazepines result in synergy that provides good sedation and muscle relaxation (neuroleptanalgesia).

Opioids, benzodiazepines, and alpha-2 agonist drugs also have specific reversal agents, so the effects of sedation can be fully or partially removed following the ER exam or if adverse effects are seen (Table 199.2).

Every patient's physical and pharmacological restraint protocol should take into account their overall demeanor and suspected underlying disease process (Table 199.3). In most cases, the judicious use of sedatives, tranquilizers, and anxiolytics in combination with safe, careful physical restraint will result in a successful and less stressful ER experience for the patient, veterinary staff, and client.

Table 199.2 Suggested doses of reversal agents for sedated, aggressive veterinary patients.

Drug	Reversal class	Dose	Special considerations
Naloxone	Opioid antagonist	0.02–0.04 mg/kg IV, IM [11]	Duration of effect 30 min to 1 h May need to redose if inadequate reversal seen
Flumazenil	Benzodiazepine antagonist	0.01 mg/kg IV, IM [11]	May need to repeat due to short half-life (1 h)
Atipamezole	Alpha-2 adrenergic antagonist	Give IM at equal volume of alpha-2 agonist sedative administered or at 5 times the dose of medetomidine/dexmedetomidine [11] Can be given IV if needed in emergency	May reverse effects rapidly; caution in aggressive patients

IM, intramuscular; IV, intravenous.

Table 199.3 Suggested drug combinations for use in aggressive veterinary patients; all sedation doses given IV or IM, except where noted.

Commonly encountered patients	Drug combinations	Dose	Special considerations
Fearful or difficult, minimally aggressive dogs or cats	Butorphanol	0.2 mg/kg	Useful for short or non-painful procedures, such as radiographs or IV catheter placement
	Midazolam	0.2 mg/kg	
	+/- Dexmedetomidine	2–4 mg/kg	
Dogs or cats requiring moderate sedation	Butorphanol	0.2 mg/kg	Consider hydromorphone, morphine, or oxymorphone instead of butorphanol if procedure may be painful
	Midazolam	0.2 mg/kg	
	Dexmedetomidine or ketamine or telazol	3–5 mg/kg (dexmed) or 2–5 mg/kg (ketamine) or 2–5 mg/kg (telazol)	
Heavy sedation for aggressive dogs or cats	Butorphanol	0.2 mg/kg	Cats may require higher dexmedetomidine doses Consider other opioids for painful procedures Caution with use of dexmedetomidine in animals with severe aggressive behavior or with possible cardiac disease Dose reduce alfaxalone when used in combination with dexmedetomidine
	Midazolam	0.2 mg/kg	
	Ketamine	5–10 mg/kg	
	or		
	Dexmedetomidine	5–20 µg/kg	
	or	1–5 mg/kg	
Fearful or difficult, aggressive dogs or cats	Alfaxalone	5–20 µg/kg	Useful for initial restraint and IV catheter placement
	Dexmedetomidine		
	Dexmedetomidine	2–10 mg/kg TM	
	Ketamine	5–10 mg/kg TM	

IM, intramuscular; IV, intravenous; SC, subcutaneous, TM, transmucosal.

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Section 8

Unique Emergency Medicine Topics

Antimicrobial Therapy in the Emergency Patient

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Introduction

The frequency and distribution of emergency room visits amongst dogs and cats per year are unknown, although dogs are reported to present 2–3 times more frequently than cats [1,2]. In the United States 3% of emergency department visits were reported to have a primary diagnosis of infectious and parasitic diseases in 2011 [3], while it is estimated that 500 000 adults and nearly 100 000 children are treated annually for severe sepsis in US emergency departments [4,5].

The criteria for defining the systemic inflammatory response syndrome (SIRS) have been variably reported in dogs and cats (see Chapter 159). Sepsis is clinically diagnosed by the presence of SIRS and a documented or suspected infection. Sepsis has most recently been defined in human medicine as a life-threatening organ dysfunction caused by a dysregulated host response to infection while septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality [6].

When considering antimicrobial needs in the veterinary emergency patient with an infectious disease, the patient may fall into one of three categories: a stable patient who will be treated on an outpatient basis, a patient with sepsis that requires hospitalization, or a critically ill patient with severe sepsis or septic shock. The level of illness affects the choice and route of administration of antimicrobials as dogs and cats with severe sepsis and subsequent organ dysfunction have increased mortality rates [7,8]. Therefore, identification of a patient in the emergency room with sepsis is of paramount importance to help guide antimicrobial administration.

General Considerations for Antimicrobial Selection

When choosing an antimicrobial, elements that should be considered include the following; patient-related factors, micro-organism-related factors, and antimicrobial-related factors, and asking the question, does this patient truly need an antimicrobial? Comprehensive coverage of appropriate antimicrobial choice for the wide variety of diseases for stable outpatient conditions is beyond the scope of this chapter, and consultation with a textbook for individual scenarios is recommended. However, the principles presented here should still be used to guide selection.

Major host factors to consider include the presence of renal or hepatic dysfunction, signalment, a documented allergy or intolerance to an antimicrobial, and prior antimicrobial use. The adverse effects of the antimicrobial may preclude the choice based on these host factors (e.g. aminoglycosides with pre-existing renal disease, clindamycin with liver failure, trimethoprim-sulfamethoxazole in Dobermans, etc.)

Important micro-organism factors that influence antimicrobial choice include the predicted bacteria at the site of infection, any intrinsic resistance to antimicrobials those bacteria may possess (e.g. *Pseudomonas aeruginosa* are resistance to amoxicillin and most cephalosporins), and local resistance data. Differing antimicrobial resistance patterns have been reported regionally in veterinary medicine [9] and human medicine [10]. Creation of a summary of antimicrobial susceptibilities of bacterial isolates submitted over a time period at one institution (an antibiogram) may increase antimicrobial stewardship in the emergency room and improve empiric decision making (Figure 200.1) [11].

UC Davis William R. Pritchard Veterinary Medical Teaching Hospital Canine and Feline 2014-2015 Antibigram

	Amikacin	Amoxicillin/ Clavulanate	Ampicillin	Cefazolin	Chloramphenicol	Clindamycin	Doxycycline	Enrofloxacin	Gentamicin	Imipenem	Methicillin	Penicillin	Ticarcillin/ Clavulanate	Trimethoprim/ Sulfamethoxazole	Amoxi/Clav and Enrofloxacin
All Organisms (n=4106)															
Gram Positive (n=2298)															
Non-β hemolytic <i>Streptococcus</i> (n=107)															
<i>Corynebacterium</i> spp. (n=163)															
<i>Enterococcus</i> spp. (n=408)															
<i>Enterococcus faecalis</i> (n=256)															
<i>Enterococcus faecium</i> (n=104)															
<i>Staphylococcus</i> spp. (n=1584)															
Gram Negative (n=1797)															
All Enteric Organisms (n=1269)															
<i>E. coli</i> (n=941)															
<i>Pasteurella</i> spp. (n=159)															
<i>Proteus</i> spp. (n=140)															
<i>Pseudomonas aeruginosa</i> (n=225)															
By Source															
Blood (n=60)															
Dermatologic (skin, ears) (n=1464)															
Ocular (n=99)															
Bone and Joint (n=86)															
Abdominal (n=72)															
Respiratory (n=231)															
Soft Tissue (n=519)															
Urinary (n=1363)															

The information needs to be considered in light of selection of the most appropriate drug for the bacteria cultured, and in light of the anatomic site (i.e., drug penetration) and patient factors. This should not be used as a substitute for culture and susceptibility testing. Green>70% susceptibility, Yellow 40-70%, Red <40%, Blue= insufficient/not applicable data, and Black=intrinsic resistance

Figure 200.1 Example of an antibiogram for use in the emergency room to help guide empiric antimicrobial selection in dogs and cats. It is important to note that an antibiogram is specific to an institution and the information provided cannot be applied at other facilities.

Antimicrobial-specific factors that may affect selection are various. Whether the antimicrobial is bacteriostatic versus bactericidal should play a role in critically ill patients, but probably not in outpatient therapy, with more ill patients receiving a bactericidal choice. Other factors to consider include whether the antimicrobial can penetrate to the site of infection, the potential toxicity/adverse effects of the antimicrobial, and any potential drug–drug interactions.

Antimicrobial utilization increased 36% globally from 2000 to 2010 in human medicine [12] and an estimated 142 000 visits to the emergency department per year secondary to adverse events associated with antimicrobial therapy occurred in the US [3]. Unnecessary prescriptions of antimicrobials in the stable emergency room outpatient are common and represent an area for improved antimicrobial stewardship in both human [13] and veterinary medicine. Examples of areas for improved stewardship in the veterinary emergency room outpatients may include cats with lower urinary tract or upper respiratory tract signs not due to bacterial causes, patients with

fevers with no documented infections, and patients with asymptomatic bacteriuria without high risk of ascending infection [14].

Approach to Antimicrobial Selection for Patients with Sepsis

Obtaining a Culture

Patients that present to the emergency room and are diagnosed with sepsis should have a sample taken for bacterial culture and antimicrobial susceptibility testing. This will allow for confirmation of an infectious organism and the appropriateness of the antimicrobial choice.

The ideal source to culture would be the one suspected to harbor the infection. If that source is not easily obtainable (e.g. pneumonia, central nervous system infection, etc.) then blood cultures can be obtained. Ideally, the culture would be obtained prior to commencing antimicrobial therapy. In patients with severe sepsis or septic

shock, if the culture can be obtained without creating a >45-minute delay, then antimicrobial therapy should be delayed until the culture is obtained. However, in this subset of patients, if there would be an anticipated delay in obtaining the culture of >45 minutes, then antimicrobials should be commenced as soon as possible [15].

There are no guidelines for patients that present with clinical signs of sepsis, but not severe sepsis or septic shock on how long a delay is considered acceptable. However, given the usual lack of information at presentation for these patients, it is the author's recommendation to treat any sick patient suspected of having sepsis as having severe sepsis until proven otherwise.

Timing of Antimicrobial Administration

The Surviving Sepsis guidelines recommend the administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) [15]. A major impetus for these recommendation was the study by Kumar et al. which demonstrated that each hour delay in initiating therapy following hypotension increased mortality by 7.6% [16], as well as many other studies in ICUs demonstrating a relationship between timing of antimicrobial administration and mortality [17–19].

Recently, there has been a focus on the impact of timing on antimicrobial administration for patients presenting to the emergency department. In both human and veterinary medicine, it has been documented that having protocols in place for emergency patients can be effective in reducing the time from presentation to antimicrobial administration [20,21]. For humans presenting to the emergency department with sepsis, numerous studies have failed to show an association with the timing of antimicrobial administration and mortality [22–27] while one study documented a survival benefit in patients receiving appropriate antimicrobials within 1 hour of triage or qualification for early goal-directed therapy [28]. It should be noted that one of these prospective studies in patients with septic shock documented a survival benefit to receiving antimicrobials prior to recognition of shock, although hourly delays did not change the mortality rate [27]. Additionally, two of these studies suggest that in a subgroup of more critically ill patients, there is a mortality benefit to early antimicrobial use in the emergency room [22,24]. Aside from mortality, the longer duration to antimicrobial initiation in severe sepsis and septic shock has been associated with increased rates of acute kidney injury, organ dysfunction, and length of hospital stay [19,29,30].

Given these conflicting findings on mortality, the lack of standardization for appropriateness of the antimicrobials, and the potential benefit of decreased organ dysfunction, it is still recommended to attempt to initiate

antimicrobial therapy in the first hour if severe sepsis or septic shock is suspected for veterinary patients in the emergency room.

Empiric Antimicrobial Selection (Escalation Versus De-Escalation Therapy)

Escalation therapy involves selecting an antimicrobial with a narrow spectrum of activity that will likely cover the pathogen causing the suspected infection. After 24–72 hours when culture and susceptibility results are received, the antimicrobial choice may be validated or switched if resistance is documented. This is the standard approach to any outpatient or stable patient requiring hospitalization with sepsis. De-escalation therapy consists of the empiric administration of broad-spectrum antimicrobials aimed to cover all pathogens most frequently related to the infection, including multidrug-resistant (MDR) pathogens. When culture and susceptibility results are available, the spectrum of activity of the antimicrobials is then narrowed if possible or, rarely, it may need to be broadened. A de-escalation approach may be considered appropriate for patients with severe sepsis or septic shock.

This approach is justified, as it is associated with lower mortality in humans and may prevent development of MDR pathogens. The American Thoracic Society recommends it for patients with pneumonia at risk for MDR bacteria [31], as does the Surviving Sepsis Campaign [15]. De-escalation therapy has been shown to be feasible and beneficial in human ICUs [32,33] and has not been shown to increase the level of MDR carriage [34].

Identification of cats and dogs with an increased risk of carrying a MDR pathogen is important as it allows the clinician to alter their antimicrobial choice to one with a broader spectrum, or potentially to choose a tier two (e.g. third-generation cephalosporin) or three (e.g. carbapenem, vancomycin) antimicrobial empirically. In veterinary medicine, prior antimicrobial use within the last 30–90 days has been the factor most frequently associated with the presence of an MDR pathogen [35–41]. Additionally, duration of hospitalization [37–39,42], duration of ICU hospitalization or a surgical procedure [40], and need for mechanical ventilation [43] have been associated with increased MDR pathogen identification. While the veterinarian can justify an empiric tier three antimicrobial for a patient with severe sepsis or septic shock based on documentation of the above risk factors as long as there is a pending culture and susceptibility, there are the ethical considerations of using these antimicrobials and the potential spread of MDR pathogens [44,45]. A list of empiric antimicrobial choices for various situations in which an animal presents with severe sepsis or septic shock is presented in Table 200.1.

Table 200.1 Suggested empiric antimicrobial drug choices for intravenous use in dogs and cats with severe sepsis or septic shock pending the results of culture and susceptibility (which should be followed by reduction in spectrum when possible).

Situation	Antimicrobial drug	Intravenous dosage	Spectrum of activity
Scenario 1			
Patients with no recent antimicrobial history (30 days) and community-acquired infection	Ampicillin/sulbactam	50 mg/kg q6h	Gram-negative bacteria, streptococci, susceptible staphylococci and enterococci, most anaerobes
	OR Clindamycin	12 mg/kg q8h	
	AND	15 mg/kg q24h	
	Amikacin		
Scenario 2			
Patients in scenario 1 with acute kidney injury or chronic kidney disease*	Ampicillin/sulbactam	50 mg/kg q8h	Most gram-negative bacteria, anaerobes, streptococci, and susceptible staphylococci and enterococci. Not effective for MDR gram-negative bacteria
	OR Clindamycin	12 mg/kg q8h	
	AND	Dogs: 15 mg/kg first dose then 10 mg/kg q24h	
	Enrofloxacin		
Scenario 3			
Patients with recent antimicrobial use or hospital-acquired infection	Third-generation cephalosporin with anti- <i>Pseudomonas</i> activity		Gram-negative rods including <i>Pseudomonas</i> and streptococci. Not active against methicillin-resistant staphylococci and enterococci [†]
	Cefotaxime	30 mg/kg q8h	
	Ceftazidime	30 mg/kg q8h	
Scenario 4			
Patients that developed new-onset or worsening severe sepsis/septic shock while on a third-generation cephalosporin	Meropenem	12 mg/kg q8h	MDR aerobic gram-negative bacteria, streptococci, and anaerobes
AND/OR	AND/OR		
have risk factors for methicillin-resistant <i>Staphylococcus</i> or MDR <i>Enterococcus</i>	Vancomycin	15 mg/kg q8h	Methicillin-resistant staphylococci and MDR enterococci

Dosages are for intravenous administration in animals with normal hepatic and renal function (except scenario 2).

*Further dosage reduction may be indicated based on assessment of renal function by serum creatinine.

[†]If an anaerobic bacterium is suspected, metronidazole can be added, or can be combined with vancomycin if methicillin-resistant staphylococci or MDR enterococci are considered likely.

MDR, multidrug resistant.

Pharmacokinetic and Pharmacodynamic Considerations

In the emergency room, there are a variety of pharmacokinetic/pharmacodynamic (PK/PD) parameters that can be important for patients with sepsis. Antimicrobials that require significantly higher concentrations to kill bacteria than are required to prevent replication are considered bacteriostatic. A bactericidal antimicrobial is one where the concentration required to kill is similar to that for preventing growth. When dealing with patients in the emergency room with any form of sepsis, a bactericidal antimicrobial that can be given intravenously would be the ideal.

In a dog or cat with severe sepsis or septic shock, there is often an increase in capillary permeability. This causes

a fluid shift from the intravascular to the interstitial space. This can result in increasing the volume of distribution for many of the hydrophilic antimicrobials (beta-lactams and aminoglycosides) and thereby lowering the concentration of these antimicrobials in the interstitial fluid [46]. Lipophilic antimicrobials such as enrofloxacin are largely unaffected by this process. As most infections occur in the interstitial fluid of tissues, this lower concentration of hydrophilic antimicrobials has the potential to decrease their efficacy. As a result, the initial dose of these antimicrobials should be increased in patients with severe sepsis or septic shock to achieve the same desired interstitial concentrations as in a non-septic patient [10].

Another important PK/PD parameter to consider is the effect of hypoalbuminemia on distribution of antimicrobials. As albumin is the major circulating protein,

when it is decreased in septic patients, this can result in an increased unbound fraction of antimicrobial for drugs that have high protein binding (e.g. doxycycline). This higher unbound fraction will result in a greater concentration of antimicrobial, but this is usually offset during fluid resuscitation as the volume of distribution is increased, resulting in lower plasma concentrations [46]. As a result, a larger or more frequent dose may be needed in these patients to achieve effective antimicrobial concentrations.

Additionally, due to diminished microvascular perfusion associated with severe sepsis and septic shock, there can be decreased antimicrobial delivery to sites of infection such as the soft tissues. In multiple studies, this effect has translated to a significant decrease in antimicrobial concentration in interstitial fluid compared to plasma levels [47,48]. The clinician must also take into account whether there is hepatic dysfunction or AKI present which can lead to decreased clearance of hepatically metabolized or renally cleared antimicrobials.

With all of these important PK/PD changes that can occur in patients with severe sepsis or septic shock, a general guiding principle for antimicrobial use is to give the maximum dose that will not create a risk for toxicity in that particular patient.

Duration of Antimicrobial Administration

The ideal duration of antimicrobial use in veterinary medicine has been minimally evaluated. Two studies evaluating short-term (3 day) versus long-term (10 or 14 days) antimicrobial use in dogs with uncomplicated urinary tract infections showed no difference in clinical cures [49,50]. Recent evidence from human medicine suggests a shorter duration of therapy (7 days) may be effective in certain situations [51,52]. The Surviving Sep-

sis guidelines suggest that the duration of therapy should typically be 7–10 days if clinically indicated, although acknowledging that there is a group of patients in which longer courses may be appropriate [15]. Antimicrobial duration driven by biomarkers such as procalcitonin has shown promise in human medicine, but until this biomarker can be reliably measured and validated in veterinary species, it cannot be recommended.

At this time, no definitive recommendation can be made as to the optimal duration of antimicrobial use. However, short duration should be considered in patients where the source of the infection has been drained or removed, and which are considered immunocompetent.

Source Control

As important as antimicrobials are in the treatment of infectious disease in the emergency patient, the clinician should not undervalue the concept of source control. If the infected tissue is amenable to drainage or removal, this should occur as soon as possible after resuscitation efforts are completed [15]. Failure to achieve adequate source control as well as inappropriate antibiotic choice can be the cause for mortality [53].

Conclusion

There are multiple factors to consider when choosing antimicrobial therapy for the emergency room patient. The recommendations made here should be considered as guidelines and not absolutes as the individual patient may need modifications based on a variety of factors. For difficult-to-manage infections, consultation with an infectious disease specialist may be beneficial for optimal patient outcome.

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Disaster Medicine

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What is a Disaster?

