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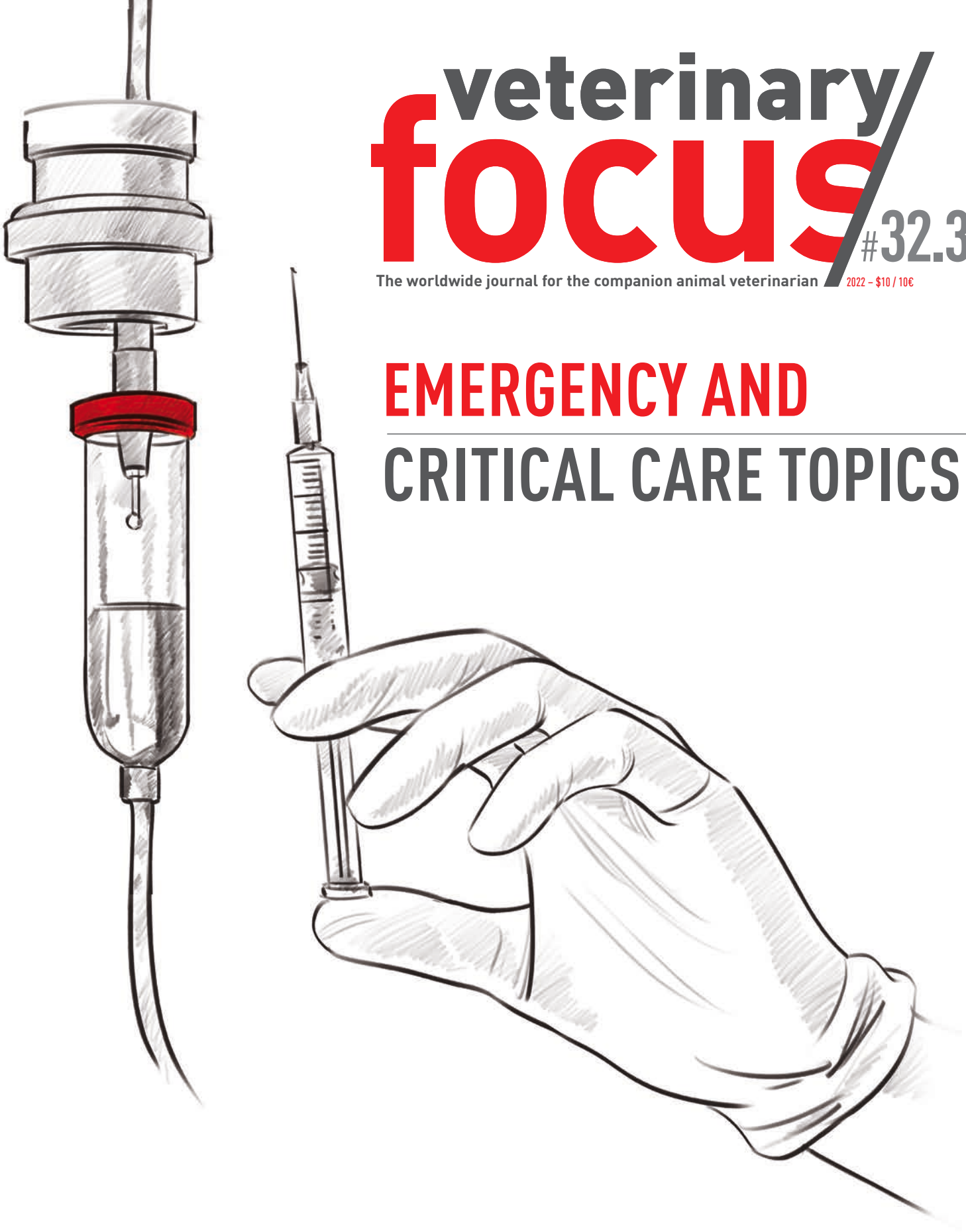
EMERGENCY AND CRITICAL CARE TOPICS



Feline pyothorax – Head trauma in dogs – Small animal transfusion medicine – How I approach... the dog in respiratory distress – Arterial thromboembolism in cats – Canine diabetic ketoacidosis

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A MATTER OF LIFE AND DEATH

"There is nothing so strong or safe in an emergency of life as the simple truth." **– Charles Dickens, author**

Although now well-recognized as an essential component of both human and veterinary medicine, the specialty of emergency and critical care, or ECC, has a surprisingly short history. It is generally agreed that the father of the intensive care unit (ICU) was Bjørn Ibsen, a Danish anesthetist who in 1952 was involved in a devastating outbreak of poliomyelitis, where hundreds of patients were dying from respiratory or airway paralysis. Standard treatment involved the use of negative pressure ventilators, but his Copenhagen hospital had only a few of the devices, and they offered limited success; the mortality rate was around 90%. Ibsen had the simple but radical idea of turning the treatment on its head – he instituted protracted positive pressure ventilation by means of tracheostomy and intubation, and enlisted medical students to pump oxygen into the patients' lungs. The results were dramatic; mortality declined to around 25%, and Ibsen went on to set up the world's first dedicated ICU ward the following year, and later jointly authored the earliest recognized account of ECC management principles.

That said, some aspects of emergency and critical care will presumably have been around since the dawn of civilization, and although the ECC acronym is modern, the words *emergency*, *critical* and *care* also go back centuries. *Emergency* derives from the Latin word *emergens*, "to rise out or up"; *critical* is from the Ancient Greek *kritikós*, meaning "of or for judging, able to discern"; and the word *care* derives from the Old English *carian* or *cearian* "to be anxious or to feel concern", (and in turn is linked to the Proto-Germanic and Saxon words *karo*, *karon* and *charon*).

So however advanced our knowledge of ECC matters might be – and this issue of *Veterinary Focus* seeks to encompass the very best within the field – the basics remain the same; show compassion when an emergency arises, make discerning judgements, and feel empathy for those we treat. To paraphrase Charles Dickens, learn the facts and do what you know to be right, and we will continue to do the best for our patients.

Ewan McNEILL
Editor-in-chief

In this issue of *Veterinary Focus*

FELINE PYOTHORAX

Feline pyothorax is a potentially fatal condition that requires prompt recognition and adequate treatment in order to ensure a good outcome for the patient, as Chiara Valtolina describes.

KEY POINTS

1. Pyothorax is characterized by the accumulation of septic exudate in the pleural space, and can be life-threatening if not rapidly recognized and treated.
2. Affected cats present with a variety of clinical signs; these can range from tachypnea, anorexia, lethargy and fever to severe dyspnea and cardiovascular collapse.
3. Emergency medical stabilization of the patient is paramount, requiring oxygen supplementation, thoracocentesis, fluid therapy and broad-spectrum antibiotics.
4. Small-bore chest drains that allow thoracic drainage and lavage, along with broad-spectrum antibiotics, are the mainstay of treatment for most cases.

Introduction

Pyothorax in the cat is characterized by the accumulation of septic purulent fluid within the pleural space. As the initial clinical signs of the condition are frequently nonspecific, diagnosis and/or presentation to the veterinary clinic is often delayed, but once the signs of dyspnea and cardiovascular compromise become more manifest, affected cats are often presented as an emergency. Prompt recognition of the problem and adequate treatment are mandatory to ensure a good outcome for this life-threatening condition (1-5). This article will review the available literature on pyothorax and discuss the recommended therapeutic options for treating affected cats.

Etiology

The pleural space is lined by the parietal and visceral pleura and contains a minimal amount of fluid to prevent friction during the normal breathing cycle. In pyothorax, bacteria can enter the pleural space by a number of different routes (damage anywhere along the respiratory tract, via oropharyngeal contamination, or via the esophagus), initiating an inflammatory septic process. The presence of bacteria causes release of inflammatory cytokines and vasoactive mediators that alter local capillary permeability and lymphatic flow; this causes a thickening of the pleura, which facilitates development and accumulation of exudate within the pleural cavity. Systemic signs of generalized inflammation, sepsis, fever and general malaise also develop (1,6).

Due to the time lapse between the initial development and the actual diagnosis, the underlying reason for the pyothorax may not be determined in many cases, and indeed the principal cause is currently unknown. It is possible that different factors may play a role in the development of pyothorax. However, it is suggested that the two most likely causes are penetrating thoracic wounds secondary to a cat scratch or bite (1,4-8), and parapneumonic spread of oropharyngeal bacteria in animals with chronic upper airway infection (2,4,6), The cat scratch/bite theory has until recently been widely accepted as the most likely etiology, an idea supported by a retrospective study that noted external scratch or bite wounds had been reported in 14-40% of cases (7). Cats living in a multi-cat household were also found to be 3.8 times more likely to develop the condition, emphasizing the idea that pyothorax is secondary to fight wounds from inter-cat aggression (7). Further support for this theory came with the idea that pyothorax could have a seasonal predisposition, with more cats being presented during late summer/fall when aggression and fighting between cats for territory and mating are perhaps more likely, although the above study noted that outdoor access and gender were not risk factors for the development of pyothorax (7). The parapneumonic spread of oropharyngeal bacteria has been suggested as the most common route of infection of feline pyothorax in another retrospective study (8), a theory supported by necropsy findings from cats that died of pyothorax which noted numerous abscess formation in the lungs, suggestive of parapneumonic spread. Animals living in multi-cat households are probably also predisposed to develop chronic upper airway infection and are more at risk for developing pyothorax (4,6).

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Dr. Valtolina graduated in 2000 from the Faculty of Veterinary Medicine in Milan and remained there as one of the team in the surgical department for some years before undertaking a residency in Emergency and Critical Care at London's Royal Veterinary College. She attained diplomate status of the American College of Emergency and Critical Care in 2009 and followed this with her diploma from the European College of Emergency and Critical Care. Dr. Valtolina was awarded her PhD in 2019 with a thesis on aspects of feline hepatic lipidosis, and she currently works as senior lecturer in the intensive care unit at Utrecht's Faculty of Veterinary Medicine.

Organisms from the feline oropharyngeal flora are commonly isolated from pyothorax cases, with bacteria such as *Pasteurella multocida, Clostridium* spp., *Fusobacterium* spp., *Bacteroides* spp., *Actinomyces* spp., *Peptostreptococcus* spp., and *Prevotella* spp. being most commonly identified (2,6,9). *Nocardia* and *Actinomyces* spp. are also frequently isolated, and in fact polymicrobial infections with both obligate anaerobic and facultative aerobic bacteria are commonly found on culture (4,6,9).

Signalment and clinical presentation

Although cats of all ages can be affected, pyothorax is more commonly found in younger and middle-aged animals, with a mean age at diagnosis between 3 and 6 years (2-4,6,7). Younger animals seem to be more affected due to their behavior and the tendency to fight and explore outdoors when compared to older animals. Male animals seem to be over-represented in some studies, although no sex predisposition has been found to be statistically significant (7,8). In addition there does not seem to be a breed predisposition (6,7).

The duration of clinical signs prior to diagnosis can be from days to weeks (4,6). Non-specific clinical signs include pyrexia, lethargy, anorexia and weight loss (5,7). In one study only half of the cats with pyothorax presented with pyrexia, demonstrating that the absence of fever, especially in this species, does not exclude the presence of pyothorax (3,5,8) – and indeed cats that also have cardiovascular compromise (see below) often present with hypothermia (7). The most common clinical sign is dyspnea due to the presence of pleural effusion (which is often bilateral); affected cats often present with rapid, shallow respiration, indicative of a restrictive respiratory pattern. Other common signs are tachypnea and muffled heart sounds, but coughing is not usually an indicator of pleural effusion in cats (4-7). One retrospective study noted that hypersalivation was not uncommon; this may be caused by difficulty swallowing due to the presence of a large volume of pleural effusion (7).

Cardiovascular compromise can be present in the form of distributive shock due to the release of inflammatory cytokines and bacterial toxins from the pyothorax. Cats suffering from distributive shock secondary to sepsis present with pale mucous membranes, hypothermia, tachycardia or bradycardia and hypotension. One study reported that cats which did not survive pyothorax had a significantly lower heart rate and were often hypothermic compared to cats that survived (7).

Diagnosis

A presumptive diagnosis of pyothorax can be made based on the clinical presentation (lethargy, depression, fever, anorexia, restrictive dyspnea and pleural effusion) and supporting clinical history **(Box 1)**. The definitive diagnosis is made by combining macroscopic assessment of the pleural effusion with a cytological and cultural evaluation (4,6). Macroscopic evaluation of the effusion often reveals a malodourous opaque, cloudy, sero-hemorrhagic fluid, often containing white/yellowish floccules **(Figure 1)**. Final confirmation is via

Box 1. Diagnostic pointers for feline pyothorax.

- More common in younger and middle-aged cats (mean age at diagnosis 3-6 years)
- No sex or breed predisposition
- Duration of clinical signs prior to presentation can be days to weeks
- Most common presenting sign is dyspnea (rapid, shallow respiratory pattern)/tachypnea and muffled heart sounds; coughing is rare
- Distributive shock (secondary to sepsis) can cause pallor, hypothermia, tachycardia or bradycardia, and hypotension
- Non-specific clinical signs may include pyrexia, lethargy, hypersalivation, anorexia and weight loss

Figure 1. Septic pleural exudate will appear turbid and flocculent on macroscopic examination.

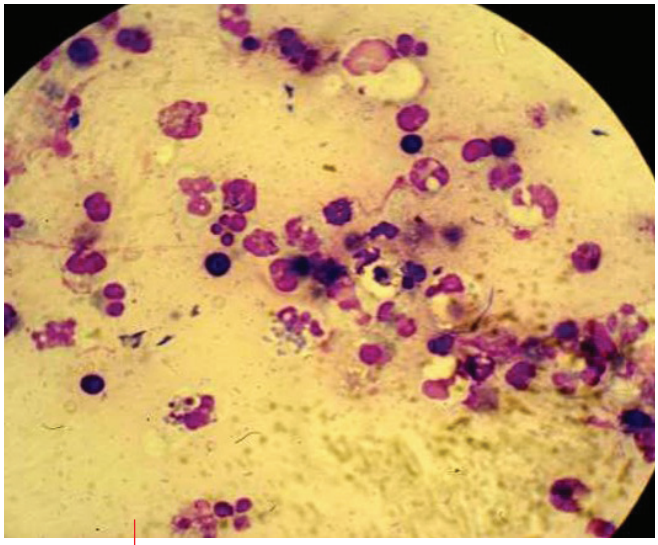

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Figure 2. A direct smear of septic pleural exudate under the microscope (x100 magnification); note the numerous degenerate neutrophils and macrophages with intracellular bacteria.

cytological evaluation of the fluid, which will reveal polymorphic inflammatory cells, predominantly degenerate neutrophils with intracellular bacteria **(Figure 2)**. Multiple bacterial species are often recognized on cytology, although if a patient has been pre-treated with antibiotics before diagnosis intracellular bacteria may not be seen; because of this, the effusion should always be cultured (4,6,7,9).

Hematology and biochemistry

The hematological and biochemical abnormalities in feline pyothorax are often non-specific and reflect the presence of the underlying inflammatory septic process and the patient's overall clinical compromise. The most predominant hematological abnormality is a neutrophilic leukocytosis with or without a left shift, which occurs in 36-73% of cats (5-7). A mild normochromic anemia is also often reported. The most common biochemical abnormalities are hypoalbuminemia, hyperglobulinemia, hypo- or hyperglycemia, serum electrolyte imbalances and mild elevations in serum liver enzymes (5,7).

Diagnostic imaging

Thoracic radiographs are often performed to evaluate the degree of pleural effusion, determine unilateral versus bilateral involvement, and to highlight any possible underlying cause, such as pulmonary or mediastinal masses and pneumonia (4,6). Radiographs are also useful to evaluate correct placement of a thoracostomy tube, as well as monitoring the effectiveness of the chosen therapy. Ultrasound can estimate the degree of effusion, determine the echogenicity of the fluid (often hyperechoic for pyothorax) and facilitate thoracic drainage (4,6,10). Moreover, pulmonary abscesses, intrathoracic masses and foreign bodies can also be detected with this modality (11).

More advanced diagnostics, such as computed tomography (CT) are often not performed as an initial diagnostic for every patient; apart from the costs, general anesthesia is required, which implies that the patient should have a stable cardiovascular system. However CT is often suggested when there is no improvement with medical therapy alone, or when there is a suspicion of pulmonary disease on thoracic radiography and ultrasound (1,4,6,12).

Treatment of pyothorax

Cats with a suspected pyothorax should be approached as any other emergency patient, with a focused evaluation of the major body systems (respiratory, cardiovascular and neurological) which will allow the clinician to both quickly determine the degree of respiratory and cardiovascular compromise and to start prompt stabilization measures.

Dyspneic patients should be offered oxygen therapy using whichever technique is readily available and which causes the least stress (*e.g.*, flow-by, oxygen cage); such animals may benefit from a few minutes of this "hands off" approach, which also permits evaluation of the respiratory pattern and allows the cat to calm down. Severely distressed dyspneic patients may also benefit from administration of a mild sedative with minimal cardio-depressant effects (*e.g.*, butorphanol at 0.2 mg/kg IM); this allows them to relax and removes the anxiety associated with the dyspnea. In any distressed patient thoracocentesis, placement of a peripheral catheter and any other stressful procedure should be performed only after administration of a sedative.

Physical examination will usually reveal signs linked to the restrictive dyspnea; decreased or absent lung sounds ventrally (uni- or bilaterally) on thoracic auscultation can be enough to diagnose the presence of pleural effusion. Thoracic radiography should not be performed in a dyspneic cat, as restraint can be fatal for the most compromised patient. The use of point of care ultrasound (POCUS) for rapid evaluation without causing too much stress to the patient has gained popularity in the emergency and critical care setting, and is a rapid and safer diagnostics procedure to detect the presence of pleural effusion and lung pathology (10,11).

If the cat's stress levels allow, intravenous access should be gained to allow administration of fluid therapy for cardiovascular stabilization and medication, but if the patient is too dyspneic to allow placement of an IV line, thoracocentesis should be performed first.

Thoracocentesis should be both diagnostic and therapeutic. Depending on the location of the pleural effusion, either unilateral or bilateral

thoracocentesis should be performed. The presence of fibrin and purulent exudate can make it difficult to completely remove the effusion, and an adequate size needle or butterfly is recommended. Collected fluid should always be sent for cytologic evaluation and culture.

Medical and surgical options are available for treating feline pyothorax, although in the available literature there is no agreement as to the optimal treatment (4,6). Prospective studies evaluating and comparing the efficacy of the two options are lacking; furthermore, the literature often reports and compares only limited number of cases, making it even more difficult to draw any meaningful conclusion. Despite this, the general consensus is that medical treatment should be considered, at least initially, as the mainstay of therapy (1,4-7). In a recent retrospective study, 85% of cats (47 animals) with pyothorax in the review were treated medically, with only 5 cats not responding and requiring surgical intervention (5).

However, thoracocentesis alone, even if repeated multiple times, is not adequate as a stand-alone treatment for pyothorax (1,4-6). Once the patient has a stable cardiovascular profile and any electrolyte abnormalities have been corrected, one or more chest drains must be placed – bilateral drains are often required. This should be done under sedation, and will allow drainage and lavage of the thorax, along with antimicrobial therapy. Intravenous antimicrobials should be started immediately whilst awaiting the results of fluid culture and susceptibility; a broad-spectrum antibiotic is usually chosen, with amoxicillin/clavulanic acid being the drug of choice as it also has some efficacy against *Actinomyces* spp. and anaerobes. Depending on the antibiotic regulations of the country, a fluoroquinolone antibiotic is also often suggested to improved gram-negative coverage (4,6,13). Antibiotic treatment should then be adjusted based on the culture results and must be continued for at least for 3-4 weeks beyond resolution of the clinical signs.

One or more indwelling thoracostomy tubes should be placed to drain and lavage the pleural space. Previously large-bore (14-16 Fr) chest drains were recommended for the exudative and fibrinous effusion seen with pyothorax (14), but these require general anesthesia for placement and cause pain and discomfort for the patient. More recently a small-bore chest drain (SBTT) (10-14 G) placed using a modified Seldinger's technique is the preferred choice in both human and veterinary medicine. SBTTs are easy to place using only mild sedation, are well tolerated by the patient, and have minimal complication rates (15,16) – the most commonly reported complication being kinking or malposition of the tube. An on-line video demonstrating the procedure is available[1].

[1] https://www.milainternational.com/index.php/videos_articles/

Note that it is important to determine how far the chest drain should be positioned within the thoracic cavity by pre-measuring; this should be from the insertion site (usually around the 8-9th intercostal space) to the cranio-ventral aspect of the chest cavity (2nd-3rd rib), and to ensure that all the side holes of the chest drain are within the thorax. The patient should be kept in sternal recumbency during placement to allow it to breath more comfortably, especially if only mildly sedated. The target area should be clipped, and asepsis maintained during the placement.