By definition, a *disaster* is a catastrophic event involving widespread loss of human life, economic and logistical hardship, and environmental damages to the point that it overwhelms the affected community's existing resources to recover on its own [1,2]. Many use the terms *disaster* and *emergency* synonymously, but an emergency is better defined as a natural or man-made incident in which a community has the resources to recover without the need for outside help [2], ongoing emergency may quickly deplete a community's resources and become a true disaster at any moment.

Each disaster is unique. It may occur at any time; result from a natural phenomenon (e.g. earthquake, hurricane, tornado, flood, etc.) or man-made incident (e.g. terrorist attack, structural fire/collapse, chemical spill, etc.); involve only a few to a large number of casualties; last only a few days or endure over several weeks; and involve a few to many different species of animals. It is therefore impossible to predict exactly what one may encounter prior to arriving at the disaster site.

During Hurricane Katrina, it was reported that along with the traditional household pet (e.g. dogs and cats), other species of large animals (e.g. horses and cattle) as well as wildlife and exotics (e.g. foxes, raccoons, deer, etc.) were also in need of rescue and medical aid [3]. Considering how specialized veterinary medicine has become, it is prudent for veterinary personnel to briefly review the main points of veterinary medicine applicable to species they may encounter during a disaster, but that they do not routinely care for. For example, a small animal practitioner in a response team should consider reviewing basic equine medicine principles in order to support the medical needs of search-and-rescue horses.

The Human–Animal Bond During a Disaster

When a disaster strikes, companion animals experience the same risk for injuries and mortality as people. Today, society expects that injured and stranded animals will be given appropriate and timely veterinary care during disaster recovery efforts. From a small animal standpoint, experience from previous disaster events has shown that the loss and/or suffering of companion animals may greatly affect the community's overall psychological well-being [4–6].

It is estimated that over 50% of US households have pets, and six out of 10 pet owners consider their pets to be family members [7]. Interestingly, some data has shown pet ownership to be a major risk factor for evacuation failure during natural disasters [5,6]. Although several risk factors for pet-related evacuation failures have been identified [5,6], one reason was due to the fact that in the past, the priority for evacuation was saving human life; as such, people were forced to leave their pets behind [3–5]. Particularly during Hurricane Katrina, complications from this arose when people would choose not to evacuate and leave their pets behind or, if evacuated, they would re-enter an unstable disaster site to retrieve their animals [3–5]. People who failed to evacuate not only placed themselves at risk for serious injury or death, but they also put first responders in danger as they entered the unsafe environment to rescue these people.

Although it is hard to determine an exact number, it was estimated that 40 000–50 000 animals were lost during Hurricane Katrina [4]. The animal-related issues that occurred during Hurricane Katrina left thousands of animals stranded to die or become severely ill. Coupled with the poor sanitary conditions in the wake of massive flooding, multiple infectious diseases as well as a public health risk developed in the area. With vigilant media coverage bringing the events of Katrina to national

attention, a large public outcry and demand for action were generated [4,6].

After seeing the impact of the human–animal bond during Hurricane Katrina, the American Veterinary Medical Association (AVMA) published *Placing the Human–Animal Bond in Context in the Face of Disasters* which stated: “When disaster strikes, saving animals means saving people – human and animal health and welfare are inextricably intertwined” [6]. In the wake of Hurricane Katrina and in order to ensure that animal-related issues did not repeat themselves in the future, Congress enacted the Pet Evacuation and Transportation Standards (PETS) Act in 2006 [4,8]. The PETS Act was enacted so that individuals no longer have to leave their pets behind during an evacuation or rescue operation. It requires state and local government entities to incorporate the needs of individuals with household pets and service animals into their disaster preparedness and recovery plans. In addition, the PETS Act granted the Federal Emergency Management Agency (FEMA) the authority to assist these agencies with developing and approving the standards of their plans.

Post Hurricane Katrina, two additional alliances were also created to help mitigate the animal-related issues encountered during Katrina for future incidents: the National Animal Rescue and Sheltering Coalition (NARSC) (<http://thenarsc.org/>) and the National Alliance for State Animal and Agricultural Emergency Programs (NASAAEP) (www.nasaaep.org). The NARSC is a coalition of national organizations in the areas of animal welfare, care, rescue, and control. Its mission is to “identify, prioritize and find collaborative solutions to major human-animal emergency issues.” The NASAAEP’s primary goal is to foster a network between all emergency management stakeholders to facilitate effective communications, information sharing, and planning at all levels of government and response. In addition, the NASAAEP has developed “Best Practices” guidelines to address key animal issues that may be encountered during an emergency or disaster (<http://nasaaep.org/best-practices/>) to include: animal decontamination; animal evacuation and transportation; animal search and technical rescue; community preparedness and outreach; disaster veterinary care; emergency animal sheltering; planning and resource management; zoo disaster preparedness.

Organizational Structure

Disaster medicine is multidisciplinary. It consists of multiple levels of organizational involvement consisting of local, state, and federal governments, tribal and territorial governments, and private sector entities that have a

functional need and vested interest in the community (e.g. local businesses, voluntary and non-profit organizations, academic institutions, individuals, and families) [9]. This multifaceted disaster management team is what the FEMA defines as the “whole community” [10], reinforcing that effective disaster management and preparedness is a shared responsibility of everyone involved, not just governmental entities.

Each of the three levels of government (e.g. local, state, federal) has an increasing span of responsibility. The intention is that each level maintains responsibility for managing emergencies in its jurisdiction until no longer feasible, at which point it may request assistance from the next higher level of government [9]. Most local municipalities have an emergency management representative or a designated Office of Emergency Management (OEM). County OEMs are primarily responsible for emergency preparedness and response planning as well as continued risk assessment for the communities within their locale. State OEMs provide assistance to all local municipalities within their state. Subsequent to a disaster or emergency, the governor may allocate resources (to include National Guard resources) to communities that lack the resources to recover from a disaster on their own. If a state’s resources become depleted or overwhelmed, the governor may request aid from the federal government.

At the federal level, FEMA acting under the Department of Homeland Security has the most direct, primary role for overseeing and co-ordinating the nation’s disaster management program [9]. Besides evaluating its own capability in responding to a large-scale, nationwide disaster, the federal government also assists and provides guidance to each state in developing and implementing state disaster management plans as well as allocating resources and assistance to support recovery efforts for communities in which the state’s resources are depleted or insufficient. The National Incident Management System (NIMS) is an essential foundation of FEMA’s National Preparedness System [9,11]. The NIMS provides all levels of government, non-governmental, and private sector organizations with a standardized template and systematic approach for collaboratively managing disaster events across the full spectrum of potential threats and hazards regardless of size or complexity [11].

Within the NIMS is the Incident Command System (ICS) which is a fundamental element for organizing and managing on-scene emergency or disaster response operations [9,12,13]. The ICS provides a unified command and control framework and establishes a common organizational chain of command for co-ordinating the activities of all agencies (federal, state, local, tribal, private sector, and non-governmental) involved in

the response. Implementation of an ICS lessens the chances for miscommunication and ensures appropriate resources and personnel are directed and utilized where they are most needed; therefore, an effective ICS ensures that the disaster is resolved as quickly and efficiently as possible. The ICS is applicable to a wide array of disaster events to include different disciplines and complexities, small- and large-scale operations, near- and long-term operations, as well as natural, man-made, and terrorist events. Any personnel that may become part of a disaster response team or may have involvement with disaster or emergency management should receive training in NIMS and ICS (www.fema.gov/incident-command-system-resources) [14,15].

Veterinary Disaster Response Programs

The federal National Veterinary Response Team (NVRT) and the AVMA Veterinary Medical Assistance Team (VMAT) are two complementary animal response programs [16,17]. They facilitate veterinary emergency preparedness plans as well as animal rescue and recovery operations during an actual disaster event. As part of the Health and Human Services (HHS) National Disaster Medicine System (NDMS), the NVRT is a federal program that operates under the ICS [17], as the primary federal resource for the treatment of animals affected during a disaster. Members of the NVRTs are private citizens (veterinarians, public health safety officers, veterinary technicians, epidemiologists, logisticians, communications specialists, and other support personnel) who, once activated to respond to a disaster, are then compensated as federal employees.

From 1993 to 2007, the AVMA VMATs worked in partnership with the HHS and, when activated, the VMAT deployed as a federal entity [16]. Following Hurricane Katrina, restructuring of the government led to the AVMA relaunching the VMAT program as a private non-governmental organization. VMAT members are now volunteers and only receive reimbursement for travel, housing, and *per diem* expenses.

The main functions of the AVMA VMATS are to provide:

- early assessment teams to assess veterinary conditions, infrastructure, and resources
- basic veterinary treatment teams to augment local veterinary resources in providing primary field care
- training on emergency-related topics (e.g. animal emergency preparedness and response) to animal health authorities, veterinary medical associations, emergency first responders, and other relevant emergency management organizations.

Phases of Disaster Management

Disaster and emergency management involves more than just those actions taken to respond and rebuild a community after a disaster strikes. It involves a lifecycle of events that the FEMA has categorized into four strategic phases: *mitigation* of hazards, *preparedness* for and *response* to an emergency or disaster, and then *recovery* from the effects of the disaster [9,13,18].

Mitigation

Mitigation strategies are “preventive” in nature, are typically implemented prior to a disaster event and are intended to prevent the occurrence of and/or lessen the damaging effects of an emergency or disaster [9,13,18]. Examples include buying flood and fire insurance or building your home away from high-risk floodplains or high seismic activity zones. For coastal communities located in a “hurricane belt,” state and local governments establish building codes and zoning requirements and construct barriers such as levees to help mitigate the severity and degree of structural damage. These actions not only reduce the need for reconstruction after a hurricane but also help diminish the loss of life and property.

In regard to companion animals, small animal practitioners should take an active role in educating their clients on mitigating strategies that may help safeguard their pets. For example, ensuring their animals remain up-to-date on preventive healthcare and that they have a method for positively identifying their pets (e.g. microchip, photos, etc.) in case they are separated from them during a disaster or relief operation. Veterinary clinics, humane societies, and other animal shelters should develop emergency procedures and evacuation plans for the animals in their care. These facilities should provide copies of their plans to the state emergency management agency. In addition to developing plans, it is advocated that veterinary clinics and animal facilities procure suitable containers to transport their animals during evacuations [18].

Preparedness

Preparedness planning enhances the whole community's ability to respond to a disaster [9,13,18]. FEMA developed a National Preparedness Goal to outline what is meant for the nation, and particularly a community, to be prepared for a disaster. The goal states, “A secure and resilient nation with the capabilities required across the whole community to prevent, protect against, mitigate, respond to, and recover from the threats and hazards that pose the greatest risk” [19]. General examples of preparedness planning include identifying potential

disaster risk areas (e.g. floodplains), locating and mapping out viable evacuation routes, installing public alert and warning systems (e.g. tornado sirens), and identifying back-up community services and utility needs (e.g. power generators, fresh water supply, sewage disposal methods, etc.) [9,18,20].

Veterinarians should identify their local OEMS and become aware of the resources that may be available to them during a disaster. Veterinary personnel may decide to join a regional disaster response team. They may utilize their expertise to help develop and implement predisaster preparedness plans, establish relationships with community relief organizations (e.g. American Red Cross), provide animal handling and first aid training to emergency responders, and participate in conducting disaster response drills. Preplanning may include mapping out viable animal shelters and veterinary clinics for injured and displaced animals, identifying resources for transporting animals out of the disaster zone, establishing alternative sources of power for heating and lighting for veterinary clinics and shelters (e.g. electrical power generators), identifying viable evacuation routes for animals housed in animal and veterinary facilities located within a disaster zone, identifying communication equipment, and establishing caches of veterinary supplies and resources in key areas for immediate availability. Plans for humane euthanasia of critically ill or injured animals as well as disposal for animals that are euthanized or may have died during the disaster should also be taken into account. In planning for potential prolonged recovery operations, preventive health programs should be developed for sheltered animals to prevent the development and spread of disease.

Small animal practitioners may work with, educate, and train various groups and organizations within their community. They may work with local animal shelters, humane societies, and animal control agencies to guide them on appropriate animal care principles, first aid, and decontamination procedures. Together, they should develop a plan for fostering/adopting animals that are not reclaimed by their owners during or after the disaster incident. Search and rescue units may need guidance on animal care, handling, and restraint, techniques for sheltering in place with injured or critically ill animals; and techniques for extraction of injured and or trapped animals. It is also important that rescue teams have a method for properly identifying animals and then reuniting the animals with their owners.

The general public should be made aware of available public resources, actions for emergency sheltering of animals, available community warning systems, and contact information for key agencies or organizations in case a disaster does arise. As part of their general health and wellness discussion, the practitioner and/or staff

should consider educating animal owners about making arrangements for their pets in case of evacuation (e.g. identify designated safe havens and caregivers), keeping emergency supplies (e.g. food, water, flashlights, batteries, etc.) on hand in case they need to shelter in place, and maintaining emergency first aid and evacuation kits. Pet owners may be directed to organizations such as the Humane Society of the United States, the AVMA, the American Red Cross, and other organizations that provide online resources to help pet owners prepare for a disaster.

Veterinary clinics should also prepare for disaster scenarios, particularly considering they may need to shelter animals in place for days to weeks. The AVMA has developed a brochure which defines the essential elements that a veterinary practice's disaster plan should include [20].

- Emergency relocation of animals
- Medical record back-up
- Continuity of operations
- Security
- General emergency planning
- Fire prevention
- Insurance and legal issues

The brochure is available for download at: <https://ebusiness.avma.org/ProductCatalog/product.aspx?ID=139>.

Preparedness planning is only effective if everyone involved is aware of their roles and responsibilities, is properly trained in disaster management principles, and the disaster plan is actually practiced and rehearsed on a routine basis. After each rehearsal, a formal debriefing should be conducted to identify deficiencies as well as aspects of the plan that worked well. All personnel that may be involved in a disaster should also receive some formal training in disaster and emergency management. FEMA's Emergency Management Institute offers several free online courses and its Center for Domestic Preparedness also offers high-quality comprehensive preparedness training programs for emergency responders [21]. Other organizations such as the Humane Society, AVMA, and various academic institutions offer varying degrees of emergency management training [22–24].

Response

Response actions take place during and after the incident and include actions taken to prevent further loss of life and property during a disaster [9,18]. During a disaster, veterinary personnel play a key role as animal advocates by ensuring the welfare and needs of animals are covered during the response. Although providing medical aid to injured and sick animals is part of a veterinary disaster

response, it often makes up only a small portion of the disaster veterinarian's duties. Other common responsibilities a veterinarian may have during a response include working with the humane society and local animal shelter to retrieve and shelter animals that have been abandoned, displaced or escaped from their owners during evacuation; assisting with the humane euthanasia and proper disposal of dead animals; arranging for the provision of food, water, and shelter for displaced animals; triaging and establishing a casualty collection point; counseling pet owners who have been separated from their animals; and serving as a liaison to maintain communications between key relief agencies, governmental organizations, and the incident command structure.

An important duty of a disaster veterinarian is providing support and aid for the operational working canines or OpK9s (search and rescue and law enforcement canines) that are involved in the recovery efforts. Many disaster responses employ OpK9s to assist with human recovery. As an advocate for OpK9s, it is the on-site veterinarian's responsibility to ensure not only that these dogs are given timely medical care when they suffer an injury or illness, but also that preventive measures are implemented to prevent injury and illness from occurring (e.g. dehydration, exhaustion, etc.). Lessons learned from past disaster events (e.g. Oklahoma City, World Trade Center on 9/11, Haiti, Oso, Washington, etc.) demonstrated that the overall number of OpK9 injuries was actually quite small [25–28]. Most were footpad injuries and cuts/abrasions on the limbs, mainly subsequent to OpK9s having to traverse over sharp surfaces and structural damage. Other common problems included fatigue, gastrointestinal problems, dehydration, and ocular irritations. Awareness of past lessons learned will help increase the chance of future successes.

Recovery

Recovery activities typically start after the event, but may occur concurrently with response efforts after immediate

basic life-sustaining needs of the community have been addressed. The focus of recovery efforts is directed towards actions needed to return a community and its infrastructure to near-normal conditions. Depending upon the complexity and severity of damage inflicted by the disaster, recovery efforts may last a few weeks to a few years. A key task during the recovery period is evaluating the incident to identify lessons learned. Communities may then use this information to develop measures to mitigate the effects of future incidents. A debriefing with all agencies and organizations involved in the event should take place to identify what worked and what didn't. An after action report is generated and distributed to all organizations and personnel involved in order to help them prepare for the next disaster.

Considerations the veterinarian may need to take into account are dealing with animal owners who lost their pets and filing insurance claims for injuries animals may have suffered during the disaster. Also, health issues in pets may continue to manifest for weeks to months after the incident, particularly if an animal was exposed to any type of hazardous material and/or smoke inhalation [29,30]. Psychological issues may develop in the pet owner while behavioral issues develop in the pet, both of which the veterinarian may find themselves dealing with in the healing process [4,9].

Conclusion

Animals suffer the same risks for injury and death during a disaster as people do. Experience from previous disaster events has demonstrated that the well-being of household pets and service animals during the disaster response and recovery efforts may have a large impact on the psychological healing of a community. As such, it is vital that veterinarians become involved in their community's disaster preparedness activities and become aware of the main concepts and structures of disaster medicine.

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Working Dogs in the Emergency Room*Cynthia M. Otto, DVM, PhD, DACVECC, DACVSMR, CCRT**Penn Vet Working Dog Center, University of Pennsylvania, Philadelphia, PA, USA***Occupations**

Working dogs represent a unique group of patients that require veterinary care. The dogs are generally highly trained and typically work very closely with an individual handler. Professional working dogs can be broken down into three major categories: police/patrol/military, detection, and service. Many of the risks and special considerations for working dogs will also apply to sport and performance dogs.

Police/Patrol/Military

These dogs generally are partnered with a police or military handler. The dog is trained to protect the handler above all else. Most of these dogs are not “attack dogs” but rather they are trained to bite and hold a suspect. Well-trained police dogs should be able to guard a suspect without contact. After release of a bite, the suspect should be able to even pet the dog. If the dog perceives a threat to the handler, however, he will initiate action (bite) without a command. In addition to criminal apprehension, these dogs are typically also trained to identify an odor, whether it is explosives, narcotics or human remains. As a rule, the handler should be with the police dog whenever possible for examination. Most handlers will muzzle the dog for an examination. Using a calm approach in an examination, paying close attention to the dog’s body language and avoiding threatening positions (e.g. hovering over the head and direct eye contact) will often make an exam more manageable; however, some police dogs will not be able to be examined without sedation. In some situations, the dog will be hospitalized and away from the handler. In this case, it is important to know the common commands used for the dog (and in what language!).

Odor Detection

There are numerous canine detection careers. Search and rescue (SAR) dogs are commonly owned by private

citizens who volunteer their time and efforts in searches. Although some dogs may be owned by an organization, they still work and are certified with a designated handler. These dogs may work in urban/disaster or wilderness (wide area) environments and may search for live humans or human remains. Other examples of detection dog careers include explosive detection, drug detection, bed bug detection, and several fields of conservation work, to name a few. All of these dogs typically work with a specific handler/owner. These dogs range from high energy to relatively calm. Depending on their job, they may or may not be friendly with people or other dogs. Search and rescue dogs must not display any aggression toward humans or other dogs. Despite their extensive training, these dogs, especially the high-energy dogs, are often not comfortable during veterinary visits. Due to the relationship with the handler, these handlers should remain with their dogs during examinations whenever possible.