Drains should be placed unilaterally or bilaterally, depending on the location of the pleural effusion **(Figure 3)**. The chest should be drained as soon as the tube is inserted, as it is not uncommon for placement to cause a mild iatrogenic pneumothorax. Once the chest is drained, the SBTT is secured to the skin; if the animal is stable, a thoracic radiograph should then be performed to evaluate the position of the drain. Radiography may show that that catheter is not in the intended position within the pleural space, but if it is working adequately and no other problems are noted, it should not be replaced **(Figure 4)**. It may be beneficial to adjust the position of the animal during drainage to optimize aspiration of the effusion, and adequate analgesia is mandatory. In critical cases, the use of an opioid (methadone 0.2 mg/kg IV or IM every 4 hours or buprenorphine 20 µg/kg IV every 6 hours, possibly with ketamine at 30-50 µg/kg/min as a constant rate infusion (CRI) should be preferred over the administration of a non-steroidal anti-inflammatory analgesic. The latter option could however be considered for a normovolemic, well-hydrated and stable patient.

"Cats with a suspected pyothorax should be approached as any other emergency patient, with a focused evaluation of the major body systems which will allow the clinician to both quickly determine the degree of respiratory and cardiovascular compromise and to start prompt stabilization measures."

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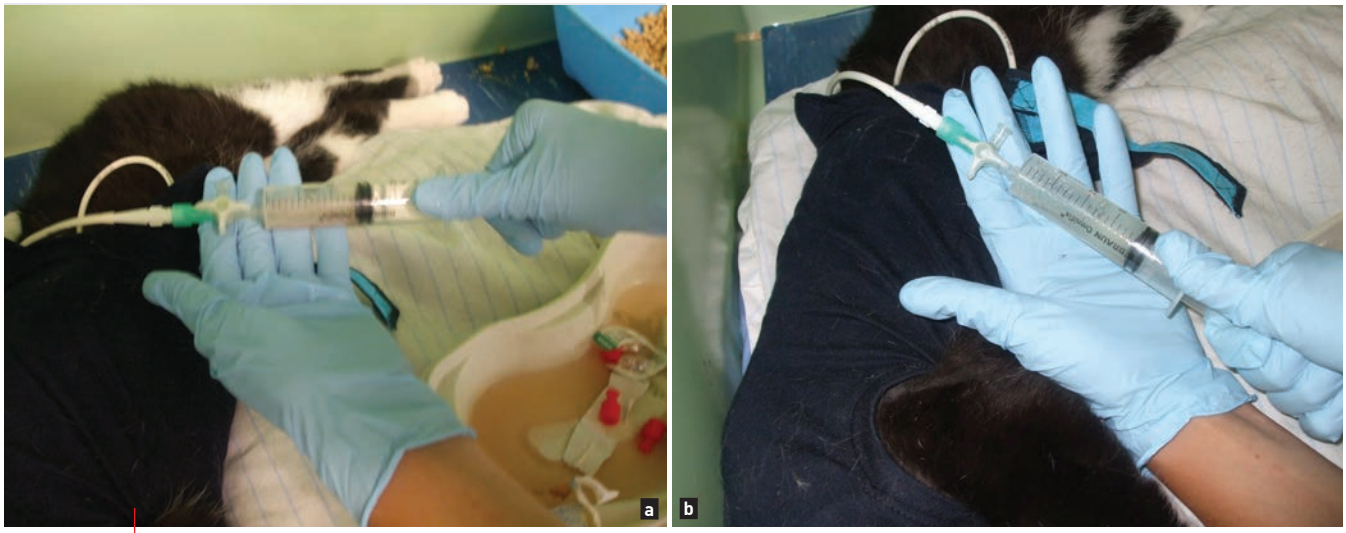

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Figure 3. Thoracic drainage and lavage in a cat with pyothorax. **(a)** Once the syringe and three-way tap are attached to the drain, the pleural effusion is aspirated. **(b)** lavage is then performed using a warmed isotonic crystalloid; lavage should be repeated until the drained fluid is clear.

Various authors have stressed the importance of thoracic lavage to facilitate the removal of the purulent, fibrinous exudate, bacteria and inflammatory mediators (1,4,6). In a small retrospective study in dogs the benefit of pleural lavage over drainage alone was reported (17). A warm sterile isotonic crystalloid infusion should be used for lavage, initially at 5 mL/kg to ensure the patient tolerates the procedure well and to verify that the fluid can be withdrawn without any problem afterwards. If the procedure is well tolerated and the majority of the lavage fluid is retrieved, then the volume can be increased (10-15 mL/kg), with lavage repeated until the drained fluid is clear. Lavage should be performed as frequently as possible, especially when the cat is first hospitalized, and at least 4-6 times per day. Before performing lavage, it is important to first drain the chest to keep track of fluid production, and it is essential to record how much fluid is infused and retrieved every time and from which side of the chest. The addition of heparin or antibiotics to the lavage fluid is not recommended.

The chest drain should be kept in place until fluid production starts to decrease to around 2-3 mL/kg/day and the patent shows signs of clinical improvement. The chest drain itself and the pleuritis will cause some fluid production. Before removing the drain, it is very important to repeat cytologic evaluation of the fluid to check for the presence of degenerated neutrophils and intracellular bacteria. In the author's institution a negative cytology result along with fluid production < 2 mL/kg/day are the criteria used for removal of the chest drain. The patient is usually monitored for 24 hours after the removal of the drain/s, and thoracic radiographs are repeated before discharge to allow comparison at recheck, which should be scheduled over the following 2-3 weeks.

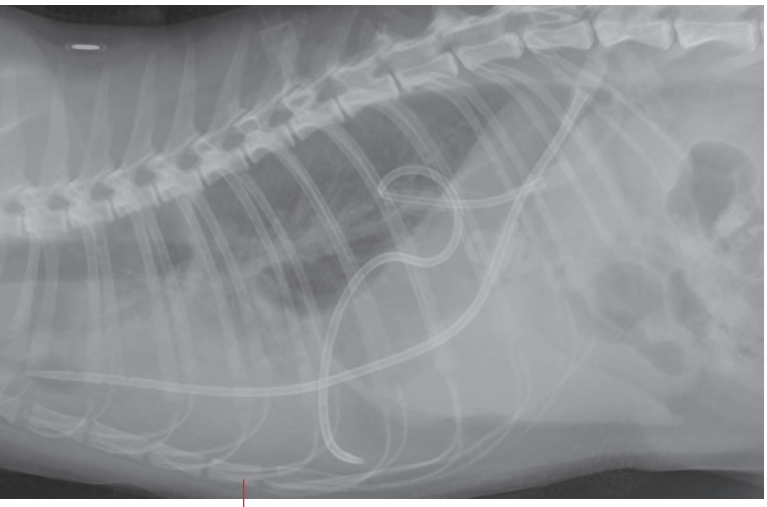

Figure 4. A lateral thoracic radiograph of a cat with bilateral pleural effusion. A right-sided SBTT has been placed around the 8th intercostal space, with the tip of the chest drain positioned in the cranio-ventral part of the chest.

"It is suggested that the two most likely causes of pyothorax are a penetrating thoracic wound secondary to a cat scratch or bite, and parapneumonic spread of oropharyngeal bacteria in animals with chronic upper airway infection."

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Surgery should be considered if there is an inadequate response to medical therapy after 2-7 days – *i.e.*, insufficient clinical improvement, continued fever, continued presence of pleural fluid or if fluid remains turbid or flocculent, and/or detection of an underlying cause on diagnostic imaging (*e.g.*, abscess, suspicion of a foreign body, loculated (compartmentalized) effusions, thickened pleura) (4-6,15). Surgery consists of an exploratory thoracotomy; this is either via a sternotomy (if the effusion or the lesions are bilateral) or via lateral thoracotomy on the affected side (15).

Overall, pyothorax cases can have a fairly good prognosis. A recent retrospective study (5) highlighted both good short- (14 days) and long-term (1 year) survival rates, with 72% and 68% cats being alive at the respective times. In addition, the recurrence rate was low, with only 2% of cases developing a relapse.

CONCLUSION

If adequately treated, pyothorax has a good prognosis, but it is important to initially discuss with the owners likely costs of hospitalization (which on average is 5-6 days) and treatment, and the possibility of relapse. Pyothorax cases should be treated as potentially life-threatening, and the clinician should be alert to the need for immediate and aggressive intervention to ensure the best possible outcome for such animals.

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HEAD TRAUMA IN DOGS

Head trauma in small animals can be challenging for any clinician, but this paper delivers a clear and concise summary of how to treat such cases.

KEY POINTS

1. Head trauma causing dysfunction of the normal brain physiology is a relatively common presentation in the small animal emergency room.
2. The immediate goal for traumatic brain injury should be to rapidly minimize secondary brain injury via appropriate fluid therapy, analgesia and adjunctive treatments.
3. Serial evaluations of head trauma patients will help guide treatment strategies and should be implemented as part of continued care.
4. The prognosis for these cases can be difficult to predict on initial evaluation, but even individuals with persistent neurological deficits will often cope surprisingly well.

Introduction

Head trauma and traumatic brain injury (TBI) are a cause of significant morbidity and mortality in small animals. One review of blunt trauma in dogs reported 25% of cases to have evidence of TBI, and these were associated with decreased survival rates (1). Causes of head trauma include blunt trauma from a moving vehicle, bite wounds, falls, crush injuries, missile injuries (*e.g.*, gunshots), and human-inflicted trauma (2). In one study, most cases of trauma in dogs and cats were from blunt vehicular trauma and crush injuries, respectively (3). Head trauma may be self-limiting, but it can also result in significant TBI, coma, and even death, with reported mortality rates ranging from 18-24% (4). Head trauma in veterinary patients can initially appear concerning, with owners questioning the prognosis for recovery, but animals appear to be rather resilient, and many can recover with appropriate care, even if radical amounts of cerebral tissue are lost (5). This article reviews the pathophysiology, patient assessment, diagnostics, and treatment recommendations for dogs suffering from head trauma and traumatic brain injury.