Assistance/Service

According to the federal government through the Americans with Disabilities Act (ADA) [1], a service dog is defined as one that has been trained to perform tasks directly related to the disability of that dog’s handler. Although guide and hearing dogs have a long history, the field of service dogs has expanded exponentially in recent years. Now dogs are trained to provide services for a variety of different disabilities. Autism dogs are particularly useful with children, as they help to keep the child from bolting and help with social adaptation. Dogs for veterans and other individuals with posttraumatic stress disorder (PTSD) provide the security to allow the individuals to interact within society. These dogs, while trained for the individual needs of the handler, will often provide a physical barrier (“block”) between the handler and other individuals. They can provide a “look out” so the handler is not taken by surprise and they often wake up individuals experiencing night terrors. Many service

dogs are also trained to provide stability or retrieve objects for their handlers with physical disabilities.

Medical detection dogs are a fairly recent addition to the service dog field. Dogs are trained to alert diabetic individuals to drops or sudden increases in blood sugar. Epilepsy alert dogs anticipate the onset of a seizure and can help facilitate the safety of their handler. Emotional support and therapy dogs do not fall under the definition of a service dog (although some state or local laws may include these dogs). According to the ADA guidelines, if it is not obvious that the dog is a service animal, only two specific questions may be asked: (1) is the dog a service animal required because of a disability? and (2) what work or task has the dog been trained to perform? People are not allowed to request any documentation for the dog, require that the dog demonstrate its task, or inquire about the nature of the person's disability [1].

Service dogs should be examined with the handler present whenever possible. Clear explanations of all the procedures should accommodate the person's disability. For example, a blind person will need a clear narration of

each step of an exam or procedure, whereas a deaf person will need written or signed information.

Occupational Hazards

Common Conditions

Working dogs have occupational risks based on their exposure, their trained tasks, and their breed (Table 202.1). Emergency care of traumatic injuries is expected to be common in working dogs. The risk of specific trauma will depend on the job and the environment.

Blast injury is likely highest in military working dogs (MWD), although explosive detection dogs and urban search and rescue dogs could be at risk. Gunshot wounds can be a hazard for most working dogs. For MWD in a battlefield setting, catastrophic injury is common, with frequent thoracic and extremity injuries [2]. In police dogs, gunshot wounds are a recognized risk, but there is no information about gunshot injuries specific to police dogs [3]. Wilderness

Table 202.1 Occupational hazards associated with various canine working disciplines.

Occupational hazards	Police/patrol/ military	Detection urban/disaster	Detection wilderness	Service/ assistance
Cause of injury/illness				
Trauma – bite wounds (i.e. dogs, other animals)	+	+	+	+
Trauma – blast	++	+	+/-	-
Trauma – blunt (i.e. falls, vehicles)	++	++	+	+
Trauma – gunshot	++	+	+	-
Trauma – impalement	+	+	+	-
Cold injury	+/-	+/-	+/-	-
Heat injury (i.e. exercise, confinement)	++	++	++	-
Infectious	+	+	++	+/-
Neoplasia	++	++	++	++
Toxin exposure	+	+	+	+
Body system				
Respiratory	-	-	-	-
Cardiac	-	-	-	-
Neurological (spinal cord, central)	+	+/-	+/-	+/-
Urogenital	++	+	+/-	+/-
Musculoskeletal (e.g. pad cuts, lacerations, lameness)	+++	+++	+++	+
Gastrointestinal (e.g. vomiting, diarrhea, GDV)	+++	++	++	++
Dermatological (e.g. dermatitis, otitis, atopy)	++	++	++	++
Dental	++	+/-	+/-	+/-
Ophthalmological	+	+	+	+

+++ , very high risk; ++ , high risk; + , moderate risk; +/- , low risk; - , negligible risk compared to pet dogs; GDV, gastric dilation-volvulus.

detection dogs may be at higher risk of being shot by hunters, whereas urban detection dogs may be at risk of being shot by criminals or police. In one study, the type of firearm did not influence outcome in gunshot wounds in pet animals [4]. Impalement injury can occur in any of the police or detection environments. Although no published reports describe impalement injuries in working dogs, anecdotal reports of injuries in both urban and rural settings exist.

Service dogs are unlikely to have a high risk of ballistic trauma or impalement, but guide dogs may be at risk of dog bites due to the inability of the handler to anticipate an attack. Police and other detection dogs are at risk of bite wounds when working off leash in environments where there are stray or wild animals. In addition, in training situations when the dogs are highly stimulated, fights could break out. Blunt trauma is a risk for working dogs, but it is unknown if the risk is higher than for pet dogs.

In general, working dogs will be under better control than pet dogs, but when they are on task (in pursuit or following an odor), they may not be environmentally aware, thus increasing the risk of being hit by a vehicle or falling from a height. Police dogs traveling in a vehicle involved in a high-speed chase are also at risk of injury if the vehicle crashes. Service dogs are expected to be at lower risk of vehicular trauma but may be at risk of being hit by a falling object if the handler is unable to anticipate or protect the dog from the incident.

One of the greatest concerns for police and detection dogs that work in adverse environments is heat stroke; in fact, it is one of the most common preventable causes of early retirement in MWD [4] (see Chapter 147). Several news reports cite heat stroke deaths in police dogs in patrol cars where cooling systems failed. One case report detailed the prehospital resuscitation and successful outcome in such a case [5]. Heat stroke in working dogs cannot be defined by rectal temperature alone since many dogs will work with core body temperatures in excess of 106 °F (personal observation). Even if dogs do not succumb to heat injury, work in the heat can lead to dehydration and other complications as observed with search and rescue dogs [6–8]. Service dogs are expected to be at low risk of heat injury. Cold injury is uncommon in adult working dogs unless the dog is immobilized from injury and exposed to cold environments (e.g. open helicopter transport of MWD) (see Chapter 148). Swimming in cold water or cold exposure, however, can be associated with an acutely limp tail [9]. This condition, often called limber tail or swimmer's tail, can be acutely painful, requiring pain control.

Inhaled, ingested or topical toxin exposure is a risk for all working dogs (see Chapter 127). Drug and explosives detection dogs are at risk of exposure through inhaling or ingesting their training aids or the source they are seeking [10–14]. Current street narcotics may contain the potent opioids fentanyl or carfentanyl. If a dog inhales sufficient

quantities of these drugs, they will show signs of intoxication which should be treated with naloxone. The dog will likely have the opioid on its fur and serve as a fomite. Handlers and individuals working with the exposed canine must be aware of the risk of opioid exposure to themselves from contact with the dog. Service dogs travel everywhere with their handlers and could ingest unrecognized toxins or medications that have fallen to the ground.

Infectious disease risk depends on the environment in which the dog is working. For wilderness (wide area) detection dogs, diseases spread by ticks or wild animals are a concern. For large-scale missions, congregating dogs can spread infectious disease such as kennel cough complex. If dogs travel, they can be exposed to endemic disease (e.g. heartworm or fungal disease in response to Hurricane Katrina).

The breeds that are commonly used as working and service dogs have a high incidence of cancer and may present acutely with the consequences, such as hemoabdomen or pericardial effusion (see Chapters 54 and 84). There is no evidence that environmental exposure during the 9/11 response increased the risk of cancer in search dogs [15]. Cancer is the cause of death in approximately 30% of service dogs and 40% of search and rescue dogs [15].

Common Systems Affected

There are no reports of cardiopulmonary risks associated with working occupations. Even dogs responding to 9/11 did not develop respiratory complications from their exposure [15].

In a study of police dogs in an urban emergency room, the most common reason for presentation was gastrointestinal disorders. Vomiting and diarrhea were more common than gastric dilation-volvulus (GDV), and more frequent in police dogs than in pet GSDs (Table 202.2) [16] (see Chapters 13 and 82). The second most frequent reason for emergency care was musculoskeletal injuries; again, lameness was more common in police dogs than in pet GSDs. Arthritis and orthopedic conditions are common in service dogs and may lead to their retirement. Non-combat injuries and illness in MWD were similar to those reported in police dogs, but more dermatological disease and soft tissue trauma, which included footpad injuries, were seen [17]. In SAR dogs, cuts and scrapes are frequent occurrences, and although most are minor, some may require emergency management (see Chapter 166) [6–8]. Many of the breeds used for working/service careers are at risk for allergies and skin disease. An acute ear infection in a working dog can impair their ability to work and will often require urgent care.

Spinal cord disease is the most common cause of retirement in MWD older than 5 years of age (see Chapters 24–26) [4]. Although some of these conditions can be chronic in nature (i.e. lumbosacral disease, degenerative myelopathy), acute disk rupture or fibrocartilaginous

Table 202.2 Primary problems of German Shepherd emergency hospital visits comparing police GSDs and pet (control) GSDs 7/2008–7/2010. Reproduced with permission of John Wiley & Sons, Ltd.

	Police GSD ES visits*		Pet (control) GSD ES visits*		P-values	Total ES visits†	
Cardiovascular	0	0.0%	12	8.0%	0.001	12	4.0%
Dental	2	1.0%	0	0.0%	0.478	2	0.0%
Dermatology	14	10.0%	8	5.0%	0.266	22	8.0%
Gastrointestinal	39	28.3%	31	22.5%	0.333	70	25.4%
Vomiting/diarrhea	33	23.9%	17	12.3%	0.019	50	18.1%
GDV/bloat	2	1.4%	7	5.1%	0.175	9	3.3%
Other	4	2.9%	7	5.1%	0.538	11	4.0%
Neoplastic condition	5	3.6%	17	12.3%	0.014	22	8.0%
Nervous system	1	0.7%	12	8.7%	0.004	13	4.7%
Ophthalmology	2	1.4%	4	2.9%	0.680	6	2.2%
Orthopedic	35	25.4%	17	12.3%	0.009	52	18.8%
Appendicular	27	19.6%	5	3.6%	<0.001	32	11.6%
Axial	8	5.8%	12	8.7%	0.486	20	7.2%
Other	5	3.6%	4	2.9%	–	9	3.3%
Postoperative complications	2	1.4%	3	2.2%	–	5	1.8%
Respiratory	5	3.6%	6	4.3%	–	11	4.0%
Toxin exposure/ingestion	3	2.2%	6	4.3%	0.498	9	3.3%
Trauma/wound	21	15.2%	12	8.7%	0.138	33	12.0%
Urogenital	4	2.9%	6	4.3%	0.747	10	3.6%

*Total visits 138.

†Total visits 276.

GDV, gastric dilation-volvulus; GSD, German Shepherd; ES, emergency service.

infarcts will typically present as an acute emergency. Pet GSDs were seen for back conditions at an equal frequency as police GSDs [16] so these conditions may not be occupational hazards as much as breed risk.

Reproductive emergencies are uncommon in working dogs. Most police and MWD are sexually intact males, whereas most service dogs and SAR dogs have been spayed or castrated. Urinary tract problems were reported at an incidence rate of 1.3/1000 dog search hours during the 9/11 response [6]. Some of the urinary tract signs may have been complicated by dehydration.

Tooth fractures, especially those involving the canine teeth, in police/patrol warrant emergency care to attempt to preserve the integrity of the tooth. One study documented that 88% of teeth remained vital if treated within 48 hours of pulp exposure although this study did not specify if working dogs had a different outcome from pet dogs [18]. Other working dogs that are rewarded by tugging or have a tendency to chew on tennis balls or bones can suffer tooth damage that could predispose them to tooth fractures.

Eye injuries were not commonly reported in the SAR dogs that responded to the 9/11 terrorist attacks [6] or

the earthquake in Haiti [7] (see Chapter 12). This is in contrast to reports of ocular infection and an eye injury in SAR dogs and an explosive detection dog respectively, during the response to the Oklahoma City bombing [19]. Routine saline flushing of the eyes is a common practice since the Oklahoma City experience and may be responsible for a decrease in ocular infections/irritations. Any eye injury in a working dog must be treated aggressively due to the potential career-ending impact of vision loss. Genetic eye disease is common in working dog breeds and can lead to progressive blindness.

Client Education

Educating handlers on the impact that any procedures or medications may have on the dogs' working performance is an important part of client communication. Another important aspect of handler education is providing them with the skills for basic first aid assessment of their dog. Emergency clinicians are uniquely positioned to help educate working dog handlers.

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Approach to Unowned and Shelter/Rescue Animals in the Emergency Room

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Introduction

Animals may be presented to the ER by non-owners/agents under various circumstances. Each ER should develop its own policy for each case, based upon local laws and hospital administration. Policies may vary depending upon location as well as prior agreements, local resources, and goals of the hospital management. It is exceedingly useful to have developed a relationship with local shelters and animal law enforcement. Find out if they have veterinarians on staff as this will help to guide your treatment plan. If they have veterinarians, they can possibly provide continued care after emergency stabilization and may be able to provide future surgical intervention, follow-up, and medications. If they don't have a veterinarian on staff, they probably use a veterinary clinic(s) that can help to care for the animals; these hospitals can be a resource as well.

Boarding kennels or pet sitters may present animals without knowledge of the owners' wishes or a method to contact the true owner. In these cases, it can be challenging to know the appropriate step; for minor illness or injuries, treatment is typically provided, and when the owner is reached, arrangements can be made for follow-up or payment. Some boarding kennels and pet sitters will arrange for payment as well. Professional kennels are more likely to have a contact for the owner, but in some cases the contact also does not know the owner's wishes, particularly if a catastrophic illness (e.g. GDV, IVDD, hemoabdomen) has developed. There is generally no easy answer in these cases; if the family veterinarian is reachable, then they often have knowledge of the individual's general approach to pet care. In other cases, while ongoing efforts to reach the owners should be made, it may be that the emergency clinician, in consultation with hospital administration and any potential agents, may need to make decisions, if life-saving treatment is required.

Animal control officers (ACO) may present animals that they have recently found or, less likely, that have been in custody either during a hold period or while waiting for a criminal trial. Most towns have a small amount of resources in their budget to support the care of unowned injured animals or those animals in their custody. However, it is essential that a clear understanding of the goals and expense of treatment is reached before proceeding with more severe injuries. Recently, in Connecticut, a Great Dane on "death row" for killing another dog, which had been in custody for almost a year, developed and was surgically treated for a colonic torsion while awaiting a final verdict for euthanasia at the expense of the town [1]. ACOs represent useful resources for the emergency clinician and good relationships should be fostered.

Animals may be presented for urgent care after potential cruelty cases; in these cases, in addition to providing care for the patient, it is essential to determine what type of forensic information will be required if the case is ultimately prosecuted. Cruelty cases brought in by ACOs generally require full work-ups for legality purposes. Remember to gather evidence – the presenting officer may have done this, but make sure evidence is obtained prior to changing the appearance of animal (such as shaving matted fur, bathing, etc.). Photographs and video may be needed to document the way an animal looks – remember that the animal should be considered as evidence. Also, you may need to collect evidence such as the fur and anything on the animals to save for use later. Every detail that you find on physical examination should be recorded in the medical record. Remember that the medical record could end up in court, so everything said should be straightforward without personal opinions.

Things that are especially important to keep in mind for your exam include the animal's demeanor, body condition score, and pain score. Make sure you obtain a weight and a TPR. Note any external parasites,

scars, wounds or injuries which should be described in detail. Give as much information as you can in the objective section of your record. Write reports in plain language without medical terminology so that records in court are understandable by the judge and jury. Starting with the subjective section, keep this as short as possible since this may be contested in court. Make sure the objective section is thorough and everything is well documented. The assessment section should include every problem and also every possible differential without any personal bias to the situation. In potential starvation cases, it is important to note the animal's reaction to food. An animal that is sick and not starved may not want to eat. An animal that is starved typically is ravenous. This should be noted in your exam notes.

Tests for cruelty cases will be tailored towards what the cruelty charge is about. Animals suspected to have been abused or used in dog fighting likely will need radiographs to document new or old fractures. Animals suspected to be starved will likely need laboratory testing, fecals, and imaging to rule out other underlying causes of malnutrition. Animals that are brought in for cruelty should be treated like any other animal and their response to treatment should be well documented. These animals will likely be kept in custody, potentially for long periods of time. In cases of starvation, it is very important to remember about refeeding syndrome. Refeed them very slowly and monitor their electrolytes. It is difficult for most people to work with these animals and not feed them, but it could be detrimental, so sticking to a strict feeding regimen should be encouraged. Resources are available to veterinarians to help address these cases [2]. In some states (e.g. Massachusetts), veterinarians are considered mandatory reporters of possible abuse cases, and the policy of hospitals should support this.

Animals may also be presented by Good Samaritans, who have found a stray or injured animal. Uninjured animals may be directed to a local shelter, but injured animals should be cared for, with consultation with local ACOs and in support of hospital policies. A microchip scanner should be available and used in any unowned animals to attempt to locate owners. Animals with unclear vaccine history should be vaccinated against rabies and species-specific infectious disease on admit.

Breed-specific or general rescue groups may present animals for care. These cases are usually more straightforward as most groups have an individual in charge of payment and deciding about treatment. These groups are also a vital resource for unowned animals matching specific descriptions (e.g. boxer rescue) or for helping owners of pets belonging to specific breeds. In some

cases, rescue groups may require counseling as to the predicted outcome and benefit for specific treatments, and each dollar spent is then a dollar that is subsequently unavailable for another patient. Common presenting conditions in rescue include infectious diseases, neglect, and trauma. It is wise to recall that nationwide efforts to rehome dogs and to a lesser extent cats have results in the potential appearance of dogs with infectious but non-endemic or common local disease (e.g. histoplasmosis in a puppy from Louisiana that was rehomed in Maine).

Common infectious diseases in felines include panleukopenia, upper respiratory disease, and retroviral infections. Common infectious diseases in canines include parvovirus, kennel cough or canine infectious respiratory disease, and distemper. Ringworm is another common infectious disease found in shelter animals and should be on your differential list for skin lesions. It is important to remember that animals with suspected infectious diseases should be treated in isolation to prevent further disease spread to other patients and also to protect them from other diseases to which they may be more susceptible. Proper disinfection protocols should be performed to prevent disease spread in the ER. Specific infectious disease management is covered elsewhere in this text.

Spay/neuter complications may present in shelter animals or in animals that were spayed/neutered at high-volume clinics. It is best to not always assume the worst case scenario, as spay-neuter clinics have exceedingly low rates of significant complications. Many times, the complications will be simple, like seromas. Keep in mind that not every animal that comes in with a swelling associated with their surgery site needs an ultrasound. Often, palpating the linea will allow better assessment of the swelling. Usually, once a linea dehiscence occurs, the whole suture line does, so it should be easy to tell if there is a defect. If you are unsure, it is easy enough to aspirate the swelling to determine if it is a seroma. Most spay/neuter complications can be dealt with by the initial veterinarian unless there is obvious dehiscence. Antibiotics and an e-collar are a quick and easy fix until follow-up can occur. It is useful, as with all veterinary hospitals that refer to your emergency service, to have contact numbers of owners/administrators in case of a dramatic out-of-hours complication.

Remember to think of shelters as your clients. Involve them in your decision-making process. Try to think of what is most humane for the animal. A shelter may not want to fix or treat an animal that is aggressive and has little chance of being adopted. It is helpful for you to provide information on behavior to the shelter so that can help in their decision on how to proceed with treatment. You would not want to put

an animal through unnecessary tests, treatment, surgery, etc. if it is only going to go to the shelter and be euthanized. Sometimes it is also important for shelters to euthanize very sick animals for the greater good,

to help save other animals if they can get a diagnosis from necropsy. This also pertains to finances, as spending thousands of dollars on one animal leaves less money for others.

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Euthanasia Considerations

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Introduction

Emergency medicine encompasses much hope and promise, but also stress and disappointment for both clients and clinicians. Their focus on serious illness and injury means that emergency veterinarians will deal with a significant amount of death – occurring from progression of disease or injury, as well as euthanasia. Precise mortality and euthanasia rates in veterinary emergency facilities are unknown, but it has been estimated that veterinarians experience death five times more than human physicians [1]. Assuming overall higher rates of death per shift in emergency compared with general practice, the emergency veterinarian is involved in some of the highest rates of death in veterinary medicine.

The impact of euthanasia on veterinarians is considerable [2–7]. While frequent euthanasia and end-of-life discussions can be some of the most challenging aspects of emergency medicine, multiple opportunities exist to minimize emotional distress, maximize goal-concordant care, and ensure sufficient thoughtfulness in euthanasia considerations. This chapter aims to help clinicians understand and navigate several unique aspects of euthanasia in the veterinary emergency setting, expose clinicians to some newer concepts related to veterinary end-of-life care, and improve clinician comfort and competency in these important areas.

Emotional Aspects of Euthanasia in the Emergency Setting

Rapport

Euthanasia in the emergency setting may be particularly stressful since veterinarians typically do not have long-term relationships with their patients and clients. Developing rapport with clients quickly is an essential skill of the emergency clinician. This becomes especially

important for end-of-life discussions. Asking the client to share non-medical information about the pet can be a means of establishing rapport quickly. For example, “*Can you tell me what Molly’s favorite thing to do was when she was healthy?*” This often helps clients relax by recalling positive memories, and also assures them that you care about their pet as an individual. Simple statements such as “*I know this is hard/painful/scary/unexpected. I am here to support you through it*” are extremely effective in achieving partnership with clients and setting the stage for shared decision making.

Goals of Care Discussions in the Emergency Setting

Research in human medicine regarding end-of-life preferences consistently demonstrates positive outcomes from early goals of care (GOC) discussions [8–11]. This is an area for further exploration within veterinary medicine. The Serious Illness Conversation Guide [10] has recently been modified for veterinary use [12] (Figure 204.1). A full discussion of GOC conversations is beyond the scope of this chapter but the guide provides a basic framework that may be used in the emergency setting to facilitate serious illness and end-of-life conversations for veterinary patients. Understanding the nuances of client beliefs and preferences enables clinicians to provide goal-concordant care.

Beliefs Regarding Aid in Dying

It is essential that emergency clinicians understand their clients’ beliefs regarding euthanasia. It is often assumed by veterinary professionals that euthanasia is acceptable to clients but this is not universally the case. Acceptance or opposition is also rarely absolute. Stated opposition to euthanasia generally falls into three categories:

- a fundamental philosophic or religious opposition
- an emotional tie that requires exploration, i.e. fear from previous experience, misunderstanding regarding

Serious Veterinary Illness Conversation Guide

CLINICIAN STEPS

□ Set up

- Thinking in advance
- Is this okay?
- Hope for best, prepare for worst
- Benefit for patient/family
- No decisions necessary today

□ Guide (right column)

□ Act

- Affirm commitment
- Make recommendations about next steps
 - Acknowledge medical realities
 - Summarize key goals/priorities
 - Describe treatment options that reflect both
- Document conversation

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CONVERSATION GUIDE

Understanding

What is your understanding now of where _____ is with his/her illness?

What questions do you have about information your family veterinarian has already shared with you?

Information Preferences

How much information about _____'s illness would you like from me? How much additional information do you feel you need to help make decisions?

FOR EXAMPLE:

Some families like to have lots of information about what to expect, others do not. Some people are very comforted by lots of diagnostic information and some people find this stressful.

Prognosis

Share prognosis as a range, tailored to information preferences. Understand that euthanasia as end point for most patients has tremendous impact on "prognosis". What is acceptable for one family may not be for another.

Goals

If _____'s situation worsens, what are your most important goals?

Fears / Worries

What are your biggest fears and worries about _____'s health?

Function

What abilities or activities are so critical to _____'s life that you can't imagine him/her living without them?

Trade-offs

If _____ becomes sicker, how much are you willing to go through for the possibility of gaining more time together?

Aid in Dying

What are your beliefs surrounding euthanasia?

Figure 204.1 Serious Veterinary Illness Care Conversation Guide. Reproduced with permission of Ariadne Labs (<https://portal.ariadnelabs.org>).

procedure, particular connection to the pet that makes purposeful ending of life feel unacceptable

- a *preference* for unaided death but euthanasia may be acceptable under certain circumstances. It is important for the clinician to determine what those circumstances are.

Some of the most common end-of-life communication challenges can be avoided by *asking* clients what their feelings are regarding euthanasia. This is ideally done by the veterinarian, but may also be done by nursing staff or even incorporated into emergency room (ER) paperwork just like code status for CPR orders. Wording on paperwork such as “*Difficult Discussions: Understanding Your Preferences*” can help frame this solicitation of information positively, reiterating that the ER team values shared decision making.

Palliative sedation is a topic of much discussion within human medicine and is deserving of attention within the veterinary profession [13–18]. Palliative sedation can be very useful in situations where clients are resistant to euthanasia, yet the patient cannot be kept comfortable while still conscious. Most emergency veterinarians are quite competent in anesthesia and analgesia for their patients; drawing upon this knowledge with the goal of alleviating suffering via continuous sedation can be a useful tool in some of the most challenging end-of-life situations.

Technical Aspects of Euthanasia in the Emergency Setting

Procedural Considerations: Pharmacology and Technique

Most emergency patients will already have established venous access via intravenous catheter(s). Therefore, the technical aspects of euthanasia in the emergency setting are usually straightforward. Whether or not to administer pre-euthanasia sedation or injectable anesthesia (i.e. propofol) must be determined on a case-by-case basis. Level of stress and alertness of the patient, and any particular emotional needs of the client should be considered. Benefits of pre-euthanasia medication include achieving stage 3 of anesthesia prior to administration of euthanasia solution, which can be helpful for client-witnessed euthanasia. Clients may have close physical contact with sedated or anesthetized patients, which can be meaningful for some families, especially if they have not been able to touch their pet since the onset of illness or injury. Sedation also provides relief from suffering such as air hunger, pain, and seizure activity while clients cope with the imminent loss of their pet and say goodbye.

It is essential that clients are not rushed into euthanasia to relieve clinical signs; euthanasia is an irreversible solution to patient suffering. Adequate analgesia and symptom management must be provided while euthanasia decision making is taking place. In the most severe cases, intubation and injectable anesthesia may be provided when patients require immediate relief but clients are not yet ready to euthanize. This may be considered a brief form of palliative sedation, and can be a useful tool for all involved.

In situations where intravenous access has not been established, or cannot be established due to peripheral edema, seizure activity, limited personnel, or other challenges, several options remain. Clinicians should be familiar with alternative routes to intravenous euthanasia, and corresponding drug dosage adjustments (Table 204.1). In particular, intrarenal euthanasia is a useful technique in anesthetized cats and has been shown to be similar in effect to intravenous euthanasia [19].

Procedural Considerations: Treatment Area and Patient Preparation

While treatment and intensive care areas are familiar to veterinarians and their teams, clients may be significantly affected by the experience of being in these surroundings with a sick or injured pet. Remembering that the various sights, smells, sounds, and general atmosphere can be traumatic to clients is important for providing compassionate care. A growing body of research in human medicine describes the mental health impact of intensive care on patients’ family members [20–23]. It is likely that families of veterinary patients are at similar risk, and this is an area for future investigation in veterinary critical care. A keen awareness of treatment area conditions while clients are present is essential; this includes the physical cleanliness of the area, condition of patients, as well as professional behavior and language of veterinarians and staff. Many veterinary hospitals have systems in place to inform staff that clients are present, such as flags or blinking lights.

Ideally, euthanasia would occur in a designated location, away from a busy treatment area or intensive care unit (ICU); however, this is not always possible. When euthanasia must occur in a treatment area or ICU, several simple steps may be taken to improve the client (and staff) experience. Remove all equipment with noisy or visible displays; they are not necessary during euthanasia, can be distracting to clients, and intensify the “medical” nature of the dying experience. Intubated patients would ideally be extubated immediately prior to euthanasia, after discussion with the clients

Table 204.1 Euthanasia methods: injectable euthanasia solutions

Route	Pros	Cons	Dose
Intravenous (IV)	Rapid death, 30 sec Reliable	Locating vein Quality of vein Extravasation Seizuring pet	1 mL/10lb
Intracardiac (IC)	Seizuring pet No venous access	Requires anesthesia, injectable or inhalant Technical skill Client response	1 mL/10lb + 2–5 mL
Intraperitoneal (IP)	Easy No sedation required for pure barbiturate solution Slower death may be preferred by clients	Prolonged time to death, 15–25 min possible (but usually 8–10) Verify death closely	3 mL/10lb
Intrahepatic	Easy Improved uptake over IP Respiratory arrest rapid Rapid death, 2 min	Requires anesthesia, injectable or inhalant Death may be prolonged if extrahepatic injection	2 mL/10lb
Intrarenal	Easier than IV in volume-depleted cats Rapid death, 30–60 sec	Requires anesthesia, injectable or inhalant Technical skill	3–6 mL/cat
Oral	Aggressive animals Safe, limited human contact	Unreliable Unpalatable Verify death closely	3 mL/10lb PO (solution) 1 tsp/40lb PO (powder)

Adapted from Cooney et al. [53] and Cooney [54].
PO, by mouth (*per os*).

regarding what will happen next. For example, “*We are going to get Molly ready for you and then we’ll bring you back in to say goodbye.*” Preparation of the patient for euthanasia can often occur while consent forms and aftercare paperwork are being taken care of, depending on the practice’s particular procedures. Extubation will require continued sedation if the patient is oxygen dependent, to prevent air hunger. However, most clients would prefer to have the last image of their pet without a tube. Removing any barriers to physical contact is especially important around the head and face of the patient, where clients are likely to be gathering for euthanasia. Clients may appreciate being able to hold smaller patients during euthanasia. Informing clients of the possibility of involuntary eliminations, and draping blankets with waterproof backing on the client’s lap is a good idea in this situation in case they occur, although many clients who wish to hold their pets do not mind getting soiled.

Patient preparation for client-witnessed euthanasia includes cleaning up any major visible wounds, body fluids, or soiled linens whether the patient has been hos-

pitalized for weeks or hours. Disconnecting the patient from all machines, capping the intravenous catheter, rewiring it with clean materials if necessary, and draping a large clean blanket (in good condition, no holes or stains) over the body, leaving the head and neck exposed, is a respectful demonstration of care and compassion for the patient and will positively affect the client experience.

During the euthanasia procedure, the team can facilitate focus on the patient and minimize surrounding distractions by bringing the family to the patient’s head and making sure they can sit down if they want to. Providing tissues and a clean trash bin is important. Asking if clients have been present for euthanasia before, explaining the procedure and physiological responses to death, and answering any questions that the clients may have are essential. This step may have been completed prior to gathering around the patient. If so, it is important to reiterate the key steps of the procedure and obtain clear verbal consent indicating that the clients are ready to proceed prior to administering drugs.

It is also important to confirm death after listening to the patient with a stethoscope, using clear language that cannot be misinterpreted. Although in the vast majority of cases, saying “*S/he’s gone*” is sufficient, there have been situations where clients do not understand that their pet is dead. Discretion as to whether to reiterate “*S/he has died*” may be left up to the individual veterinarian; however, it may be necessary, especially with very distraught clients.

Procedural Considerations: Client Visiting with Deceased Patients

Clients will often visit with deceased patients, even if they do not choose to be present for euthanasia. Families with small children may elect to have only adults present for euthanasia, but wish to have children view the deceased pet so that they know s/he has died. Clients may also come into the hospital after they have been notified via phone that their pet has died. These visits should be prepared for with care, as if they are a client-witnessed euthanasia. Most often, deceased patients can be moved out of the treatment area for visiting; this is strongly recommended even if clients are only visiting briefly. No matter where the visit takes place, it is important that no evidence of aftercare preparation is in view, such as garbage bags, cremation paperwork, body tags. While some of these things may appear to be of minimal significance, it is important to remember that the manner in which veterinarians handle patient death has the potential to alleviate or aggravate client grief. Research shows that veterinarians have significant influence on client coping with pet loss [4,24–26].

Current Concepts in Veterinary End-of-Life Care

Veterinary–Social Work Partnerships

Veterinary social work is an emerging field with innumerable benefits for patients, clients, and veterinary professionals [27–30]. The human needs that arise in relationships with animals, particularly in end-of-life situations, are tremendous. Veterinary hospitals are encouraged to partner with social workers who are experienced in grief and bereavement, and who embrace a strengths-based approach to human–animal interactions. Emergency practices in particular stand to benefit from social work support, given their highly stressful and emotionally charged environments.

Veterinary Hospice and Palliative Care

In parallel with a rising interest in end-of-life care for people, increased attention is currently being given to death and dying within veterinary medicine [31–33]. Interest in hospice and palliative care (HPC) for companion animals is on the rise [34–48], and emergency veterinarians in particular are likely to benefit from referral relationships with HPC providers. These relationships enable smooth transitions to home care, expanding the available options for emergency and critical care cases. Building networks of these providers is invaluable for cases that may require support beyond what is typical for a particular veterinary hospital.

Client Request for Home Death

Much attention has been given to preferred place of death (PPD) in human medicine [49–52]. While similar research in veterinary medicine is lacking, it is possible that client preferences regarding place of death may carry over into preferences for their companion animals. Emergency veterinarians should be aware that clients might not want their pets to die in the hospital, even if death is imminent. Clients may wish to spend final hours or days with their pet in a familiar setting where they can receive the support of friends and family, and express their grief more openly. Referral relationships with mobile practitioners are useful in cases where home is the PPD. Incorporating place of death preferences into end-of-life conversations is good standard practice for emergency veterinarians. Euthanasia is rarely an emergency procedure; relief of suffering is what must be done urgently. Clients should be able to choose the time, manner, and place of their pet’s death.

Conclusion

Life and death decisions are frequently made in the ER. Severe presenting signs, uncertain outcomes, emotional and financial stress, and legal availability of euthanasia for animals all contribute to the reality of euthanasia as a procedure commonly performed by emergency veterinarians. Fortunately, several steps can be taken to minimize the negative impact that euthanasia may have on clients and the entire veterinary team. Engaging in goals of care conversations, prioritizing emotional support for clients, self-care for veterinarians, and relief of suffering for patients are important practices that will enable euthanasia to be performed well, and placed in an appropriate context within emergency medicine.

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Emergency Room Design and Staffing Models

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Introduction

In human healthcare, “emergency care” is often defined as the diagnosis and treatment of acute injury and/or illness that pose an immediate risk to life or long-term health. Similarly, but at a lower severity of illness, “urgent care” is defined as the diagnosis and treatment of medical conditions that are serious or acute but pose no immediate threat to life and health but that require medical attention within 24 hours.

In veterinary medicine, the term “emergency” applies to both urgent and emergent conditions – those that a pet caretaker and a doctor agree require immediate attention no matter what the problem. This may involve medical, surgical, reproductive, or even non-medical issues. There is a general rule in veterinary emergency practice that if a client believes that their pet’s problem is an emergency, it is until proven otherwise.

Designing a facility for emergency care extends to all phases of hospital planning – location, accessibility, hours of operation, facility, equipment, drugs, supplies, medical staff, and management. All veterinarians are confronted with an emergency at one time or another, independent of their workplace or type of practice – teaching hospital, referral center, emergency clinic, general practice, vaccine clinic, spay/neuter clinic, or even a mobile house-call practice. In addition, an emergency can occur anywhere at any time. Every space is a potential emergency room, including a client’s car, a parking lot, or an outdoor exercise area. A practical design for providing excellent emergency care is a challenge that extends to all aspects of hospital design.

General Design Concepts

Goals

Emergency response depends on readiness. Doctors must be educated and current. Staff must be trained, capable

of caring for multiple patients simultaneously, and able to shift into “high gear” when under pressure. The hospital’s armamentarium of equipment, drugs, and supplies must be adequate to the task. The hospital design should reflect the organization and efficiency needed to respond rapidly and effectively in an emergency.

Ideally, an emergency hospital should be central to the population it serves. It should be very accessible (no more than one turn off a major highway) and easy to find. Signage should be highly visible, particularly at night. Emergency parking should be available close to an entrance that permits rapid transfer of a patient to an emergency room (ER) or response area. This area should be organized and maintained ready for an emergency at any time. Staff should be immediately available to respond to an emergency, including receptionists to process information and care co-ordinators who are ready to support anxious or grieving clients. Because emergencies also occur with in-hospital patients, this level of readiness should be established in multiple areas of the hospital. This includes, in addition to the primary ER, the ICU, surgery, procedures, radiology, or any room where anesthesia is performed or unstable patients are treated or housed.

Limitations

There is another general rule in emergency practice that you can’t always have what you want, or even what you need. You can only have what you can afford. We must often compromise on our goal to provide the highest level of readiness due to limitations on our resources. There are communities too small to support a 24/7 emergency center, and general practitioners must fill that role in a general practice setting, often on call at night. There are always financial constraints that affect hospital design, equipment purchases, and staffing levels. There are shortages in the supply of quality emergency doctors and technicians as the work is stressful and most emergency hours

are nights and weekends. For practical reasons, staffing levels are based on an average anticipated caseload so it is not uncommon for a very busy shift to overwhelm the resources of even the most prepared practice. The cost of quality care is already high and steadily increasing faster than the overall inflation rate. Pet owners are already stressed to meet these costs. The “ideal” design must yield to practical and affordable considerations.

Practical Design

Quality care is still possible within the constraints of the imposed limitations. Facilities can be built on cheaper commercial or even industrial land. Construction costs can be controlled with intelligent choices of structural and design elements; still expensive at up to \$500 + (2016) per square foot, but still half the cost of a comparable human hospital. The hospital design focuses on making effective use of space, minimizing hallways, and designing rooms that can support multiple functions.

In smaller clinics, equipment is shared among several areas, which is an acceptable compromise since the spaces are small and time is not wasted moving resources from one area to another. The primary treatment room serves as the ER with space dedicated to immediate response. Staff are cross-trained, with receptionists and technicians often serving as care co-ordinators in addition to their primary functions. There is a premium on technician training as they can be called upon to play a role often performed by a veterinarian in a larger, multidocotor facility.

In large hospitals, each major service should be ready for emergency response. This usually includes ER, ICU, medical procedures, and surgery departments but can extend to oncology, imaging, and other areas. With the possibility of an emergency occurring anywhere, the design must still be flexible, permitting the patient to quickly and safely get to an emergency response area, or the personnel, equipment, and medical supplies to quickly get to the patient. The cost of independently equipping multiple areas in the hospital can be considerable. A practical design can be accomplished using mobile cart systems, lightweight mobile equipment, an alert staff, and an excellent system of in-hospital communication so that the range of effective ER response can be extended from a few rooms to all areas of the hospital.

Entrance

Current building codes that establish access requirements for handicapped persons also benefit the emergency patient. Lighting for vehicle ingress and egress must meet minimum standards. Handicapped parking must be generous and a similar design should

be used for emergency parking near the entrance. Parking lot slope cannot be excessive, access to the entrance must be without obstacles, curbs must be cut to permit wheelchair use, entry doors must be large enough with hold-open function or automatic openers. These design elements all permit medical staff and gurneys to reach a patient that cannot be carried in by an owner.

Ideally, hospital design provides for a separate emergency entrance or entrances to permit rapid access to an ER. If only the main entrance is available, there should be a straight path from waiting room to ER, through the exam room area, that is as short as possible. A gurney should be stationed near emergency entrances to shorten response time.