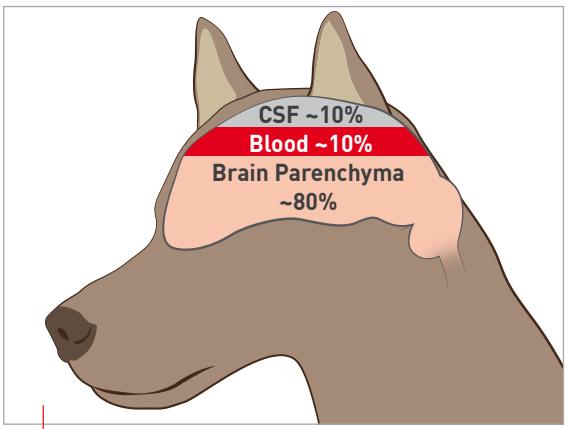

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Figure 1. The Monro-Kellie doctrine; the skull is a fixed space composed of brain parenchyma, blood, and cerebrospinal fluid, and any increase in one or more of these components, or the addition of a mass-like component, causes a compensatory decrease in the other components. If this intracranial compliance fails, increased intracranial pressure results.

Pathophysiology

Normal brain physiology

The cranium is considered a fixed space, with the Monro-Kellie doctrine **(Figure 1)** stating that the volume within the cranium (composed of brain parenchyma, blood, and cerebrospinal fluid) must remain constant. An increase in any of those components, or the addition of a mass-like component, causes a compensatory decrease in the other components; this is known as altered intracranial compliance. A lack of compensation will lead to increased intracranial pressure (ICP).

Intracranial pressure is the pressure exerted on the cranium by the tissues and fluids. Cerebral blood flow (CBF) provides oxygen and nutrient delivery to brain tissue and is primarily determined

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by cerebral perfusion pressure (CPP). This can be represented by the equation CPP = MAP – ICP, where MAP is the mean arterial pressure. The driving pressure of CBF is the CPP, as exemplified in the equation CBF = CPP/CVR, where CVR is the cerebrovascular resistance.

Autoregulation maintains the cerebral blood flow despite changes in blood pressure (MAP 50-150 mmHg) by regulating cerebral vessel size. Under normal conditions, intracranial compliance is high, such that changes in intracranial volume will minimally affect ICP. However, head trauma can lead to an increase in ICP with loss of autoregulation, resulting in pressure-dependent flow (*i.e.*, the CBF becomes more dependent on MAP). A significant increase in ICP can ultimately lead to decreased CPP and CBF, which in turn causes ischemia and neuronal death (6).

Primary and secondary injury

Primary injury **(Table 1)** refers to the physical disruption of tissues within the cranium that occurs immediately at the time of the traumatic event **(Figure 2)**. It can be classified according to the location, the type of injury, and whether it is focal or diffuse (7). Once primary injury is present it cannot be changed, but it affects and influences *secondary injury*, which occurs after and in reaction to the primary injury. This involves a complex series of biological events that may lead to neuronal death, involving the release and accumulation of excitatory neurotransmitters, cytotoxic edema, and activation of proteases and inflammatory mediators, as well as mitochondrial dysfunction and generation of reactive oxygen species (ROS). The brain parenchyma, with its abundance of lipid, is particularly at risk of lipid peroxidation (8), which can be exacerbated by intracranial hemorrhage and the release of iron ions. Neuronal cell destruction through these processes leads to activation of nitric oxide (NO) pathways, with consequential cerebral vasodilation and alterations in CBF and vascular permeability, contributing to the loss of autoregulation.

Table 1. Classifications of primary injury.

Concussion	• Defined by loss of consciousness without any histopathological lesion. Considered the mildest form of primary injury
Contusion	• Bruising of the brain parenchyma
Hematoma	• Swellings of clotted blood • Can occur within the brain parenchyma (intra-axial) or outside the parenchyma (extra-axial) in spaces such as the subarachnoid, subdural, or epidural spaces
Laceration	• Tearing of the brain tissue • Considered a severe form of primary injury
Diffuse axonal injury	• Shearing of the brain axons when the brain shifts and rotates inside the skull • Considered a severe form of primary injury

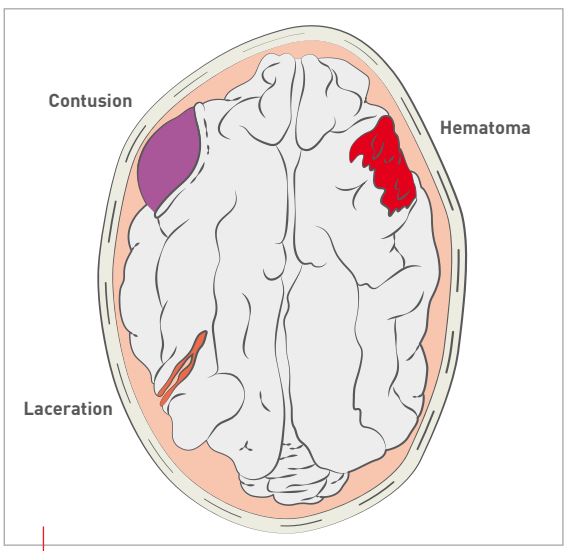

Figure 2. A visual depiction of select primary brain injuries. Further descriptions of primary brain injuries can be found in **Table 1**.

Other intracranial factors can also exacerbate secondary injury, including intracranial hypertension, lactic acidosis, compromise of the blood-brain barrier (BBB), vasospasm, hemorrhage, infection, mass effects, and seizure activity (9). Systemic factors can worsen secondary injury via compromise of CBF, including hypotension, hyper- or hypoglycemia, hyperthermia, hyper- or hypocapnia, hypoxia, and acid-base or electrolyte derangements.

The combination of hypertension and bradycardia in a neurological patient is known as the *Cushing reflex,* and it can be indicative of severe intracranial hypertension. As brain herniation may be imminent with TBI, rapid recognition and immediate intervention is required. The presence of the Cushing reflex has been shown to be specific for brain herniation in dogs, but its absence does not exclude intracranial hypertension (10) and the clinician should be aware of this; it is therefore reasonable to assume intracranial hypertension is present if the clinical findings are generally supportive.

Patient assessment

Patient assessment should encompass a brief primary survey evaluating the ABCs (airway, breathing, and circulation) followed by a more thorough secondary survey. Hypoxemia, changes to ventilation, and hypotension contribute to secondary brain injury and require rapid recognition and treatment. Respiratory assessment should minimally include evaluation of the airway, respiratory rate and effort, SpO_2, and thoracic point-of-care ultrasound (POCUS). Cardiovascular evaluation should minimally include mucous membrane color, capillary refill time, heart and pulse rate, pulse quality, blood lactate, distal extremity palpation for relative temperature, and blood pressure. With severe head trauma, deranged cerebral autoregulation makes CBF and CPP more dependent on MAP, which makes maintaining blood pressure essential when managing such patients.

Neurological assessment

Neurological assessment should ideally be performed before administrating analgesics and after adequate resuscitation if possible. This should focus on the animal's level of consciousness, posture and brainstem reflexes. Dogs with head trauma and TBI may demonstrate either a decerebrate or decerebellate posture, although normal posturing does not rule out TBI **(Figure 3 and 4)**. A decerebrate patient may be identified by extension of the head and neck (opisthotonos) as well as all four limbs; decerebellate posturing is characterized by opisthotonos and extension of the forelimbs, with normal to flexed pelvic limbs. In both situations mentation is also often affected, as these patients can have significant intracranial disease. When assessing brainstem reflexes, pupil size, pupillary light reflexes, and physiologic nystagmus should be evaluated **(Figure 5)**. Since cervical trauma can occur concurrently with head trauma, it is also beneficial to evaluate motor and sensory function.

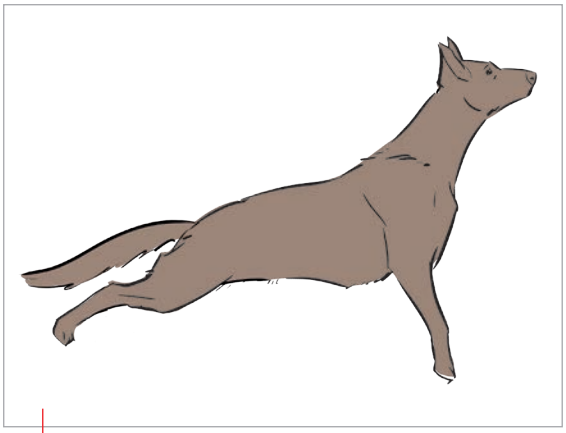

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Figure 3. Decerebrate posturing is characterized by the dog in lateral recumbency with extension of the head, neck (opisthotonos) and all four limbs.

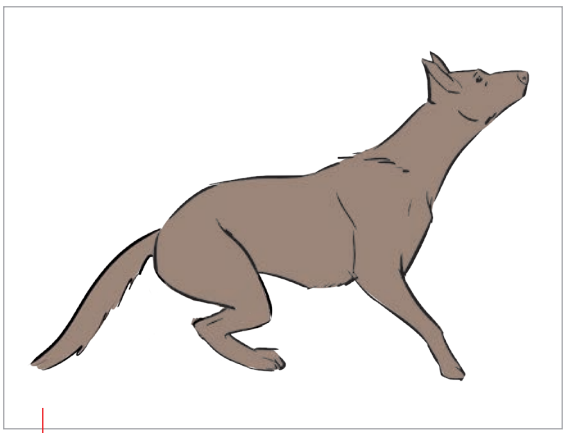

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Figure 4. Decerebellate posturing is characterized by the dog in lateral recumbency with opisthotonos and extension of the forelimbs; the pelvic limbs are normal or flexed.

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Figure 5. Brainstem reflexes can be evaluated using an ophthalmoscope to assess for pupil size, pupillary light reflexes, and physiologic nystagmus.

The Modified Glasgow Coma Scale (MGCS) has been validated in dogs (and cats) (11) to assess the severity of neurological deficits **(Box 1)**. This scale scores three categories – motor activity, brainstem reflexes, and level of consciousness – from one to six, with one study showing an MGCS score of 8 on admission to be consistent with a 50% probability of survival in the first 48 hours of hospitalization (11). Serial MGCS measurements (*e.g.*, performed every 30-60 minutes after the initial presentation) can help monitor response to therapy. Other scoring systems, such as the Animal Trauma Triage (ATT) score have also been validated.

Diagnostic imaging

Imaging can involve both extracranial and intracranial imaging. Extracranial imaging includes radiography of the thorax, abdomen and any affected limbs to evaluate for comorbidities (*e.g.*, rib fractures, pulmonary contusions, pneumothorax, abdominal free fluid, diaphragmatic herniation, luxations, long bone fractures).