Reception

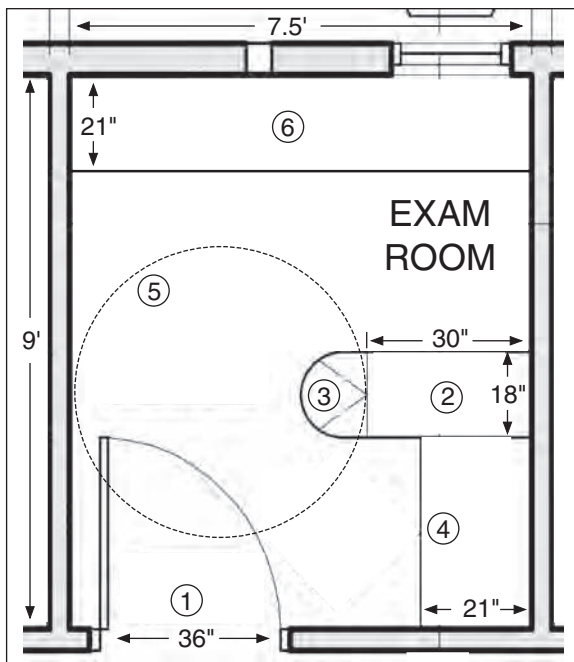
Reception areas should have sight lines to the parking lot and emergency parking area. The front desk should be designed so that a receptionist does not have to leave this area to do their job while observing waiting patients at the same time. The phone, intercom, and/or paging system should be robust and able to rapidly call for assistance when needed at the front of the hospital. Each phone should be paired with a laminated list of emergency conditions – those client complaints that a receptionist can easily recognize, either on the phone or in the waiting room, that these are problems that should be addressed immediately.

Waiting Room

Client waiting areas should be partitioned so that families and pets can find some personal space. If possible, cats should be separated from dogs, and fractious dogs (and boisterous children) should be separated from others by the design of the waiting room. The challenge is to provide these areas of separation while keeping clients and pets visible to hospital staff. Children should have their own area with games, toys, and television. Adults should have access to television to help endure longer waiting times. Current hospital design tends toward smaller waiting rooms in favor of adding more exam rooms. The exam rooms double as personal waiting areas for individual families and pets and help to ease the stress of a waiting room full of clients and patients.

Exam Rooms

A well-designed exam room can serve as a receiving room, a waiting room, a consultation room, a grieving



1. Single entry door
2. Fixed exam table, 30" above floor level (AFL)
3. Folding 12" exam table extension
4. Doctor's work space, 42" AFL
5. ADA-compliant wheelchair access
6. Full room width client bench seating, 18" AFL

Figure 205.1 Compact exam room design.

room, a room for patient history and examination, a client education room, and a discharge room. It is unusual for an exam room to be used for emergency procedures or treatments, except in the context of minor, outpatient urgent care.

Current hospital design plans for a smaller waiting room and more exam rooms. In addition, exam rooms can be designed smaller than the traditional 8' × 10' space thought to be the minimum size. With careful design, 10 exam rooms can be built in the space normally filled by eight (Figure 205.1).

Historically, exam rooms were designed with a hallway on each side with a separate entry door for clients on one side and doctors on the opposite side. Considerable space can be saved by creating a pod of exam rooms, each room with a single door with rooms aligned on each side of a semi-private hallway that is accessed from the waiting area at one end and the private, secure, staff-only area toward the back of the hospital. Client seating is in the back of the room with the doctor's workspace near the door. The doctor and staff can enter and leave the room at will without disrupting the client or patient.

Veterinarians may have strong opinions about having sinks in exam rooms, but with the high cost of plumbing and the trend toward all procedures being performed away from the client, a single sink can serve all exam rooms in a pod.

Visitation, Consulting, and Grieving Rooms

If the facility and the budget are large enough, there may be benefit to planning client rooms that are not as stark as the typical exam room. Space dedicated for client privacy and comfort can be a good investment, and may be used for consultation, grieving, or visiting a hospitalized pet that is well enough to be moved from its cage or run. These rooms can be designed with more subdued lighting, more comfortable furniture, and rugs on the floor. If this space is to be used for patient visits, an oxygen outlet should be provided. This type of room can also be fitted with a folding exam table to be used when extra examination space is needed.

Emergency Room

Ideally, whatever space is designed for a practice's primary emergency response would be dedicated to that response so that an incoming emergency patient had immediate access to the workspace, supplies, and equipment needed for their urgent care. These resources would be reserved strictly for emergency use and considered to be so vital to that purpose that they would never be taken for use elsewhere in the hospital. However, for most practices, the cost to duplicate the space, equipment, drugs, and supplies is simply too high, so they are used in support of the non-emergency caseload as well.

Most small and medium-sized hospitals (3000–12 000 square feet) integrate their emergency patient care into their central treatment area. During the day, it shares functionality with the non-emergency caseload of the hospital. If the facility is open nights, weekends, and holidays, this area becomes the ER. This room is usually at the center of the hospital where staff tend to converge and where, because the hospital is small, the room is in reasonably close proximity to everything needed for patient care.

To serve as an efficient ER, the treatment room must be organized, equipped, and supplied for the task. Both wet and dry treatment tables should be available, organized along a wall as peninsula projections or in the center of the room in treatment islands. Oxygen, suction, waste gas, plumbing, and electrical lines to any island should arise from the floor below the island and *not* be installed

in columns that extend to the ceiling. Contractors may resist this design element since installation is considerably more difficult, but patients and hospital staff benefit from having unobstructed lines of sight around the room.

High-intensity surgical lighting should be installed in the ceiling centered on each treatment table within easy reach. IV tubing and med gas lines should not interfere with the overhead exam lights or with access to the patient, so IV hangers should be installed on medical carts or on the exam light columns overhead. Medical gas connections for oxygen, suction, and waste gas should be at the end of each treatment table along with a bracket to hang a suction canister. These items should be recessed below the end of the table, along with electrical outlets and a switch for a small shop vacuum installed inside the cabinet for vacuuming clipped hair.

Emergency room practitioners have different opinions on whether “readiness” means that all emergency drugs and supplies should be out in the open or whether well-labeled drawers and cabinets provide an adequate level of accessibility without the clutter. This author prefers multiple levels of organization, all in close proximity to the treatment tables.

1. A “crash” cart reserved for cardiopulmonary resuscitation. On or in the cart should be:
 - a bag of balanced electrolyte solution with an attached administration set, pressure infuser, and infusion pump
 - a biphasic defibrillator with connected external paddles
 - a multiparameter patient monitor capable of displaying ECG, NIBP, SaO₂, temperature, and ETCO₂
 - endotracheal tubes and laryngoscope
 - Ambu bag and oxygen masks
 - supplies for intravenous and intraosseous catheterization
 - supplies for obtaining diagnostic samples
 - bandage material
 - examination and surgical gloves
 - a surgical pack and supplies
 - chest and abdominal retractors
 - tourniquets.
2. An oxygen flowmeter plugged into the oxygen fixture at the treatment table attached to a patient line. An E-series oxygen tank attached to the crash cart is acceptable if the hospital does not have piped medical gas lines.
3. A surgical suction regulator plugged into the suction fixture at the treatment table attached to a suction canister, suction tubing and a Yankauer or Poole suction catheter. A Gomco or similar suction pump on the crash cart is acceptable if the hospital does not have central suction.
4. Procedure carts to be shared with non-emergency patients for use throughout the hospital. The most popular are:
 - a “set-up” cart with supplies for placing IV lines, starting IV or IO fluids, collecting samples for diagnostic testing, and for performing minor procedures. This is used with almost all hospitalized patients, permitting the crash cart to be reserved for CPR only
 - a bandage cart containing bandage, casts, and splint materials
 - a treatment cart to organize and deliver scheduled medication for hospitalized patients.
5. A gas anesthesia machine, preferably with an anesthetic ventilator and a multiparameter patient monitor.
6. A cart with a small, highly mobile ultrasound machine.
7. Open bins at the treatment table islands to provide access to the most commonly used supplies without having to open a drawer or cabinet, e.g. syringes, tape, bandage material, gauze, etc.
8. Cabinets and drawers throughout the treatment room containing those items that are used for both emergency and non-emergency patients.

The ER room should be designed to array all of these elements around central treatment tables. Islands arranged in an “H” pattern allow for four patient tables in close proximity – two wet tables, one fixed dry table, and one docking station for a mobile lift gurney. With one or more such islands in the center of the room, the periphery of the room can be used for storage cabinets, rolling stock (crash cart, procedure carts, anesthetic machine, ultrasound machine), cages, and for doors leading to surrounding rooms.

A room designated exclusively for use as an ER is probably practical only in very large hospitals with a large daytime emergency caseload and the space available for this single use. Design and organization are similar to that described above, with a minimum of two patient tables. This space has the advantage that it does not interfere with more routine non-emergency care, does not add to the stress of the quieter pace in the treatment room, and can be located to permit client access without entrance into the main treatment area.

Other Hospital Space

Hospital space surrounding the primary treatment room or ER is considered to be “prime real estate,” reserved for important patient support functions. Unfortunately, as larger and larger hospitals are constructed, everything cannot be close to the ER. A list of hospital space assigned

by proximity to the ER and designed to optimize patient support might be as follows.

Nurses' Workstation

This is an area for medical staff to complete records and other administrative tasks while maintaining close observation of emergency patients. It may be part of the main treatment/ER room or in a room in close proximity with large windows for observation.

Doctors' Workstation

This is compact desk space where doctors can complete records, make phone calls, access the hospital library, or consult with colleagues. This should be an enclosed area with a large window wall that permits monitoring of all activity in the treatment/ER room.

Intensive Care

In a 2016 study by VECCS and Horizon Veterinary Services, nearly 90% of emergency care providers reported that they had primary ICU patient responsibility while working emergency shifts. Even though the quiet, contemplative environment of the ICU seems only remotely related to the hectic pace of a busy ER, this joint responsibility means that these hospital areas need to be closely associated. Only in very large hospitals in which these services can be manned separately can they be separated in the facility.

Radiology

Digital technology permits safer and more rapid radiological assessment of the emergency patient. Radiology rooms should be easily accessed from the departments that need rapid access to this technology – ER and surgery.

Laboratory

The dramatic advances in point-of-care testing will eventually mean that hand-held analyzers can be used in the ER and the main hospital laboratory can be located farther away. At this time, rapid laboratory access and rapid turnaround times are still a high priority for the ER, the ICU, and the surgery department.

Care Co-ordinator Workstation

These are the people who bond the client to the medical staff. They maintain client communication while the medical staff are busy with patient care. Care

co-ordinators must have easy access to both clients and medical personnel so this bond is not broken.

Surgery

A number of surgical procedures are carried out in the ER, including open chest CPR, emergency tracheotomy, laparotomy or thoracotomy for massive hemorrhage control, and minor wound repair. Usually, patients that require less urgent or more extensive surgery are stabilized in the ER so that they can be moved safely to a more remote surgery department. That said, many emergency rooms in large practices are designed with a dedicated surgical suite nearby.

Isolation

There are differing opinions on the best strategy for the design and location of isolation rooms. Many patients that should be isolated present through the emergency service. Once identified, they should be housed and treated in an area away from other patients at risk. Placing this area close to the ER seems appropriate, but also invites contamination between these areas. An isolation room more remote in the hospital with a vestibule for storing supplies and for decontamination after contact with patients is also an acceptable solution. The space should include a wet table and everything necessary to care for the patient. The room should have audio and video monitoring displayed in the nurses' and doctors' workstations. It should also have an outside entrance and isolated exercise yard.

Advanced Imaging (CT and MRI)

Magnetic resonance imaging studies are unlikely to be performed on emergency patients until they are stable enough to undergo a fairly long anesthetic procedure. On the other hand, multi-slice CT scanners are becoming more affordable, making for more rapid studies that can be performed with minimal, if any, sedation. CT is becoming a more useful tool for the assessment of the emergency patient and future hospital design should consider placing this imaging modality closer to the ER.

Other Design Considerations for the Emergency Room

Flooring

Flooring is the Achilles heel of a veterinary facility. It should be impervious but ideally soft underfoot. It should be stain resistant and bacteriostatic or even bactericidal.

The flooring material should be seamless and coved onto walls and cabinet bases to eliminate open seams where fluids and debris can collect, unable to be cleaned. The surface should be smooth to allow easy movement of carts and gurneys but not so smooth as to be slippery when wet. There is no perfect flooring system and many poor ones. Most reasonable solutions are sheet goods with heat-sealed seams, or epoxy or epoxy/acrylic troweled-on materials that harden in place and create a seamless floor cover. Newer acrylic combination products show promise and have the advantage that repairs can be made seamlessly.

Lighting

The trend in lighting design to save energy is to provide less overhead general lighting and to rely on more focused task lighting. Many building codes now make this a requirement and limit the amount of general lighting that can be installed. Hospitals can benefit from this approach, but should still recognize areas that should be brighter than a normal office building would be. Extra general overhead lighting should ideally be provided in the parking lot, waiting rooms, exam rooms, ER, ICU, and isolation. Dimmable lighting should be provided in imaging rooms, ICU, anesthesia recovery, wards, and visitation rooms.

Plumbing

Stainless steel is an obvious choice for handwashing stations, patient wet tables, dog runs, or anywhere there is a drain. Exam room sinks can be replaced with one sink in the hallway of each exam pod. Wet tables should be equipped with sprayers and a garbage disposal if local building code allows. Fixtures should be single spout with a single lever mixer to permit one-handed operation. The area around the entrance, the run wards, and outdoor exercise areas should have hose bibs. Building codes will often require a drinking fountain in public areas or near public bathrooms.

Heating, Ventilation, and Cooling

Multiple, independent heating and cooling ventilation systems are required to separate public, interface, private, and animal housing areas. Systems are often overdesigned when the designer tries to meet the air exchange standards of an animal housing facility such as a boarding kennel. In a hospital, most odors result from contamination with feces, urine, vomitus, or body fluids that are more serious threats to patients and staff than just the odor. An inexpensive solution for odor control is to install high-capacity switched exhaust fans, able to dump the entire air volume in a room within minutes.

Surgery rooms should have Hepa filters or at least laminar flow supply and return vents installed at the periphery of the room. Isolation should have its own HVAC (usually a mini-split system) with negative pressure in the room so all air flow around the door is inward. All return air should be exhausted to the outside when the room is occupied. Ceiling fans can be used help to circulate air downward into runs.

Electrical System

The electrical system must be robust and even smaller clinics will require at least 400 amp service. If possible, circuits to computers and lab equipment should be conditioned or the equipment should have surge protection. Back-up power should be provided, either with battery power or a generator. Multiple outputs or high-density plug strips will be needed in the laboratory and in any area where patient care involves multiple pumps, monitors, warmers, clippers, and other electrical devices.

Security

The front entrance or vestibule should be locked during off-hours and controlled from the reception desk. Access to the clinical areas of the hospital should be limited and controlled with electronic locks that can be armed when security is needed between public and private areas. Narcotics cabinets must be double-locked and monitored. Video monitoring is recommended throughout the exterior and interior of the hospital, with focus on important areas that include the entrance, reception desk, isolation, narcotics storage, and outdoor exercise areas. Video monitoring can also be used to monitor cages and runs where emergency or ICU patients are housed. Some hospitals monitor and record video and audio feeds from exam rooms to minimize risk to hospital personnel, to use in the event of any dispute or legal action, or even for staff training purposes.

Cart Systems

To prevent duplication of expensive equipment and supplies, cart systems are becoming more popular. Carts have the advantage of organizing supplies and equipment for a targeted task (e.g. initial patient set-up, scheduled treatment for patients in wards, bandaging, anesthesia monitoring, computer record keeping) and can be stationed anywhere near the patient when needed, but stored along a wall or in a ready room when not in use. They have the added advantage that they can be rolled to central supply when they need to be restocked.

Medical Gases

Emergency rooms and ICUs use a large quantity of oxygen. This can be supplied by an appropriately sized oxygen generator, liquid oxygen tanks, or a manifold of large H tanks. Oxygen should be piped to outlets in walls where anesthesia is performed, above cages and runs to provide supplemental oxygen, and in the face of treatment stations for both purposes. Overhead oxygen lines should be avoided if possible, or at least strategically placed to not interfere with patient lighting or patient access. Oxygen alarms must be audible throughout the hospital.

A hospital-grade compressor to provide both surgical suction and waste anesthetic gas scavenging should be part of the medical gas system. Smaller clinics can realize savings with low-tech scavenging systems and point-of-care portable suction pumps. Nitrogen may be needed in surgical suites for power tools, although surgeons are more commonly opting for electrical devices.

Cages and Runs

Stainless steel is the best choice for animal housing. Laminate cages have an advantage in cost and can be installed with an in-floor heating system, but they are not as cleanable or as durable. Any electrical heating system should be closely monitored so patients are not burned. Heating patients with warmed air or water blankets is preferred, but these systems are much more cumbersome to use on awake patients.

Cages should be banked in two tiers. Modules of three cages, one 36" high×48" wide below and two 30" high×24" wide above, can be arranged in line to provide efficient accommodation anywhere patients are housed. Above each module is a shallow cabinet that contains fluid pumps, hanging fluid bags, and patient monitors that support the patients housed below.

Run doors and walls should be stainless steel with an impervious floor of epoxy or acrylic blend sloping to a drain. The floors can be heated at reasonable cost. The drain should be selected to minimize the likelihood of a dog's nail or digit being trapped. If glass is used in the run door to improve patient monitoring, the lower one-third of the door should be stainless steel wire to permit hanging pumps and monitors and to permit air circulation in the run. Overhead ceiling fans can improve this circulation. Runs should be equipped with multiple places to hang pumps and monitors, preferably outside the cage or on the cage door. In ER and ICU areas, oversize runs are required to permit access to a recumbent patient from at least three sides.

Design Summary

All the elements of a practical hospital design capable of providing excellent care for emergency patients anywhere in the hospital can be seen in Figure 205.2.

Staffing the Emergency Room

Staffing the ER is an administrative challenge. Emergency care has become increasingly more sophisticated, requiring greater levels of expertise from both doctors and medical staff. Emergency patient care demands constant vigilance and meticulous attention to detail with little room for error. The caseload is unpredictable – a staff schedule can be created to cover an average shift, but it can easily be overwhelmed on any given shift. Emergency work is highly stressful due to the volatility of clients and caseload. It is also not conducive to a "normal" lifestyle in which people typically do not work nights, weekends, and holidays.

The cost of staffing an ER can exceed 60% of the budget and is rising due to a shortage of applicants for emergency positions. The cost of medical care in general increases at a rate 2–3 times faster than the increase in the average cost of living. Staffing challenges will only increase in the foreseeable future.

How emergency services are coping with these challenges can be summarized in the results of a 2016 survey performed by Horizon Veterinary Services and the Veterinary Emergency and Critical Care Society. The results are listed below.

- Over 1000 responses were obtained from emergency service personnel from all regions of the United States.
- 77% of responders were female, with 83% younger than 50 years old.
- Emergency services are either provided during routine general practice office hours (8am–6pm Monday through Saturday), emergency clinic hours (5 or 6pm–8 or 9am Monday through Friday and all day weekends and holidays), or central hospital hours 24/7.
- 47% of respondents have at least one board-certified ACVECC diplomate on staff.
- 24% use other specialists to provide emergency services.
- 21% employ ACVECC residents, 10% other residents, 19% E/CC interns, and 32% rotating interns.
- 87% employ regular emergency doctors.
- 21% employ part-time and relief doctors.
- 88% of reporting hospitals use certified technicians, 81% non-certified technical assistants.

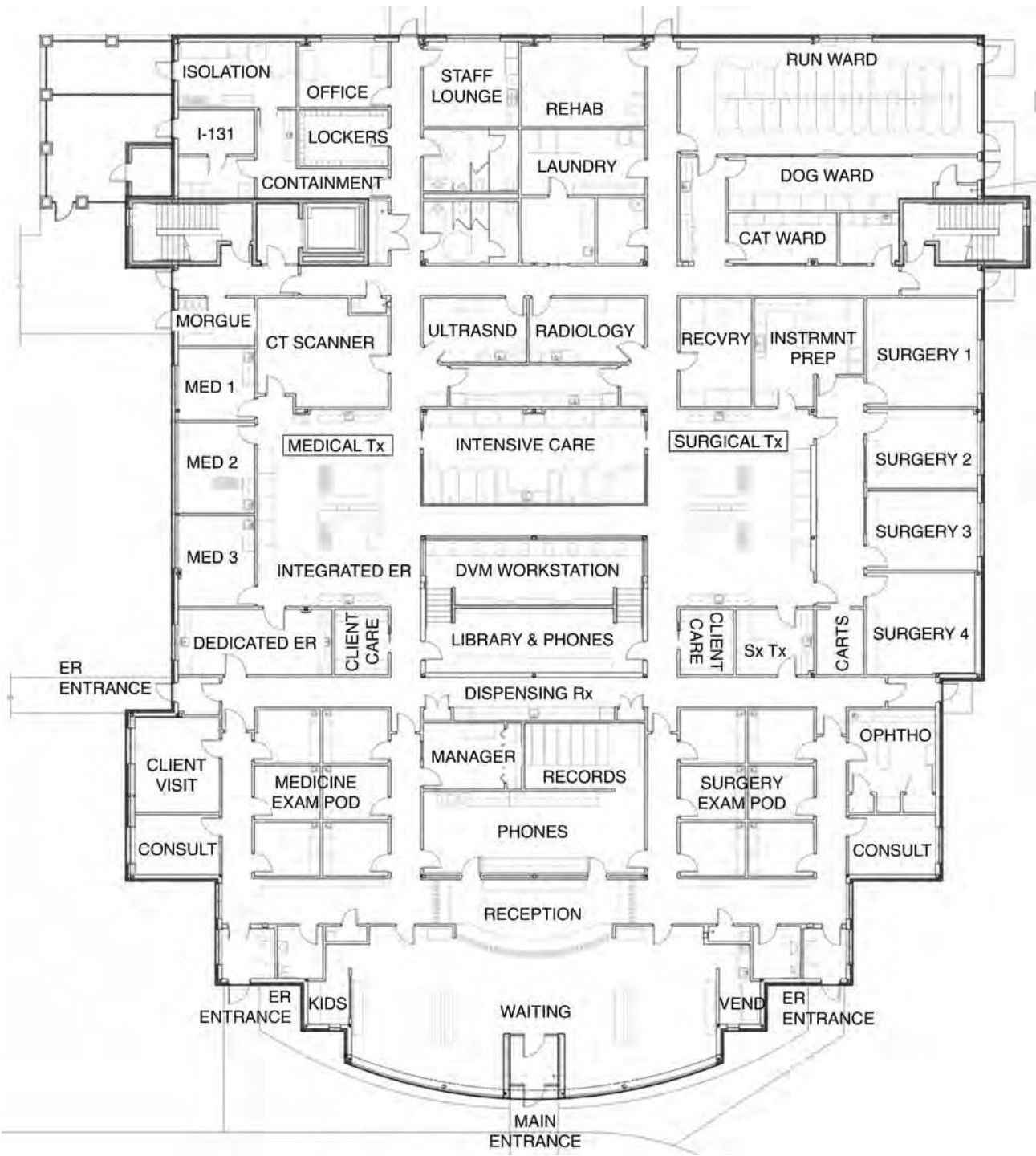


Figure 205.2 Hospital design for effective delivery of emergency services.

- 80% are staffed with a separate team of receptionists, 23% with care co-ordinators, 35% with dedicated kennel staff, and 45% with managers on duty at least part of the emergency shifts.
- 69% are structured as a single business, 31% are an association of multiple businesses.
- 21% of responding hospitals are owned by large corporations that own more than 50 practices, 11% by medium-sized companies that own 11–50 practices, and 20% by groups that own 2–10 practices.
- Ownership interest is held by all types of hospital personnel: 70% are doctors, 7% medical staff, and 6% managers.
- Caseload ranges from less than 1000 patient visits per year to over 20 000 per year. Dividing hospitals into four groups based on number of patient visits, the lower quartile sees 1000–3500/year, the second quartile 3500–6000/year, the third quartile 6000–12 000/year, and the upper quartile 12 000–20 000/year. Seven percent of hospitals have over 20 000 patient visits each year.
- 60% of the caseload is canine, 37% feline, and 3% avian and exotic.
- Staffing levels are highly variable and dependent on caseload. For each doctor on duty, there are typically 2–2.5 technicians, 0.3–0.5 receptionists (i.e. shared among 2–3 doctors), 0.5–1 assistant, and 0–0.5 care co-ordinators. The use of care co-ordinators and separate kennel staff increases with higher caseloads.
- An emergency doctor will typically see 5–10 cases on a weekday shift, 5–20 cases on a weeknight shift, 5–15 cases on a weekend day shift, 5–25 cases on a weekend night shift, and 5–30 cases on a holiday shift.
- 88% of emergency doctors have primary ICU patient responsibility when working an emergency shift.
- 83% of emergency doctors have surgical responsibility, with the majority performing procedures, wound repair, laparotomies, and management of penetrating wounds of the abdomen and thorax. Only 19% perform thoracotomies.
- Emergency doctors work full or part time; 70% are scheduled for 12–16 shifts per month.
- The vast majority of responding doctors have worked less than 25 years in emergency practice. Only 4% have been in emergency practice for over 25 years.
- 44% of doctors are paid by salary, 17% by the greater of salary or production, 24% by base salary plus production, 6% by production only, and 9% hourly.
- Over 70% of doctors receive benefits that include health insurance, dues and license fees, continuing education, paid personal days, and retirement plans. 10% participate in a formal profit sharing plan. 32% receive unscheduled bonuses.
- Emergency doctor income (from all sources) ranges from less than \$10 000 per year to over \$1 000 000 per year.
- Earnings from the practice of emergency medicine range from less than \$10 000 to over \$500 000 per year.
- 70–88% of doctors receive no additional income from general practice, teaching, training, administrative duties, or veterinary practice ownership.
- 78% of doctors have some level of ownership interest in their practice or their owner corporation.
- The majority of emergency practitioners average from \$300–600 per transaction, with a range from \$200–3000.
- Doctors give a passing grade for quality to themselves, their colleagues, their support staff, their equipment, the level of collaboration, and their practice overall.
- Doctors give <70% approval to their building, their owners, and their managers.
- Most emergency doctors plan to retire before the age of 60.

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Conflict in the Emergency Room*Jim Wohl, DVM, MPA, DACVIM, ACVECC**University of Connecticut, Storrs, CT, USA***Introduction**

Conflict can be defined as a form of competition for perceived or actual incompatible needs, goals, desires, ideas, or resources [1]. When managed constructively in the ER, conflict can harness intellectual growth, foster innovation, promote change, and even enhance relationships. Left unattended, conflict can be a destructive influence on patient care, profitability, and quality of life for ER personnel. The negative organizational consequences of a high-conflict work environment include internal competition, visible disputes, sabotage, inefficiency, low productivity, low morale, and withholding knowledge [2]. Consequences can be equally destructive to individuals. Resignation, absenteeism, going slow, complaints, legal suits, gossip, anonymous attacks, fear of loss of privacy, loss of dignity, and fear of retaliation and labelling are typical results affecting individuals. These individual concerns can be more acute for women, minorities, and non-traditionals who experience a greater risk of being stigmatized as troublemakers rather than as self-confident professionals [3].

The ER has many features that contribute to a high-conflict environment. Time-sensitive high-stake decision making on patient care, a high expectation for spontaneity, demanding clients, scarce resources, informal and formal hierarchy, shared responsibilities associated with shift transition, team-managed care, and high levels of uncertainty about the effect of medical interventions are just a sampling of contributory environmental characteristics of emergency medicine. Working long hours within this compassion fatigue-inducing milieu are highly trained and driven clinicians, administrators, technicians, and professional staff, many of whom are competitive by nature and may be drawn to veterinary medicine for deeply personal reasons involving their core values. In such an environment, embracing the inevitability

of conflict permits caretakers of the workplace culture to focus on diverting destructive conflict toward constructive ends.

Leaders in the ER with management and policy-making authority have special responsibility in transforming conflict. At the same time, nearly every individual, regardless of their positional authority, can influence the way conflict is managed although undoubtedly, some individuals will be more predisposed to collegiality than others. An understanding of the environmental factors of the ER, the nature of interpersonal conflict, and the role management can play in influencing a culture of conflict competence can be the tools for transforming destructive conflict in the ER.

Interpersonal Conflict

The interpersonal dimension of conflict within the ER setting is composed of the characteristics of the individual members of the emergency service. Each member's personal history, style of approaching conflictual situations, communication preferences, and values will affect the ways in which disputes manifest in the ER. When two or more people in the ER are involved in a conflict, the goals of the parties can be analyzed as content, relationship, identity, or process oriented [4].

Content goals refer to the substance of the disagreement or the topic of what is being disputed. For example, during a dispute between two clinicians over patient management decisions, the parties typically describe the problem in terms of content (the conflict is over the best treatment for the patient). Generally, conflicts that solely involve content goals are resolvable or, even when left unresolved, are handled professionally and are rarely destructive to the organizational culture or co-workers (e.g. agreeing to disagree). Indeed, when a conflict is destructive, it is likely that other goals, in addition to the content, are present for those involved even though the

parties themselves would describe the conflict as having to do solely with the content.

In such cases, some combination of *relationship*, *identity*, and/or *process* goals is almost always present. Relationship goals are emotionally based and center on hierarchy, power, or social roles between the parties in conflict. Often, a sense of injustice, offense, and victimization is an unspoken driver of the conflict (that, again, is usually described in terms of content only). A relationship-based conflict driver for a clinician in a dispute over a treatment plan may be the perception that the counterpart clinician's decision to change the treatment only occurred because of another unrelated problem in their relationship (e.g. rivalries, prior offensive interaction, differences in philosophical approaches).

Identity goals involve a party's self-esteem, face, or social identity and can be quite powerful drivers of conflict and are typically unarticulated. Identity goals imply a psychological and emotional basis where the importance of the conflict is connected to how one sees oneself. For the clinician driven by identity goals, the change in treatment plan represents a judgment of the quality of their expertise, or even their value as a human being.

Process goals as drivers of destructive conflict involve how decisions are made or how conflicts get resolved. In an organizational setting like an ER, process goals may involve perceived inconsistency in following policy, differing opinion on best practices, and lines of authority. In the preceding example over treatment plans, a process-oriented driver of the conflict may be disagreement as to whether treatment plans should be guided by evidence-based best practice or the autonomy of a clinician's judgment.

In particular, relationship and identity goals, when projected onto the content of a dispute, can explain the severity or rigidity of a party's response.

Further complicating the analysis of interpersonal conflict is the fact that each party to a dispute is driven by their own personal combination of goals (Figure 206.1). Despite the variability of the combination of goals, some

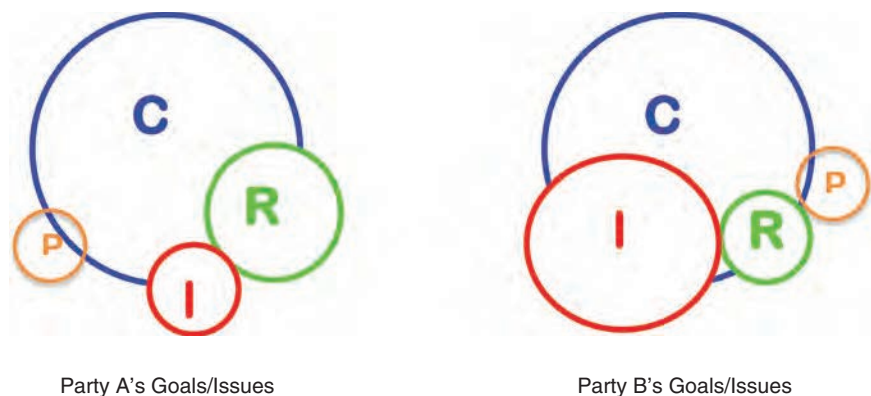
people can seemingly specialize in one or another type of goal. Analysis in the conflict literature describes threats to "core concerns" such as appreciation, personal autonomy, feelings of affiliation to colleagues, personal status, and professional role as drivers of interpersonal conflict [5].

In a given conflict, an individual's conflict style can be understood as a balance between (a) how concerned the person is about achieving their preferred outcome in the dispute, and (b) how concerned he or she is for their counterpart's ability to achieve their preferences [6]. For example, a team member who is highly focused on achieving their own outcome but negligibly interested in their counterpart's interests is said to have a *competitive* conflict style (Figure 206.2). Conversely, one who is mostly concerned with their counterpart's satisfaction at the expense of their own concerns would demonstrate an *accommodating* style. An *avoiding* style suggests that the person is most interested in averting a conflict to the degree that they will ignore their own potential beneficial outcomes as well as those of their counterparts.

Compromising and *collaborative* styles reflect approaches that share some combination of pursuing one's own and the counterpart's goals with an important difference. An individual with a collaborative style seeks to optimize the outcomes for themselves and their counterpart and this approach necessitates more time and effort in discussing the range of outcomes sought by each party. A compromise mode instead seeks an equal or fair outcome in which the attainment of goals for each (or, often, the lack of attainment for each) approximates one another.

It is helpful in understanding this aspect of conflict theory to know that although individuals tend to gravitate to one particular conflict style as a regular response, all people are generally capable of demonstrating each of the five conflict styles depending on the situation. Broadening the exposure of conflicts outside the workplace, it's easy to imagine various circumstances when one might

Figure 206.1 Often, conflicts are presented about a specific topic or issue – a content issue. However, there are almost always underlying relational and identity goals and often these categories of issues overlap. C, content; I, identity; P, process; R, relationship,



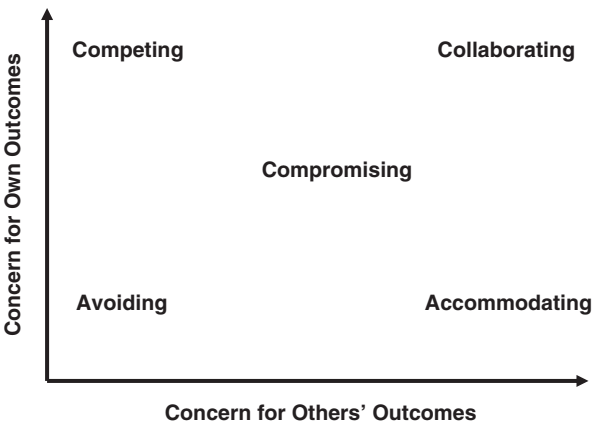


Figure 206.2 The conflict style demonstrated by a party in conflict reflects a balance between two competing goals: concern about one’s own outcomes and concern about the counterpart’s outcomes.

choose any of the styles (Table 206.1). Exploring the style options one has in responding to conflict or examining the appropriateness of the styles exhibited in a past situation can be a very helpful tool towards transforming workplace conflicts. Intuitively, most people can imagine

Table 206.1 Features of various conflict styles that might be adopted by a party to a conflict and characteristics of the conflict that are appropriate for each style. Evaluating conflict styles can elucidate perceptions of the conflict and the relationships involved or whether the adopted style is appropriate for the conflict situation.

Conflict style	Features	When appropriate
Avoiding	Quick, no effort, leaves possible solutions unachieved	Unimportant issues Ongoing relationship unimportant No time unavailable for engagement
Competitive	Quick, minimal to moderate effort, leaves counterpart goals unmet	Important issues Ongoing relationship unimportant Little time available for engagement
Accommodating	Quick, minimal to moderate effort, leaves own goals unmet	Unimportant issues Ongoing relationship important Little time available for engagement
Compromising	Quick, minimal to moderate effort, goals partially met for both	Important issues Ongoing relationship important Some time available for engagement
Collaborative	Takes time, maximal effort, goals optimized for both	Creative solutions needed for important issues Ample time available for engagement

what different actions they may have adopted, how the communication would have changed, and in what ways the trajectory of the conflict would have changed if one of the parties had chosen an alternative style in approaching a past conflict.

Other perspectives from the conflict theory and communication literature can illuminate the nature of interpersonal conflict in the ER. Incompatibility of communication styles contribute as much to conflict as the intersection of conflict styles. Communication styles have been described as action oriented, process oriented, people oriented, and idea oriented [7,8]. When discussing a work-related plan in the ER (e.g. case rounds, therapeutic planning, new facilities, training of staff), a person’s communication style and language reflect the aspects of the topic that is most important to them (Table 206.2). Differences in communication priorities during such interactions can be fertile ground for conflicts. Differential power between interlocutors due to seniority, position, expertise, or decision-making responsibility can amplify this stylistic miscommunication. Indeed, initial assessment of new employees’ competence or ability to “hit the ground running” is often more a reflection of their communication compatibility with supervisors than their task-related capabilities. Contrasting communication styles can obviously exacerbate attempts at dialogue during interpersonal conflicts.

Enhancing Constructive Conflict

Leadership’s role in fostering a culture of conflict competence focuses on controlling the environmental stressors that foment conflict where possible, establishing good management practices, and empowering ER team members with the skills and abilities to respond to conflicts constructively. Practice considerations regarding workflows, proper staffing, and clear lines of authority can mitigate the time stress, chaos, and uncertainty that breed conflict. In-depth awareness of and a prophylactic approach towards veterinary regulations and employment law are obvious ways to limit destructive conflict. Adhering to clear and consistent practices regarding decision making, rather than an *ad hoc* style of change management, can also be a key stress reliever for staff. Understanding what types of decisions will be made by what type of process (e.g. group decisions, decision by a single leader after soliciting input, feedback system for revisiting decisions) is often more important to the environment than the actual decisions themselves.

Attention to identifying patterns where conflicts commonly arise can reveal to leaders in the ER where policy or practices require change or clarity. For example, the potential for conflict between people exists whenever

Table 206.2 Typical characteristics of people and the language used in four communication styles. Differences in communication styles can be a source of conflict itself as well as explaining how attempts to resolve conflicts through dialogue can escalate conflict.

Orientation	They talk about...	They are...
Action	Results, responsibility, objectives, feedback, performance, experience, productivity, challenge, efficiency, achievements, moving ahead, change, decisions	Pragmatic, direct, impatient, decisive, quick (jumping from one thing to another), energetic, challenging of others
Process	Facts, trying out procedures, analysis, planning, observations, organizing, proof, controlling, details, testing	Systematic, logical, factual, verbose, unemotional, cautious, patient
People	People, self-development, needs, sensitivity, motivations, awareness, teamwork, co-operation, communications, beliefs, feelings, values, team spirit, expectations, understanding, relations	Spontaneous, empathetic, warm, subjective, emotional, perceptive, sensitive
Idea	Concepts, what's new in the field, innovation, creativity, interdependence, opportunities, new ways, possibilities, new methods, grand designs, improving issues, problems, potential alternatives	Imaginative, charismatic, difficult to understand, ego-centered, unrealistic, creative, full of ideas, provocative

opposition is expressed towards an individual or group. The focus of opposition may be ideas, behaviors, or decisions. Opposition is expressed across the dimensions of clarity (direct or indirect opposition) and intensity (high or low intensity) [9]. Highly conflict-competent work environments typically utilize direct and low-intensity communication when expressing opposition rather than other combinations of expression (direct-high intensity, indirect-low intensity, indirect-high intensity).

Voluminous resources on effective management practices and leadership skills can assist leaders in aligning management's role with the mission of the ER [10–12]. The salutary effects of coherent management style and workplace policies can be supplemented with specific approaches that empower all team members.

1. Provide negotiations skills training (or mediation training) to all team members with supervisory responsibility and non-supervisory staff who express an interest. Negotiation and/or mediation trainings can be completed in short frequent sessions, are fun, and instill effective communications skills that focus on surfacing people's interests when conflicts arise. Transitioning the dialogue from one of blame and demands for some desired outcome (positions) toward dialogue based on what people want and why (their interests) can be the most effective method to pivot conflict toward a constructive experience [13].
2. Develop and then articulate to team members specific methods by which leadership will respond to episodes of unprofessional behavior [14]. Disciplinary responses have three components: the swiftness with which they are delivered, the certainty that they will be delivered, and the severity of the response. It has been argued that when swiftness and certainty are constantly present, severity becomes the least important component [15].