Box 1. Modified Glasgow Coma Scale (MGCS).

Motor activity	Score
• Normal gait, normal spinal reflexes	6
• Hemiparesis, tetraparesis, or decerebrate rigidity	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 PLR and oculocephalic reflexes	6
• Slow PLR 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
• Semi-comatose, responsive to visual stimuli	4
• Semi-comatose, responsive to auditory stimuli	3
• Semi-comatose, responsive only to repeated noxious stimuli	2
• Comatose, unresponsive to repeated noxious stimuli	1

MGCS Score	Prognosis
3-8	Grave
9-14	Guarded
15-18	Good

POCUS may be more sensitive in detecting pulmonary contusions and small amounts of thoracic or abdominal free fluid (12). Where available, whole body computed tomography (CT) scans can have the advantage of quickly obtaining a vast amount of information with minimal sedation and manipulation of the patient.

Intracranial imaging is warranted in patients not responsive to medical therapy, those that deteriorate after an initial response to medical therapy, and patients with focal or asymmetric neurological disease (13). Skull radiographs are insensitive and are not recommended (8). CT **(Figure 6)** is preferred over MRI in the emergency setting since it does not require general anesthesia, is typically faster to perform, and is more sensitive for detecting fractures and areas of acute hemorrhage or edema (4,8). However, MRI may provide prognostic value and can aid prediction of developing post-traumatic epilepsy **(Figure 7)** (14).

Intracranial disease treatment

Head elevation

Elevation of the head at an angle of 15-30° may decrease intracranial pressure by promoting venous drainage without compromising CBF (15). A stiff board or plank should be used to support either the entire animal **(Figure 8)** or at minimum from the shoulder and above, to reduce the risk of compressing or distorting the neck that could occlude venous drainage.

Oxygen therapy and ventilation

The goal of oxygen supplementation is to maintain normoxemia. Routine oxygen supplementation should be avoided, as hyperoxemia can worsen reperfusion injury. If oxygen supplementation is needed, flow-by oxygen may be considered until further stabilization is performed. Nasal cannulae

"Intracranial imaging is warranted in patients not responsive to medical therapy, those that deteriorate after an initial response to medical therapy, and patients with focal or asymmetric neurological disease."

Kendon Kuo

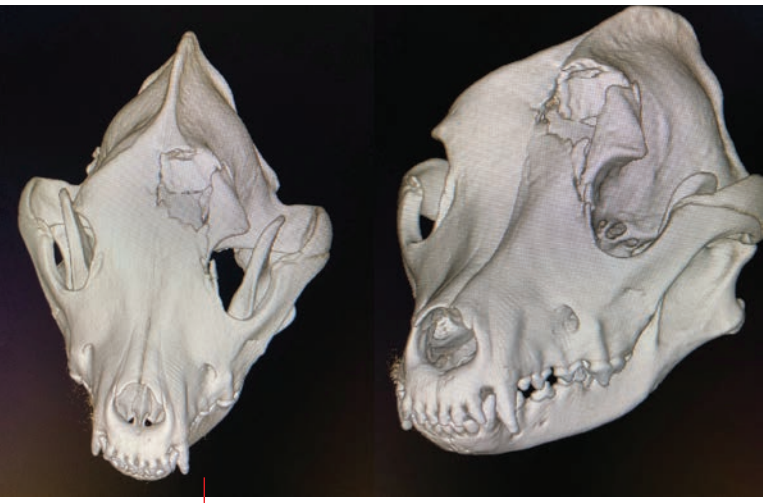

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Figure 6. 3D renderings from whole-body CT of a dog presented for head trauma showing a fracture associated with the frontal bone and zygomatic process. Whole body CT scans are becoming more widely available, and they have the benefits of obtaining a large amount of information about a trauma patient with minimal manipulation of the animal.

should be used cautiously, as fractures may alter the normal anatomy, and in extreme circumstances may cause communication into the cranium. High flow oxygen therapy has the benefits of increased comfort by providing warmed and moistened oxygen, but sneezing from nasal irritation can lead to increased ICP. Oxygen cages may be less stressful, and some allow climate control, but have the disadvantage of creating a barrier between the patient and care team, which can compromise the intensive care and monitoring often needed.

Carbon dioxide plays a significant role in CBF. Hypercapnia causes vasodilation and increased ICP, whilst hypocapnia causes vasoconstriction and decreased ICP. While hyperventilation was previously recommended, this can be detrimental; even small amounts of hypocapnia ($PaCO_2$ < 34%) can cause excessive vasoconstriction with decreased CBF, ischemia, and neuronal death (16).

Intravenous fluid therapy

Intravenous (IV) fluid therapy is a mainstay of shock treatment, but controversy remains as to the most appropriate fluids to administer for head trauma, and a consensus has not been reached. Fluid therapy should be directed towards resolving hypovolemia, preventing hypotension, and maintaining CBF. Patients with head trauma commonly present in varying degrees of hypovolemic shock, and maintaining systolic blood pressure > 90 mmHg is recommended (4). A human study showed a 150% increase in mortality in patients that had even a single episode of hypotension with systolic blood pressure < 90 mmHg (17).

Due to the potential for breakdown of the blood-brain barrier (BBB) in patients with TBI, fluid therapy may contribute to continued damage of the brain parenchyma via vasogenic edema, cytotoxic edema, and fluid shifts. However, maintaining an adequate CPP is vital since autoregulation is frequently compromised and dependent on blood pressure. The fluid plan must be selected, frequently monitored, and adjusted as needed for each patient.

Isotonic crystalloids

High amounts of intravenous free water may contribute to cerebral edema due to the loss of cellular tight junctions in the damaged brain parenchyma, so 0.9% NaCl, which contains the least amount of free water, is a potential choice. However, due to the higher amounts of chloride and the lack of a buffer, it is also an acidifying solution that may worsen any pre-existing acid-base derangements, and it is associated with acute kidney injury (18). Buffered isotonic crystalloids are a reasonable and justifiable choice. Regardless of the crystalloid selected, therapy should be directed at correcting the derangements noted above (*e.g.*, shock). The authors recommend 10-20 mL/kg given over 10-15 minutes to effect.

Colloids

Colloid solutions are designed to be plasma expanders, as they increase oncotic pressures to retain volume within the intravascular space. As such, they may be an attractive tool in the

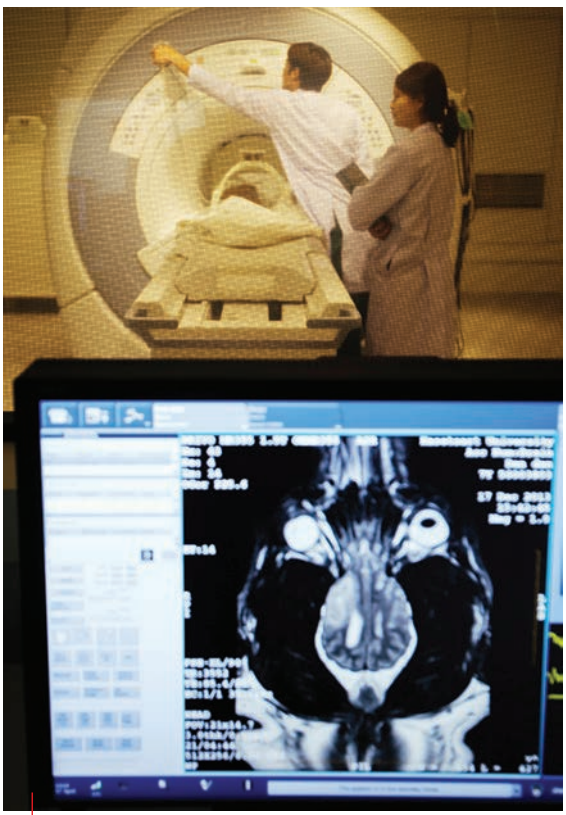

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Figure 7. MRI can be useful in assessing TBI patients, for example in assisting prognosis of a case.

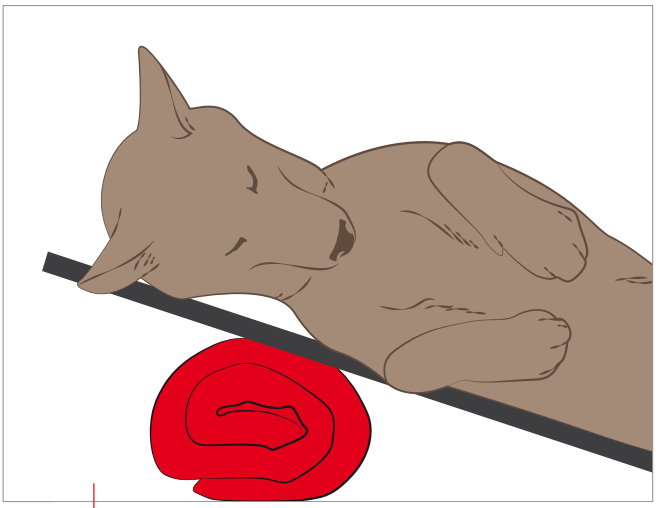

Figure 8. A rolled-up towel and stiff board can be used to place the patient on a 15-30° incline to help improve venous drainage without decreasing cerebral perfusion.

resuscitation of the hypovolemic or hypotensive head trauma patient. There is a concern that oncotic particles might leak into a traumatized brain due to disruption in the BBB, but no veterinary randomized trials have been performed to test the effects of colloids in TBI cases. However, post-hoc evaluation of a study in human TBI patients comparing resuscitation with saline versus albumin (19) did find a significantly increased risk of death associated with albumin. Until definitive studies show a clear benefit of colloids over crystalloids, the authors do not recommend the use of colloids in TBI.

Hypertonic saline

Hypertonic saline has several attributes that make it an attractive treatment in patients with TBI. It creates an osmotic potential for cellular shifts of water from the intracellular and interstitial spaces into the intravascular space to increase intravascular volume. In doing so, it also increases cardiac output. It also provides intravascular volume expansion greater than its own volume. With these properties, it is particularly effective for hypotensive TBI patients, but as a crystalloid it will rapidly redistribute into the interstitial space, so its IV volume expansion properties only last 45-75 minutes. Other benefits of hypertonic saline are discussed below.