Equally important is empowering non-supervisory staff to confront episodes of unprofessional behavior informally themselves. Excellent trainings, videos, and short articles are available for staff [16]. A cornerstone to empowering both management and non-supervisory staff to confront unprofessional behavior in the workplace involves distinguishing whether the behavior is an isolated episode, a pattern of behavior, or focused on the relationship between the people involved in the unwanted behaviors [17].

3. Incorporate communication, practice management, conflict management, and leadership articles or topics into the in-house continuing education framework. When done sporadically, such sessions can be a welcome diversion from the medical or hospital policy-oriented topics and help reinforce commitment to conflict competence.
4. Reward team members who contribute to civility and respect in the work environment. Identifying this contribution as a specific domain in annual performance evaluations (rather than a component of a more vague categorical dimension such as "works well in a team") signals that handling conflict constructively is a priority and provides acknowledgment to those who are enhancing conflict competence in the ER.
5. Communication protocols, consensus statements, and Circles can be effective tools for smaller units within the ER setting to break through long-standing negative behaviors affecting morale. Communication protocols are a form of consensus-building exercise that focuses on answering three or so process-oriented questions on how to respond when someone in the unit is causing a problem for another [18]. The goal is for the unit to arrive at a consensus agreement to follow the process they develop in the

protocol. A Circle is a central element of restorative practices and formalizes a way to discuss a problem or address harm that has occurred to a team member [19]. It is essential that participation in these practices is voluntary. They are likely to do more harm than good if the people involved do not buy in or the practice is imposed on perceived problem units. When embraced voluntarily, they can be transformative to units plagued with destructive conflict.

Conclusion

Managing conflict in the ER requires attention to the environmental setting inherent to emergency practice,

the people working in the ER setting, and the ways in which management and leaders can influence the workplace culture. Despite the challenges in high-conflict ERs, remaining mindful of two realities provides some degree of optimism. First is that the goal is not to eliminate conflict but rather to capitalize on its occurrence and harness conflicts toward constructive ends. The second is the fallacy that “everyone needs to be on board” for effective culture change to occur. Results of research in conflict studies and game theory suggest that if just 25% of people in a given work environment are committed to co-operation, significant culture change can ensue over time [20,21]. Leaders in the ER can therefore provide their greatest service in allowing those 25% (or hopefully more) to thrive.

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Maximizing Communication

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Core Communication Skills

Too often, the ability to communicate with clients effectively is considered an inherent skill – you either have it or you don't. However, a multitude of studies in the field of human medicine, from all over the world, have shown that the skills involved in communication can be defined and, indeed, learned [1–6]. Several constructs exist by which to outline and describe techniques for communication. This chapter will focus on the four core communication skills: open-ended questions, reflective listening, empathy, and non-verbals, and how they can be used in an ER setting. Applying the skills requires intent; in interacting with the client, one must attend not only to *what* is being said but *how* it is being said. Studies in human medicine, including in the emergency setting, confirm that patient satisfaction and clinical outcome are associated with the doctor's communication skills [7–15].

Open-Ended Questions

Open-ended questions start with “what” or “how” and they invite the client to tell the history in their own words. Open-ended questions are not only important in obtaining an accurate history, they also greatly increase the client–veterinarian bond by allowing a client to tell their story, a key part of feeling understood and valued as a person. This “story telling” does not need to be very long; using other core skills such as reflective listening and empathy, a veterinarian can guide the answers in situations where they may be lengthy. Very often, open-ended questions save time in an interview, as they allow the veterinarian to understand the true nature of the client's concerns without misleading answers that the use of only closed questions may provide. Closed questions may be necessary when the case presents in crisis; these questions can be softened by a quick empathy statement and then signposting, or informing of what will be

happening. “I can't imagine how scary this is for you. I'm going to need to ask you a series of quick questions so we can get started taking care of Bertie. I'll send a technician to get a more complete history and give you an update as soon as possible; that may be 30–45 minutes.”

Open-ended questions are not just for history taking; they play a vital role in discussions of treatment options and prognosis and can help prevent misunderstanding in difficult conversations. For example, rather than asking “Are you thinking about euthanasia?” and having an owner get upset because they were not, ask “What are your thoughts about options from here?” Also, “ask rather than tell” is a great rule of thumb. When a new diagnosis has been made, asking a client what they know about the disease, rather than jumping into a description of the problem, can save time and avoid unnecessary client education. This asking not only allows the clinician to begin the discussion at an appropriate level, but also importantly shows the client that their knowledge is valued; this leads to a better client–veterinarian bond as the client feels treated as a unique and important individual.

Reflective Listening

Reflective listening involves paraphrasing what the client said or how they appear (which relates to empathy). The classic stem, or starter, for a reflective statement is “What I hear you saying is...”. Other stems may feel more natural and include “So, you are saying...”, “It sounds like...”, “You are...”. A complete statement could be something like: “It sounds like you are worried that Turner is having a hard time breathing right now.” The client can then correct if that is not their main concern, or if correct, can feel a sense of relief or gratitude that the clinician listened to and understands them. Reflective listening allows for improved information accuracy between the client and the clinician and also improved connection between them.

Empathy

Empathy is the skill of imagining standing in the other person's shoes and showing that imagining back to the person. Empathy does not mean one feels what the client feels, but rather that one can try to imagine what the client has or is experiencing. Showing empathy is a key part in building rapport with a client. Just feeling empathy is not enough; the client will not know the clinician has it if they do not show it. Empathy can be shown in both verbal and non-verbal ways. Reflective statements can be used to show empathy verbally. Expression of empathy by the veterinarian has been shown to correlate with improved client satisfaction [16]. When thinking about how to show empathy, consider the three key points of having a client know that they are seen, heard, and accepted.

"Being seen" means not only physically seen, but seen as an individual person and not just a client. Ways to reflect back to the client that they are seen are to comment on a unique aspect of that individual unrelated to their pet's medical concerns, such as their clothing (for example, if they are wearing a sport team's logo), their pet's collar, etc. It is also important that the client knows they are seen as a person when it comes to the medical issues, and that their emotions about these issues are noticed. A good way to show this is by verbally stating what is seen: "You seem worried," "You look very scared." While this may seem awkward or obvious at first, clients appreciate having their concerns noted and bond more with the clinician who shows it.

Strong client emotions are daunting. A common fear is that the client's emotion, once acknowledged, will escalate. In actuality, validating the client's emotions often allows them to focus back on the situation at hand and move on in the discussion about their pet. A statement as simple as "It must be so hard to hear that your beloved pet has a life-threatening condition" can be grounding for a client and allow them to refocus on the medical conversation. Other non-verbal means to show a client they are seen is to use an appropriate speaking tone and rate, such as quiet, slower speaking in times of sadness. Handing a box of tissues to a crying client is an effective and helpful means of showing empathy.

"Being heard" is similar to being seen; the veterinarian not only needs to listen to the client but needs to show them that they are heard, and ideally understood. Saying something like "It sounds like a terrible night" is both quick and effective at showing empathy.

"Being accepted" is an inherent desire in everyone, and this acceptance will help an owner to be open and honest with the clinician and also to voice concerns or questions that they may be embarrassed to mention otherwise. It also helps clients to work through difficult problems and

see the veterinarian as supportive as opposed to adversarial. There are several categories of statements that can be made to help a client feel accepted, and intentionally using these will take conscious effort but can be of great benefit in improving the client-clinician bond. These types of statements include:

- non-judgmental comment: "You were in a very difficult situation."
- normalizing comment: "We see many dogs that escape from their yard and get injured."
- self-disclosing comment: "My cat gets into fights too."

Intentionally expressing empathy becomes even more critical with clients for whom it is difficult to naturally feel empathy; verbally showing acceptance via the above phrases can help the client-veterinarian bond even for clients with whom it is very hard to bond.

Non-Verbal Aspects

Non-verbal cues of both the veterinarian and client play a role in all discussions. The stress of working in the ER may be portrayed to clients non-verbally, and unintentionally, by the clinician and can heighten the challenges in these communications. Self-awareness and control of body position, speaking tone and volume, eye contact, etc. are crucial to help create a feeling of safety and comfort for the client. Shaping these non-verbal attributes adds no additional time to the visit, and the improved atmosphere will help clients to develop trust and make decisions more quickly. Monitoring the client's tone of voice, rate of speaking, and physical stance, such as clutching the animal to their body, is an excellent way to assess the client's level of comfort with and comprehension of what they are being told. If a disconnect is noted between the client's words and their non-verbal cues, the non-verbal message is more accurate and needs to be addressed. If the response to "How does that sound?" is a hesitant "Fine" with eyes looking at the floor, the client clearly is not fine with things. Paying attention to that fact and opening discussion about concerns at that time will often save misunderstanding and upset in the future.

Breaking the News/Presenting the Diagnosis

Clients need time to adjust to the idea that their pet has a serious illness or injury, yet in an ER setting such time may not be available. Small "sound bites" work best, especially for people who are feeling overwhelmed. For example, prepare the client for the most likely diagnosis before test results are back. "One of the most likely causes of such a big belly like this is a twisted stomach.

We would like to take x-rays; I'll let you know what we find as soon as I can." Explaining things in layperson's terms is always important in communication with a pet owner, but it is even more critical in the highly charged discussions surrounding emergency situations. Clients can easily become overwhelmed by the crisis, and may be too distraught or embarrassed to ask for explanations about what they don't understand.

Offering Options

Once the diagnosis is made, it is still important to keep the information provided on a basic level. Even with prior warning that the diagnosis could be serious, some clients may be shocked and not be able to take in all they are being told. Providing information about treatment and prognosis should be done verbally and, ideally, in writing to make sure that the facts are clear. While clients may seem to understand, because much of the information may be new or frightening, they may not remember what they are told. Be prepared to repeat and use reflective listening and empathy during this difficult time for the clients.

In discussing treatment options, it is important to present a range of options, and also to balance presenting options with not overwhelming an owner with too many choices. Once some information has been provided, use open-ended questions to ascertain a client's thoughts or more specifically goals or limitations. This question can be phrased with an opening empathy statement: "I've covered a lot of information at what must be a very difficult time for you. What are your thoughts about the options I presented?" "What are your goals for treatment?"

Specific Pointers

When asking a client if they have questions, an open-ended "What questions do you have for me?" is much more welcoming and likely to elicit an embarrassing or reluctant concern than the close-ended "Do you have any questions?" While this open invitation may seem a recipe for disaster in the ER, and would not be recommended when a critical case is ongoing, many clients state that they do not have questions, and the appreciation generated by the openness will be an asset in future interactions.

Lastly, just say no to "but"! Be conscious of the use of the word "but", especially after an empathy statement, and replace it with "and" or separation of the sentence into two sentences. "But" negates the empathy – think of it as saying "but I don't care." "I can see how hard it is for you to leave Fiona overnight, but it's what's best for her" versus "I can see how hard it is for you to leave Fiona, and it's what's best for her." Both of these statements are true, no "but" is needed. "However" is just a "but" in a tuxedo; in other words, "however" also argues against the empathy.

Conclusion

Applying core communication skills in an emergency setting can help provide comfort to a pet owner, allow the clinician to get accurate information, guide diagnostic and treatment decisions, and overall allow the patient to be diagnosed and treated in a timely manner. These skills will also increase the bond clients have with the ER clinician and thus increase client satisfaction in a difficult time.

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Basics of Clinical Study Design

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Introduction

The anatomy of designing clinical research usually includes six major areas: the research question, choosing the appropriate subjects, planning the measurement, choosing the type of study to answer the question, analyzing the data, and writing the final manuscript for publication.

The Research Question

The clinical research question should pass the test of “Is the answer to this question useful to the care of our patients? Will the answer lead to better care of our patients or will it provide insight into the pathophysiology of disease?” The question doesn’t have to appeal to everyone but it should be a question that will at least provide useful information, however you define “useful.” Your clinical question should be succinct and straightforward. It should ask a very pointed question and should not be vague. For example, “Does radiographically determined vertebral heart size predict the presence of heart disease in cats with respiratory distress?” or “Does intravenous normal saline lower potassium faster than intravenous Normosol-R in cats with urethral obstruction?” Try to avoid vague terms and be as specific as possible. Starting with a clear and answerable question makes the research project that much easier to perform and the results easier to interpret.

Not all research projects involve specific questions. Some of the most common studies in veterinary clinical medicine are purely descriptive reports of disease conditions. Although this type of study is relatively low in the hierarchy of evidence-based medicine, clinical veterinary medicine has not fully characterized even the most common diseases. These types of clinical reports form the basis for the generation of hypotheses regarding etiology, diagnosis, prognosis,

and therapy which can be tested with analytic studies (see below).

While developing the research question, you should review the electronic library databases to see if this question has been answered in the clinical literature. There is no sense in reinventing the wheel but corroboration of previous evidence does have value. Unfortunately, journal editors and reviewers are not always open to corroboration of previous studies and you may end up performing a study that is rejected “because it has been done before.” If an appropriately performed literature search does not come up with a study that has answered your clinical question, then clinical research to answer that question appears warranted.

Choosing the Appropriate Subjects

One of the major goals of clinical research is to infer the findings from the animals in the study to the general population of animals that have that condition. This is called “external validity” or “generalizability.” No one necessarily cares what happens to one set of animals if it only happens to that specific group. What clinicians care about is whether the study findings can be applied to their clinic patients with that condition. Therefore, selection of the animals to be studied should keep this generalizability in mind. For example, a study of diabetics referred to a teaching hospital may not be a good group to generalize to diabetics seen in general practice. You must keep in mind the target population you are trying to generalize to and make sure that the inclusion and exclusion criteria help meet that goal.

To clearly specify the group of animals to study, you must thoroughly define the parameters that must be included – whether they need to be male or female, neutered or intact or both, age range, breeds, condition (how that condition is determined). For example, in a study performed by Clifford et al. entitled “Magnetic

resonance imaging (MRI) of canine focal splenic and hepatic lesions” the patient population was clearly specified as follows:

Twenty-five cases were prospectively enrolled for MR imaging at the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania (VHUP). Criteria for case recruitment included an abdominal ultrasound, owner consent for MR imaging, and either lesion biopsy or fine-needle aspiration. Case selection was also based upon the availability of MR imaging and patient’s health status, specifically, critical patients requiring immediate surgery were not selected due to timing constraints of MR imaging accessibility.

The last statement, though not specifically stated as such, is an exclusion criterion. There were animals that filled all the inclusion criteria but had to be excluded because of how critically ill they were. You can see from these specifications that you would have to put in the discussion how this study could apply to critically ill patients, because these patients were not part of the study group. You can see, based on the principles of MRI, that justification for this generalization can easily be made, but again, it was not proven by this study.

Once the inclusion and exclusion criteria have been specified, then you must identify the accessible population. Is it all animals that present with the condition to your clinic or would it be too difficult to get all animals? Perhaps you only need a representative sample. It is important that if you are not taking every case that fits the inclusion and exclusion criteria, you must be careful that you truly have a random sample of your accessible population; otherwise you could end up with a biased sample that is not representative of the population to which you want to generalize your findings.

Planning and Recording the Measurements

When planning your study, it is important to determine which variables will be assessed; these will depend upon your research question and study population. In general, when in doubt about whether you should record something, record it! You can always eliminate it later, but you can’t add data that you didn’t record (particularly in a prospective study).

The types of variables most commonly used in clinical veterinary research are categorical variables and continuous variables. Categorical variables are unordered categories such as sex, blood type, breed, dead, alive, etc. These variables are statistically described using counts, proportions, percentages etc. The most common statistics assessing categorical variables are relative risk, odds

ratios, chi-square, regression, and Fisher’s exact test. Ordinal variables are categorical variables but there is an inherent order to the categories. Examples include degree of pain, body condition score or anesthetic risk category. Descriptive statistics for this type of variable include what was mentioned for categorical variables but also can be described by median and minimum and maximum values. These can be analyzed using statistics mentioned for categorical variables as well as the Mann–Whitney (Wilcoxon rank sum test) test and rank correlation.

Continuous variables have an infinite number of values (e.g. weight, rectal temperature). Discrete variables have a finite scale (e.g. heart rate, number of times vomiting per day – you can’t have half of a heart beat or one-third of a vomiting episode). Discrete variables that are ordered and have a large number of possible values can be statistically treated similar to continuous variables. Depending upon whether the data are normally distributed or not, continuous and ordered discrete variables can be described by mean and standard deviation, median and quartiles or range, and statistically analyzed using t-test, Mann–Whitney test, Kruskal–Wallis test, analysis of variance, correlation, and regression.

In general, a continuous or ordered discrete variable should be recorded as such and not dichotomized. Dichotomizing loses information. Dichotomization can always be performed later even if the data are recorded as continuous or ordered discrete, but one cannot convert data recorded as dichotomous or categorical into continuous or ordered discrete.

For most statistical programs, data recording on an Excel spreadsheet works well. If you are working with a statistician, consult with him or her regarding how the data should be recorded on the spreadsheet prior to entering the data.

Choosing the Study Design

There are a variety of different clinical study designs that fall into two general types: analytic studies and descriptive studies. Analytic studies include the experimental study, prospective cohort study, retrospective cohort study, and case control study. Descriptive studies include analyses of secular trends, case series, and case reports. Each of these studies provides different types of information and levels of evidence.

Case Report

A case report is a clinical description of a single patient. Its primary use is for hypothesis generation and it has limited generalizability (or how much or how reasonable

it is to apply the findings in this one case to the overall population of animals with that condition). Case reports in the veterinary literature tend to describe unusual conditions or techniques.

Case Series

A case series is a clinical description of a number of animals with a disease. This type of study is primarily used to characterize an illness or a technique. Its main limitation is that there is no control group and therefore you cannot determine which factors in the description are unique to the condition. Case series are relatively common in the veterinary literature.

Analysis of Secular Trends

Analysis of secular trends is a study comparing geographic and/or time trends of a condition to trends in risk factors for that condition. Its primary use is for rapid and easy support for or against hypotheses, but the primary limitation is that you cannot differentiate among those hypotheses consistent with the data. This is not a commonly used study design in small animal veterinary medicine.

Case Control Study

The case control study is one of the more commonly used analytic study designs in clinical small animal medicine. It compares diseased patients (cases) to non-diseased patients (controls), looking for differences in risk factors. It is primarily used for the study of any number of risk factors or etiologies for a single disease. It is particularly useful for studying rare diseases. One of the biggest limitations is trying to avoid specific biases. In addition, selecting proper controls can be very challenging.

Cohort Study

This type of study is not commonly used in veterinary medicine. It compares animals with a risk factor or exposure to other animals without that risk factor or exposure, looking at differences in outcome. This study design is used when evaluating any number of outcomes from a single risk factor or exposure. Depending upon the length of time between exposure and outcome, this type of study, when done on a prospective basis, can be very prolonged.

Experimental Study or Randomized Control Trial

In an experimental study, the investigator controls the risk factor/exposure of interest and randomization is

generally used. This study provides the most convincing evidence of causality. An excellent example of this type of study is the randomized control trial, the gold standard of clinical study designs, in which a group of animals are randomly allocated by the investigator to two or more treatment groups and the outcomes evaluated. Theoretically, if performed properly and with a large enough sample size, the groups will only differ with respect to the treatment they have been assigned and nothing else. The major disadvantage to this type of study is cost, depending on what you are studying.

Retrospective Versus Prospective Studies

Studies can also be categorized by the timing of data collection. In a prospective study, data are collected by looking forward and obtaining new data after the start of the study. Retrospective studies look “backward” at data that have already been collected for other reasons. The advantage of prospectively collected data is that the nature of the data, the definition of inclusion and exclusion criteria, the definitions of signs/symptoms and other factors can be determined ahead of time and are consistent throughout the study. The variability in retrospective studies tends to be much greater because the data were collected for reasons other than for the purpose of the study at hand. This variability can decrease the power (the ability to detect a difference between two groups) of the study. In addition, it is more difficult with retrospective studies to determine the directionality of events or what occurred first and what happened later.

Many of the different study designs described above can be performed on a retrospective or prospective basis, except for randomized clinical trials which must be performed in a prospective manner.

Analysis

To gain the most from the data of a study, you should be fairly familiar with statistics. Most statistical evaluations of veterinary clinical studies are relatively straightforward, but inappropriate application of statistics can result in erroneous conclusions from the data. In addition, you should plan in advance what should be analyzed and things that are analyzed should make biological sense. Analyzing anything and everything without any rationale enhances the probability of a type I error (finding something significant when it truly is not). Planning in advance what should be analyzed and limiting it to what makes sense will minimize errors.

If you decide to analyze variables that are a *post hoc* decision, correction to a more rigorous P-value for those extra multiple comparisons may minimize type I error.

There are different thoughts on multiple comparisons but the author's philosophy is that if you had a prior hypothesis about certain variables, then P-value comparison adjustments for those comparisons should not be necessary. Opinions differ regarding this point.

Presenting the Results

Once you have performed your study, collected the data and analyzed it, you must report your findings. You should choose a journal that is appropriate for your topic and will capture the readers who would benefit most from your findings. Once you have decided which journal, you should read their "Instructions to Authors" so that you can format your manuscript to their specifications. It is much easier to do this before beginning writing because journals vary in their format style and how data should be reported.

The *title* of your manuscript should accurately represent your study. The *abstract* should be a short and concise synopsis of the paper. It should be to the point, yet adequately describe the study design, what was studied, the results, and pertinent conclusions. The *introduction* should bring the reader rapidly up to date with what is known about the topic of the manuscript. It is not meant to be a review of all the literature on the topic. The goal of the introduction is to "build a case" for why the study was performed. It should be concise and the information should be directly relevant to the objective of the study. The final culmination of the introduction should be a statement of the purpose or objectives of the study.

The *materials and methods* should be thorough and clearly stated. The goal of materials and methods is to give the reader the ability to repeat the study exactly as it was performed. Materials and methods generally include

explicitly stated inclusion and exclusion criteria for the animals in the study and how the animals were initially identified. A clear description of the study design and all parameters that were evaluated is also an integral component of this section. Explicit description of analytic methods used in the measurement of certain parameters should also be provided or referenced appropriately to the original study that developed the assay. Statistical methods are also described in the materials and methods section and should include all tests performed.

Results should have a logical presentation to them and are most easily presented in "chunks" of related data. The best papers are ones that are focused on their objective and collect data relevant to their objective or hypothesis. Interpretative statements do not belong in the results section and are more appropriate to the discussion section.

The first paragraph of the *discussion* should summarize the findings and significance of the study. There should be organization to the discussion and it should follow a logical order and not jump from point to point. Many authors follow the order of how the results were presented. The discussion points should be focused on the findings of the study and their significance. Conclusions should be limited to the facts provided by the study and anything beyond that should be explicitly stated as conjecture or speculation by the authors. It is allowed and often helpful for the authors to provide speculation about the findings, as they are often the experts in the area of study. Any discussion about no difference or statistically non-significant findings in the study should include information about the power of the study. Without a discussion on power, any discussion of no difference between groups should be viewed with caution. Finally, many discussions will introduce possible future studies of interest based on their results and conclusions.

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Designing and Participating in Clinical Trials

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Clinical Trial Design

Because of the potential to minimize biases, randomized controlled clinical trials (RCTs) are the “gold standard” study design methodology by which practitioners make decisions about the efficacy of interventions, such as drugs, devices or procedures studied for diagnostic, therapeutic or prophylactic value. Therefore, the RCT, more than any other study design methodology, can have a powerful and immediate impact on patient care. Whether the results of a clinical trial are truly unbiased, however, depends on the many features of how the trial was designed and implemented.

Controlled Clinical Trial Design

Defining the Study Population

Ideally, study subjects in a trial are representative of patients routinely seen in practice. Narrow inclusion and exclusion criteria confine enrollment to a subset of patients with the disease. This makes analysis of results more straightforward (internal validity) but may impose limitations on how useful the results are to a practitioner (generalizability).

Balancing internal validity with generalizability occurs early in trial protocol development. Internal validity is always the primary concern, because generalizing results of an invalid study, one with biases in design or uncontrolled confounding factors, is not useful. Figure 209.1 describes the progression of defining the study population from the reference population to the actual study participants, with cats with urinary obstruction as an example. Describing the inclusion and exclusion criteria for the study and documenting the number of qualified subjects whose owners opt not to include their animal in the study, along with their reason for choosing not

to participate, allows the reader of the study to decide whether the results are generalizable to the population of animals that they regularly treat.

Defining the Control Group

Placebo-treated controls are often ideal, as they can be used to obtain an unbiased estimate of the effects of an intervention by subtracting the effects in the control group from the effects in the treated group. The control group may receive placebo only or may receive standard of care intervention in addition to placebo. How the control group is defined is determined by the question the study is intended to answer, how the intervention is intended to be used in practice, and the characteristics of the study population which may make a placebo-only control group impossible or unethical.

Assignment to Intervention Versus Control Groups

Randomization minimizes bias in the assignment of animals to intervention or control groups by ensuring that each study subject has the same chance of being placed in either group. Then, with an adequate sample size, the study groups tend to be comparable with respect to all variables except for the intervention being studied. Selection bias occurs when study subjects with one or more influencing factors appear more frequently in one study group than in another. For example, if younger age is associated with better outcome in dogs with gastric dilation-volvulus (GDV) and the proportion of younger study subjects is greater in the intervention group than in the control group, there could be an observed benefit of the intervention that did not really exist. Randomization ensures that dogs of every age are evenly distributed amongst the study groups.

The ultimate power of randomization is that even factors that are not known to be important at the time the trial is initiated end up being evenly distributed amongst

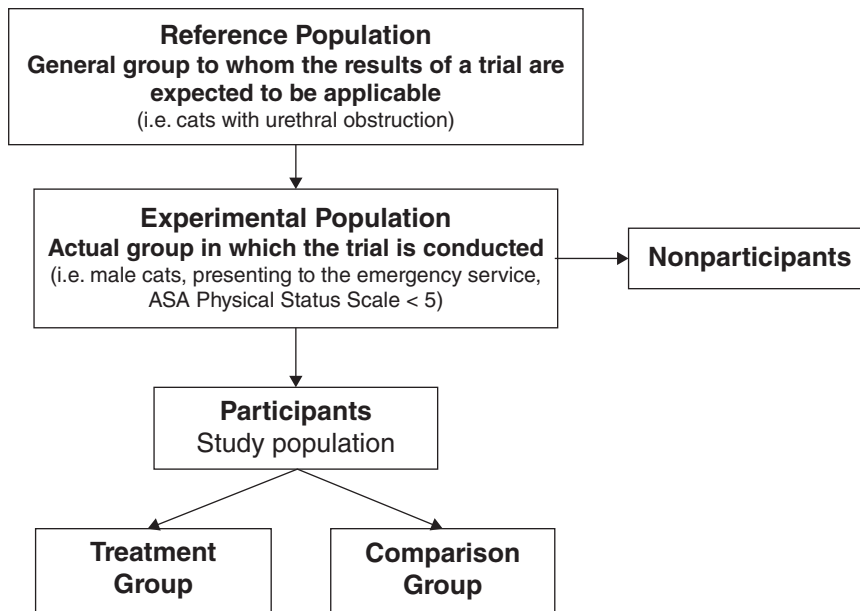


Figure 209.1 The progression of defining the study population from the reference population to the actual study participants, with cats with urinary obstruction as an example. Describing the inclusion and exclusion criteria for the study and documenting the number of screened subjects not enrolled, along with the reason for non-enrollment, allows the reader of the study to decide whether the results are generalizable to the population of animals that they regularly treat.

groups. For example, if it were discovered after the GDV trial was reported that thin dogs do better than obese dogs, the results of the trial would still be valid because randomization would have roughly equally allocated obese and thin dogs between the study groups, thus negating the potential for body condition to bias the results. To effectively eliminate selection bias, randomization must include two important processes [1].

Generation of a Random Sequence

The first step of randomization involves generation of an unpredictable allocation sequence based on a random procedure. The most common method of generating a random sequence is via computer, but random number tables and flipping a coin to generate a sequence are also appropriate. Other methods of generating an allocation scheme, such as alternating assignments between intervention and control groups or assigning animals to groups according to day of the week or hospital number, are systematic methods of allocation but are not appropriate for randomization because the sequence cannot be concealed.

Allocation Concealment

The second step of randomization is concealment of the randomization sequence (allocation concealment), preventing those admitting subjects to the trial from knowing the upcoming assignments. This is distinctly different from blinding, discussed later in this chapter, which pertains to being unaware of the animals' treatment group as data are collected on the outcome of interest *after* the

animal is enrolled in the study. Randomization concealment ensures that those screening candidates for inclusion and exclusion criteria have no way of knowing to which group the animal will be allocated *prior* to it being randomized. While certain studies cannot be blinded, it is *always* possible to conceal the randomization scheme.

Traditionally, biomedical researchers focus on only the sequence generation process of randomization, but concealment is crucially important. When a system of assignment is known, there is potential for bias. For example, in a study in which dogs enrolled on Tuesdays receive intervention A and dogs enrolled on Thursdays receive intervention B, even if individuals screening animals do not know what interventions A and B are, if they believe that dogs enrolled on Thursdays are "doing better," they may consciously or subconsciously enroll dogs with different prognostic factors to different groups. Knowledge of the next assignment can also lead to exclusion of animals on the basis of prognosis because they would have been allocated to the perceived inappropriate group.

Without adequate allocation concealment, even random, unpredictable assignment sequences can be undermined, allowing individual preferences to influence the assignment of animals to groups such that important differences between groups result, affecting the study outcome.

Concealment can appear to be a challenge in studies involving emergency and critical care medicine because services, such as a pharmacy that would keep the concealed randomization scheme, may not be available

24 hours a day. A valid approach in these instances is to have the pharmacy generate the random sequence and then allocate that sequence to sequentially numbered opaque-sealed envelopes which are then housed in the emergency and critical care units. After an animal is screened for study inclusion, if it qualifies, the next envelope in the sequence is opened to reveal to which group that animal is allocated.

Blinding and Outcome Assessment

Observation bias occurs when knowledge of a study subject's group allocation influences identification of relevant events during the study. For example, if investigators know which animals received an active intervention, they may monitor that group more closely than the control group in a way that could seriously affect the trial outcome. If an owner knows their dog is receiving an active intervention, they are likely to overreport improvement, whereas those who know their dog is in the control group are likely to overreport no improvement (or perhaps deterioration). This leads to exaggerated estimates of intervention benefits. Blinding of investigators and owners to which group animals are allocated prevents these biases [2–4].

The potential for observation bias is related to the subjectivity of the outcomes under study. If an outcome for a trial is change in lactate levels, observation bias is unlikely because lactate measurement cannot be affected by knowledge of the animal's study group. In contrast, when the outcome of interest is subjective, such as owner or veterinarian assessment of pain, knowledge of the animal's group allocation could affect the pain score attributed to that animal. Blinding also mitigates the problem that owners administering a known active drug to their pet may be sensitized to its condition and may tend to ascribe every sign or unusual occurrence to the intervention, thus increasing the side-effect profile of that group. To obtain unbiased estimates of intervention effect, regardless of whether the outcome measured is subjective or objective, is to subtract the effect documented in the control group from the effect documented in the intervention group.

Placebo Effects

Placebo effects are improvements documented in a control group with no active intervention. Commonly, the assumption is that the animals are not really improved, but merely a bias of owners or investigators who want to believe that animals in the study are improving. However, animals in a control group can actually improve, even with no active intervention. This can be due to regression to the mean.

Many diseases, particularly chronic ones, have waxing and waning signs and symptoms. Owners may seek out enrollment in a trial when those signs and symptoms are at a peak. Over time, even without intervention, these animals will cycle back to their average level of symptom burden or disability. In these cases, animals in control groups can show improvement even with no intervention. The animals have indeed improved. One way to combat regression to the mean in the design of trials is, when possible, to screen animals for study inclusion when interested owners present them for consideration for inclusion, but delay baseline data collection until a follow-up visit occurs 7–10 days later.

Minimizing placebo effects in the design of the study provides the benefit of needing fewer animals enrolled to document a significant difference between groups.

Sample Size Considerations

A trial undertaken with an insufficient number of animals is of little scientific value and can be scientifically harmful if the results are misinterpreted as demonstrating that an intervention has no effect when, in fact, the sample size was not sufficient to draw that conclusion. Performing a sample size calculation requires data on the outcome of interest in the target population to be studied. This often comes from the literature. When data for a sample size calculation do not exist, a pilot study can be undertaken to collect data on a small group of animals which are then used to determine the sample size required for the larger controlled study. The target sample size for the study is increased above that suggested by the sample size calculation to maintain the ability to identify a significant difference between groups, even if some animals are lost to follow-up or do not follow the protocol as intended, because ideally, even animals that do not comply with the protocol are included in the analysis.

Statistical Analysis

A statistical testing plan is developed during study design and is necessary to perform the sample size calculation. Ideally, an intention-to-treat analysis is planned, which means that once animals are randomized to a study group, their outcomes data must be analyzed along with those of all others in that group, regardless of whether there is compliance with their assigned regimen in the protocol. In other words, “once randomized, always analyzed” [5,6]. While the goal is to study the effect of the intervention, randomization is done only on the basis of *offering* it. To preserve the power of randomization, the data must be analyzed on this basis. Only the entire groups allocated by randomization are truly comparable.

If analyses are performed on a subset of animals randomized to a group, it is impossible to achieve balance in the distribution of unknown factors that had originally been achieved through randomization and the results of the subgroup of compliers may be biased.

Clinical Trial Implementation

Recruitment

Even meticulously designed trials fail if an appropriate number of animals are not enrolled. The ability to recruit animals is dependent on the owner incentive to include

their animal as well as the recruiting budget available to reach out to owners of potential study participants. Many times, access to care for their pet that is financially covered by the study sponsor is a major incentive, as well as access to interventions that may not be available outside a trial. While owners are informed that their animal may not directly benefit from inclusion in a trial, many are very invested in the concept that the information gained by choosing to include their animal will benefit other animals and potentially people in the future. Owners balance these incentives with potential risks and time commitment of the study. Studies that are very long or require many visits can be more difficult to achieve adequate recruitment.

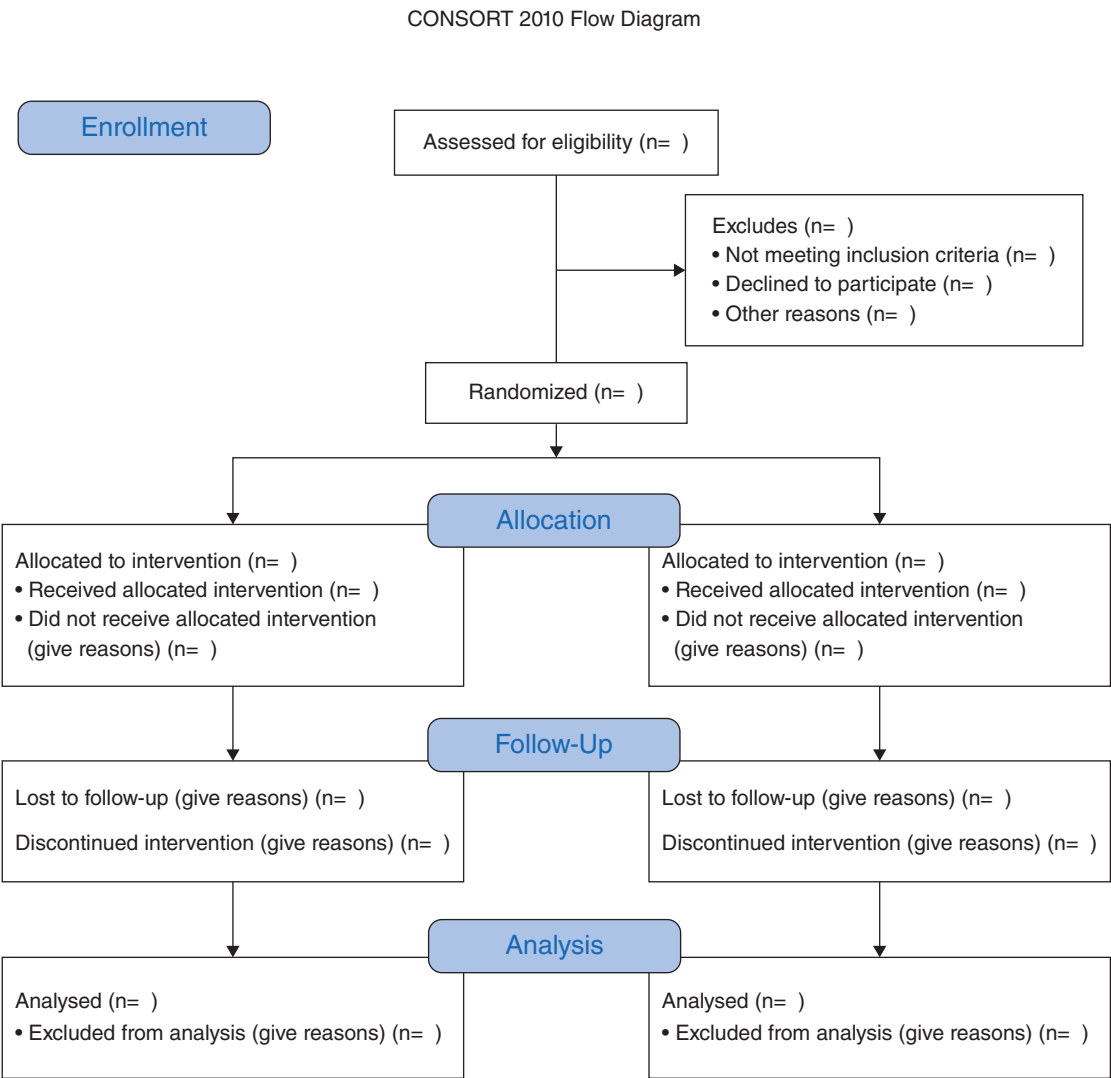


Figure 209.2 The study participant flow chart recommended by the Consolidated Standards of Reporting Trials (CONSORT) Group [7]. The CONSORT guidelines are adopted by most biomedical journals for reporting RCTs, with this flow chart in particular required for publication of study results.

It is best to have a recruitment strategy based on how difficult it might be to enroll animals as well as how quickly the study needs to be completed. While recruiting from the hospital population may eventually allow one to achieve the appropriate sample size, active recruitment outside the hospital clientele is often needed to complete enrollment. Cost-effective methods of outside recruitment include social media campaigns and lawn signs in local dog parks. When a large number of animals need to be recruited in a short period of time, more extensive and expensive recruiting methods are often necessary, including print ads in local or regional papers, or local radio ads.

Data Collection

Data are collected using data capture forms (DCFs) designed for the study to ensure complete data collection. DCFs support both primary (real-time) data collection and secondarily recorded data originating elsewhere (e.g. the medical record). While electronic data capture systems are becoming more available, DCFs are most commonly paper based. The data are then transcribed into a database for analysis, but DCFs are saved for future reference.

Meticulous data collection is crucial to successful trial completion. This is true both for animals enrolled in the study and those that are screened but not enrolled. Figure 209.2 is the study participant flow chart that is recommended by the Consolidated Standards of Reporting Trials (CONSORT) Group [7]. The CONSORT guidelines are adopted by most biomedical journals for reporting RCTs, with this flow chart in particular required for publication of study results. The CONSORT statement also contains a 25-item checklist which focuses on reporting how the trial was designed, analyzed, and interpreted

Good Clinical Practice

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, performance, analysis, and reporting of clinical trials [8]. While compliance with GCP is required for trials registered with regulatory agencies such as the Food and Drug Administration (FDA) [9], all investigators interested in the design of high-quality clinical trials should be aware of these guidelines and use a minimum trial implementation standard that is in the “spirit” of GCP.

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