Hyperosmolar fluids

Either mannitol or hypertonic saline can be beneficial due to their hyperosmolar properties. Mannitol is an osmotic diuretic that also has free radical scavenging properties (13) and additionally reduces blood viscosity and improves microcirculatory blood flow. Vasoconstriction of the pial arterioles also decreases cerebral blood volume and ICP (20,21). The recommended dose is 0.5-1.5 g/kg IV over 15-20 minutes (7,8,21), and it can reduce intracranial pressure for 2-5 hours (21), but since it causes diuresis, patients should be volume-resuscitated before administration and euvolemia maintained.

Hypertonic saline is a volume expander via its osmolar effects, but it has other additional benefits. These include reduced endothelial swelling and improved regional blood flow, rheologic properties that decrease blood viscosity and improve perfusion, decreased brain excitotoxicity by promoting reuptake of excitatory neurotransmitters such as glutamate, and immunomodulatory effects (4,7,13). Hypertonic saline may be superior to mannitol in reducing intracranial hypertension (7), but it should always be followed by isotonic crystalloids to maintain adequate hydration, and caution must be taken if used in dysnatremic cases. The recommended dose is 4 mL/kg of 7.5% or 5.4 mL/kg of 3% saline IV over 15-20 minutes.

Antiepileptic therapy

Seizures can cause further secondary injury via increased ICP, increased oxygen demand within the brain, and decreased CBF. Human TBI patients have increased rates of seizures as high as 12% (20), whilst one study showed a rate of 6.8% of canine patients developed post-traumatic seizures (22). Prophylactic antiepileptic drugs may be considered, but no evidence-based recommendations can be made. Benzodiazepines are recommended in the emergent setting followed by initiation of a continued antiepileptic medication, such as levetiracetam or phenobarbital.

Corticosteroids

Steroids are not recommended; whilst they are potent anti-inflammatory agents historically used to manage TBI patients, a large human clinical trial showed an increased risk of death at two and six weeks (23), and the Brain Trauma Foundation does not recommend their use (20).

Hypothermia

As TBI is associated with increased metabolic demands, hypothermia may help mitigate those demands and decrease secondary brain injury. There is currently conflicting data in human medicine about

"Neurological assessment should ideally be performed before administration of analgesic therapy and after adequate resuscitation if possible; evaluation focuses on the level of consciousness, posture, and brainstem reflexes."

David Sender

Table 2. Drugs commonly employed in treating head injuries in dogs.

Drug	Dose	Side effects
Opioid – Full mu agonist Fentanyl Methadone Morphine	 2-5 mcg/kg IV, then CRI 2-5 mcg/kg/hr 0.2-0.5 mg/kg IV/IM 0.25-0.5 mg/kg IM	Sedation Respiratory depression Mydriasis Panting Dysphoria Nausea
Opioid – partial mu agonist Buprenorphine	0.01-0.03 mg/kg IV/IM	Sedation Respiratory depression Mydriasis Panting (less common) Dysphoria Nausea
Dissociative NMDA antagonist Ketamine	0.1-1.0 mg/kg IV, then 2-10 mcg/kg/min	Tachycardia Increased myocardial oxygen demand Disorientation
Sodium channel blocker Lidocaine	1-2 mg/kg IV over 5-10 minutes, then 25-50 mcg/kg/min	Nausea Arrhythmias
Alpha-2 agonist Dexmedetomidine	0.5-3 mcg/kg IV/IM, then 0.5-1 mcg/kg/h	Sedation Hypotension Respiratory depression
Benzodiazepine Midazolam	 0.1-0.5 mg/kg IV/IM/IN	Paradoxical excitement
Phenothiazine derivative Acepromazine	 0.005-0.02 mg/kg IV Maximum effect takes 20-30 minutes	Hypotension
Hypnotic anesthetic Propofol	1-5 mg/kg IV, then 100-400 mcg/kg/min	Hypotension Decreased cardiac output Respiratory depression
Anticonvulsant Levetiracetam	 40-60 mg/kg IV, then 20-40 mg/kg IV/PO q8h	Sedation (minimal)
Barbiturate anticonvulsant Phenobarbital	4 mg/kg IV q6h for 24 hours, then 2-2.5 mg/kg PO q12h	Behavioral changes Sedation Ataxia (truncal) Polyuria/polydipsia Liver enzyme changes

the benefit of therapeutic hypothermia via barbiturate-induced coma, with no recommendations made (20), and there is a paucity of evidence in veterinary medicine on this subject. The authors recommend allowing any hypothermic patients to warm passively, with temperature monitoring in all TBI patients to avoid hyperthermia and excessive hypothermia.

Systemic management treatments

Analgesia

Adequate analgesia cannot be understated for the head trauma patient. Opioids are a reasonable first-line, as they provide good analgesia and are generally cardiovascularly safe, but multimodal analgesia is strongly recommended once the patient has been sufficiently stabilized and evaluated.

Lidocaine is a sodium channel blocker that can be used systemically as an analgesic. Aside from providing mild to moderate analgesia, it has been shown to scavenge ROS and lipid peroxidation (21).

Ketamine is a dissociative anesthetic and an antagonist of N-methyl-D-aspartate (NMDA) receptors which may be particularly useful in TBI patients. While some previous studies suggested that it may increase ICP, new data indicate that its properties of glutamate activation inhibition, neuroprotective effects, NO synthase inhibition, and vasoconstriction all might help improve systemic blood pressure and CBF, minimize secondary brain injury, and decrease ICP (24).

Sedatives

Alpha-2 agonists such as dexmedetomidine are reliable sedatives with mild analgesic properties. Studies in humans and case reports in veterinary patients are mixed in terms of support for or against use in TBI patients, and no randomized, prospective studies have been performed in veterinary TBI patients to date, so until further data is available it is recommended this class of drug is used sparingly for cases of TBI (4).

Benzodiazepines work by modulation of gamma-amino-butyric acid (GABA) to provide sedation and anxiolysis (21), which – coupled with their

concurrent anticonvulsant properties and minimal cardiovascular and respiratory effects – make for an attractive management tool.

Phenothiazines (*e.g.*, acepromazine) work via non-specific antagonism of alpha-1 and alpha-2 receptors to provide sedation and anxiolysis (21), and although they were originally thought to lower the seizure threshold in epileptics, this has since been re-evaluated (21). At low doses, they appear to be relatively cardiovascularly safe, but at higher doses they cause vasodilation, which can lead to hypotension. Additionally, they are not reversible and provide less reliable sedation and anxiolysis.

Propofol is a short-acting hypnotic that has been used in cases of refractory status epilepticus (21). It may have neuroprotective effects via its modulation of GABA, but it also can cause hypotension, negative inotropy, and profound respiratory depression.

Miscellaneous therapies

Hyperglycemia is a relatively common finding in both human and animal TBI patients, and in the latter, it has been shown to correlate with the severity of TBI, but not with outcome (3), so the use of insulin for glycemic control is not recommended (13).

Parenteral nutrition can be considered for patients deemed at-risk of aspiration. In people, TBI is also associated with gastric ulceration and bleeding (7), and the use of prophylactic antacids, such as proton pump inhibitors (*e.g.*, omeprazole, pantoprazole) or H_2-blockers (*e.g.*, famotidine) can be considered. Surgical treatments warrant further research before recommendations can be made.

A summary of drugs commonly used for dogs with head injury is given in **Table 2**.

CONCLUSION

Dogs that have suffered a traumatic brain injury (TBI) can be a challenge to assess and treat, yet with appropriate intervention many will show significant improvement and often appear to be able to compensate for any remaining neurologic deficits. It is, however, difficult to predict the prognosis after a TBI, as this is dependent on the severity of injury and the timing and efficacy of treatment. Serial evaluation using the coma score can be used to assess prognosis for recovery in individual cases, and owners should be informed their pet may have residual neurological deficits, including (but not limited to) seizures.

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SMALL ANIMAL TRANSFUSION MEDICINE

Confused about what blood product to use and when? This paper offers a review of the current options available for transfusion in small animal medicine.

KEY POINTS

1. The advent of commercial blood banks in many countries now means that transfusion of blood products can be done in most first opinion clinics.
2. Various blood products are obtained from whole blood, and the clinician should select the most appropriate product for each case.
3. Blood typing and cross matching are essential precursors to any blood product transfusion.
4. Transfusion reactions can occasionally occur, and patients must be carefully monitored before, during and after a transfusion.

Introduction

Transfusion medicine has a substantial place in small animal clinical practice, mainly in emergency and critical care situations, and the emergence of blood banks in many countries now permits easy access to, and rapid delivery of, various blood components to the clinic on demand. This, along with innovative and quick methods for blood typing and crossmatching, and recent advances in knowledge, means that transfusions can be done in most clinics. Even though transfusion of blood products can be life-saving, it can also potentially be life-threatening, and this article aims to review the current situation in order to provide useful information for the front-line practitioner.

Blood products

When blood is collected from a suitable donor, it is transferred to a bag or syringe containing anticoagulant and nutrients for the cells. Some veterinarians may choose to collect blood in their own clinic, using commercial collection bags; for dogs, these are typically supplied containing the correct amount of anticoagulant (usually CPD (Citrate-Phosphate-Dextrose)) for the volume of blood to be donated **(Figure 1)**. When taking feline blood, a syringe should be pre-filled with 1 mL of anticoagulant for every 7 mL of blood to be collected **(Figure 2)**. Alternatively, ready-to-use products can be purchased from dedicated blood banks **(Figure 3)**, which offer several advantages; it allows

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Figure 1. Blood being taken from a dog into a commercial collection bag, which is supplied with an appropriate anticoagulant.

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the best product to be used for a specific condition; it reduces the risk of transfusion reactions; and it ensures efficient use of all blood resources (1,2). Several different products can be obtained from collected blood; these are broadly classified into red blood cell (RBC) products and plasma components, as shown in **Box 1** (3).

Red blood cell products

- Fresh whole blood (FWB) – this contains red and white blood cells, platelets, coagulation factors, and plasma proteins such as albumin (4). To be considered "fresh" it has to be transfused within 6-8 hours after collection (5).

- Stored whole blood (SWB) – this is whole blood not transfused within the first 8 hours after collection, which means it has reduced levels of platelets and clotting factors. It should be stored in a refrigerator at 1-6ºC, and can be used within 21-28 days of collection (3,4).

- Packed red blood cells (pRBC) – centrifugation of whole blood separates the erythrocytes from the plasma to produce a product with less oncotic pressure and no coagulation factors, and with a packed cell volume (PCV) of around 70-80% **(Figure 4)**. If required, filtration will allow removal of the white blood cells to make the leukocyte-reduced pRBC (3-5).

Plasma products

These are obtained from whole blood centrifugation and contain all functional blood proteins at their original concentrations if performed within 8 hours of collection.

- Fresh frozen plasma (FFP) – Unless the fresh plasma is administered within 1 hour after processing (6), it should be frozen; to be classified as fresh frozen plasma, it must be

Figure 2. Blood being collected from a cat from the jugular vein using a syringe which has been pre-filled with an anticoagulant.

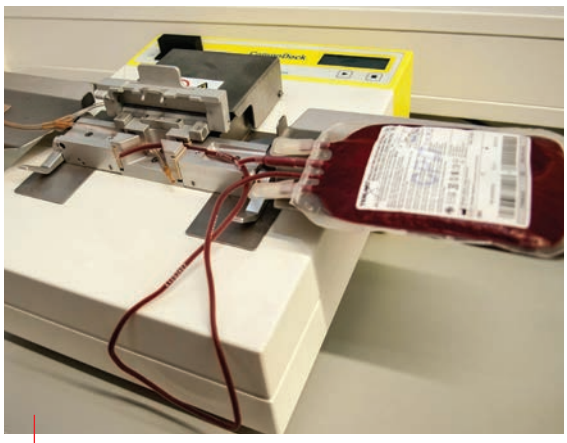
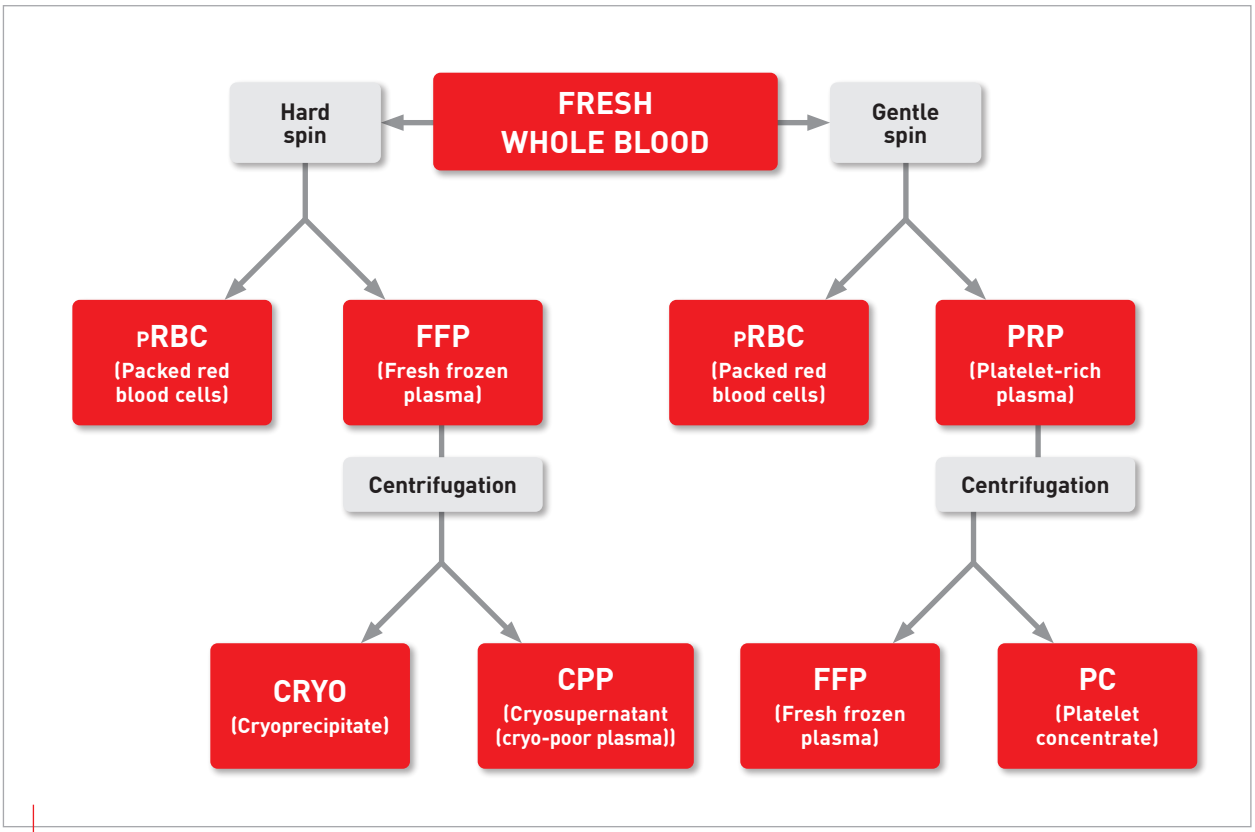


Figure 3. Commercial blood banks have sophisticated equipment that ensures blood products are collected, packed and stored under optimum conditions.



Box 1. A breakdown of products that can be obtained from canine or feline blood.

Figure 4. A unit of feline packed red blood cells.

frozen within 6-8 hours of collection, allowing the plasma to retain all the coagulation factors and proteins (3) **(Figure 5)**.

- Stored frozen plasma (SFP) – Also simply designated as frozen plasma, this term is applied to fresh frozen plasma if it has gone past its expiry date, or where centrifugation or freezing is performed more than 8 hours after collection, or to FFP which has been thawed and then refrozen without being opened. SFP has fewer clotting factors and proteins than FFP (3,6).

- Cryoprecipitate and cryosupernatant – Cryoprecipitate is produced by controlled thawing of a FFP unit followed by centrifugation; this results in a concentrated product containing insoluble proteins, factor VIII, von Willebrand factor (vWF) and fibrinogen (1). The supernatant removed from the preparation of cryoprecipitate is called cryosupernatant (or cryo-poor plasma); it lacks vWF, fibrinogen and insoluble proteins, but retains albumin, hemostatic proteins and immunoglobulins (6).

- Platelet-rich plasma (PRP) and platelet concentrate (PC) – Platelet products have a short life and limited demand, so blood banks only produce these to order. Platelet-rich plasma results from a gentle spin of fresh whole blood (1) **(Figure 6)**, whilst platelet concentrate is obtained by centrifugation of PRP which "pellets" the platelets (7).

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Figure 5. Fresh frozen plasma; this has to be prepared and frozen within 6-8 hours of collection.

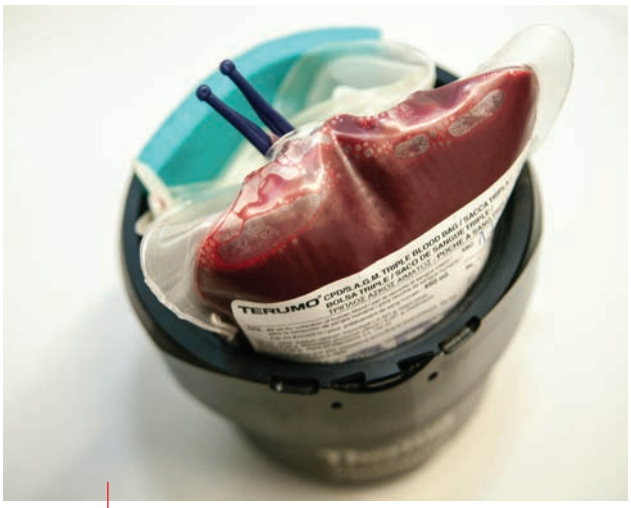

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Figure 6. A unit of dog blood in an insulated sleeve ready for centrifugation in order to prepare plasma products.

Indications

Anemia, coagulopathies, sepsis, disseminated intravascular coagulopathy (DIC) and specific factor deficiencies are some of the indications for transfusion with an appropriate blood product (3), but the decision to proceed should be made after considering all potential risks and benefits. A careful evaluation should be performed to address the recipient's transfusion needs and to choose the correct blood component if there is no indication for whole blood transfusion. This maximizes the use of a blood unit and reduces the risk of transfusion reactions (8,9).

Red blood cell products

Correct tissue oxygenation depends on the hemoglobin levels in the circulation and the cardiac output (3). Since almost all the oxygen in blood is carried by hemoglobin, the way to increase oxygen transport is through transfusion of a RBC product. Determining the packed cell volume (PCV)/hematocrit (HCT) and hemoglobin concentration (HGB) of the patient, along with a physical evaluation, will help the veterinarian to decide if an animal needs blood therapy (8). Although there is no exact PCV value below which a patient is deemed to need a transfusion, anemia (from hemorrhage, hemolysis or ineffective erythropoiesis) is the main reason to perform RBC transfusion, with some studies suggesting that blood loss is the main indication for transfusion in dogs and cats (10). The preferred options are FWB or pRBC. FWB has all the physiological blood components (functional platelets, plasma proteins, coagulation factors) and is an excellent choice for anemia cases where there is also a coagulopathy or thrombocytopenia (8). In cases of massive hemorrhage (loss of > 50% of circulating volume), FWB is also the product of choice in order to restore the oxygen transport function and the oncotic pressure (11).

The administration of pRBC is indicated when there is an anemia in a normovolemic patient (hemolytic or non-regenerative; either acute or chronic). Because pRBC has an HCT of 70-80% and a lower oncotic pressure then whole blood, it is less likely to cause fluid overload in normovolemic recipients (1,11). Packed red blood cells can also be used in hypovolemic cases, but since there is a need to increase oncotic pressure and replenish other blood elements, FFP should be transfused as well (8).

Plasma products

The use of plasma products has been reported in various situations, including treatment of hypotension and to give oncotic support, to restore clotting factors in coagulopathies, for internal bleeding and uncontrollable mucosal bleeding, and as supportive treatment in cases of sepsis, trauma and gastric-dilation-volvulus (12).

Fresh frozen plasma has been proven to retain the functionality of hemostatic proteins for a year (13) and is the main choice to treat coagulopathies (12). Frozen/stored plasma can retain non-labile coagulation factors such as Vitamin K, and is indicated for the treatment of coagulopathies due to rodenticide (anticoagulant) toxicosis (1).

Cryoprecipitate is the most indicated plasma product to provide vWF, for the treatment of hemophilia A and fibrinogen deficiency or dysfunction (6), whilst cryosupernatant is the most cost-effective option to treat vitamin K deficiency (6).

The use of plasma products has also been described in cases of hypoproteinemia, using FFP and cryosupernatant containing albumin. However, a dose of 20-25 mL/kg is required to raise albumin levels by 0.5 g/dL (6).

Platelet products are mainly recommended for hemorrhage situations secondary to severe thrombocytopenia or other thrombopathies. If the bleeding is caused by DIC or immune-mediated thrombocytopenia, platelet products can also be helpful, but are less beneficial, since transfused platelets can be quickly destroyed (14).

From the authors' experience, with the increase in blood product distribution by blood banks, pRBC and FFP are the most readily available components and therefore the most used to fulfil all the needs listed above (6).

Blood types

Both dogs and cats have species-specific blood types, defined by antigenic proteins on the surface of the red blood cells, and which can induce adverse reactions when introduced in another patient's circulation. For this reason, it is not enough to emphasize that only compatible blood should be administered to the patient, and all animals should be blood typed and/or cross-matched.

Dogs

The canine blood types are grouped using the DEA (Dog Erythrocyte Antigen) system, which originally included DEA 1.1, 1.2, 1.3, 3, 4, 5, 6, 7 and 8. Antigens 6 and 8 are no longer routinely identified due to the absence of typing sera, but a new antigen, *Dal,* was reported in 2007 (15) and more recently another two antigens have been identified – *Kai 1* and *Kai 2* (16). DEA 1.1 has been shown to have the highest antigenicity, and is known to have autosomal dominance inheritance, so dogs are now classified as being DEA 1.1 positive or negative (17). This antigen can precipitate a severe hemolytic reaction in DEA 1.1 negative dogs that receive a second transfusion due to previous sensitization (since there are no natural alloantibodies) (18), so all blood donors and recipients should be tested for DEA 1.1.

One study has reported acute hemolytic transfusion reactions (AHTR) after sensitization to the DEA 4 antigen, but since 98% of dogs carry this antigen, only the 2% of dogs that are negative for this antigen are at risk of AHTR, and only after a previous transfusion. The other DEA antigens (3, 5 and 7) appear to have low importance in clinical practice, with no documented transfusion reactions (19).

"Ready-to-use blood products can be purchased from dedicated blood banks, which offer several advantages; it allows the best product to be used for a specific condition; it reduces the risk of transfusion reactions; and it ensures efficient use of all blood resources."

João Araújo

Cats

Feline blood is categorized using the AB system, with 3 main types (A, B and AB) described, type A being the most frequent one. Unlike DEA 1.1 in dogs, cats have naturally occurring alloantibodies that can be responsible for hemolytic reactions (20). Recently, a new blood-group antigen was identified, known as *Mik* (21). This has clinical relevance, since there is a report of a hemolytic transfusion reaction in a type A cat which had never previously received a transfusion (21). With this in mind, a crossmatch should be performed in all cats before a transfusion (22).

Blood typing

Blood typing can be done either at a commercial laboratory or in-house. There are currently three sorts of blood typing kits available: card agglutination, immune-chromatographic strip (ICS), and gel tube, but they all function in a similar way, with a sample of the patient's blood being added to a mono- or polyclonal antiserum; a positive result (hemagglutination reaction) is identified by a color change **(Figure 7)**. One study has reported that the card and ICS methods are a reasonable option for emergency situations, but the gel-based method appears to be the gold standard for typing DEA 1.1 donors and recipients (23).

Crossmatching

Whilst blood typing relates to *antigens* on the RBC, crossmatching – which can be done in-house – focuses on *antibodies* in the plasma, and can indicate if there may be a reaction between the blood of the donor and the recipient. It is a two-stage process, with a major and minor crossmatch (19). The major crossmatch tests for compatibility between the donor erythrocytes and the recipient's plasma; the minor one tests for compatibility between the donor plasma and the recipient's erythrocytes. Any agglutination reaction implies incompatibility between donor and recipient.

The main indications for performing a crossmatching test in dogs are for where the patient has an unknown transfusion history, where it has had previous transfusion reactions, or if it has received a red blood cell transfusion more than 4 days previously (9). As noted above, crossmatching should always be performed in cats.

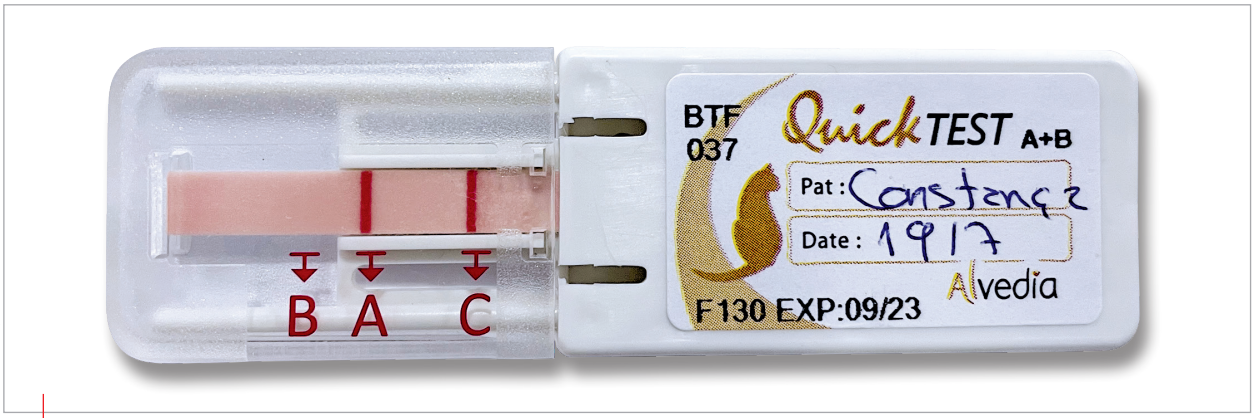

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Figure 7. A strip (ICS) test for typing feline blood.

At present, there are three types of tests available: the standard tube agglutination assay, the gel-tube assay and the immunochromatographic strip, with the first one currently being the gold standard (19).

How much to transfuse?

The volume of a blood product to be administered depends on various factors, including which product is being administered, what the desired effect is, and the patient's response to the transfusion.

For pRBC's, the following formula can be used:

Volume (mL)= 85 (dog) or 60 (cat) x bodyweight (kg) x [(Desired PCV - Actual PCV)/Donor PCV]

When using a plasma product to treat hypotension or hypoalbuminemia, or to increase a patient's passive immunity, the recommended rate is 10 mL/kg over a period of 2-4 hours; the transfusion can be repeated every 6-24 h as necessary. In severe cases, (*e.g.*, refractory hypotension) the rate can be increased to 20-60 mL/kg. For severe hypoalbuminemia, a single transfusion at 10-20 mL/kg over 2-4 hours will increase albumin levels by 0.2 g/dL.

Plasma can also be administered in hypoalbuminemia patients using a constant rate infusion (CRI) of 1.5-3 mL/kg/hr over 12-24 hours to achieve an increment of 0.3-0.5 g/dL.

If platelet concentrate is being administered, 40-70 mL/10 kg SID-TID should be used until effect. Each transfusion should increase platelet number by 10-40 x 10^3/µL.

Preparing and administering the blood product

When performing a transfusion, certain aspects may affect the quality of the blood product and the success of the transfusion. Firstly, before starting the procedure, it is important to evaluate the integrity of the storage bag, the color of the component and its consistency. Any unit with clots, an abnormal color or unusual appearance should not be used. A double check should be made that the correct unit will be given to the right animal.

Warming refrigerated RBCs is regarded as unnecessary in normovolemic and normothermic patients, since this may cause quicker deterioration of the cells and encourage microorganism growth. It should only be considered for hypothermic recipients, neonates or animals receiving a large amount of blood. Where warming is needed, the unit can be kept at room temperature for 30 minutes or placed inside a sealed plastic bag and put in a water bath (< 37ºC) for 15 minutes (3,8).

Frozen plasma products need to undergo a slow thaw before being administered to the patient; again placing the product inside a sealed bag before warming in a circulating water bath (< 37ºC) is appropriate, with careful monitoring of the temperature (9).

The preferred route for blood product administration is the intravenous route, using a 20-22G catheter (which should be placed no earlier than 24h prior to the transfusion). The catheter should only be used for the transfusion; concomitant administration of medications, non-isotonic fluids or lactated Ringer's should be avoided. If it is necessary to flush the catheter during the transfusion, this should be done using 0.9% saline. When the transfusion is finished, saline can then be attached to the perfusion set in order to avoid wasting the blood product that remains in the IV line. It is recommended to avoid giving antihistamines and antipyretics during the transfusion (22). Where intravenous infusion is not possible (*e.g.*, neonates), an intraosseous catheter can be used; cells will reach the blood circulation within minutes (4).

Infusions should be performed with a blood administration set that contains a filter (170-260 µm) which will retain clots and micro-aggregate particles (9), especially if whole blood is being transfused **(Figure 8)**. If administering the blood product via a syringe pump, a pediatric filter with reduced dead space or a microaggregate filter of 18-40 µm should

be used. Administration can usually be done simply using gravity flow, and infusion pumps should be generally avoided, especially with RBC products, since they may cause hemolysis (24). If an infusion pump is necessary, the manufacturer's instructions must be consulted to verify if the unit is safe for transfusion of blood products (8).

The rate of the transfusion depends on the clinical status of the patient. In a normovolemic animal the initial rate should be slow (0.25-0.5 mL/kg/hr) for the first 15-30 minutes to allow for any potential adverse reactions, before increasing to 2-10 mL/Kg/h in dogs and 3-5 mL/Kg/h in cats. An hourly rate of 10-20 mL/Kg is the maximum recommended in order to avoid fluid overload. Where this is a possibility (*e.g.*, in cardiac or renal cases), the rate should be between 1-3 mL/Kg/h, starting at the lower end and increasing it to the maximum if there are no adverse reactions (1). In cases that have severe blood loss and hypovolemia, a rapid volume correction may be tolerated using pRBC at 20-60 mL/Kg/h (8). If higher rates are necessary, manual compression of the blood bag or a syringe bolus may be used.

Infusion times should not exceed four hours, as this increases the risk of bacterial contamination. In patients at risk of fluid overload, the recommended lower infusion rate may be incompatible with a four-hour window, and here the transfusion should be split, with refrigeration of the unused product as necessary (4).

Recipient monitoring

Monitoring the patient should begin before administration of any blood product, with evaluation of the PCV, total solids, heart rate, respiratory rate, mucous membrane color, body temperature and (if there is risk of overload) arterial blood pressure. The color of the urine can also be useful (4). A physical exam should be performed every 15-30 minutes during the procedure and at 1, 12 and 24 hours after the end of the transfusion. The PCV, total solids and urine color should also be assessed immediately post-transfusion and then at 12 and 24 hours (3,22). In patients receiving a plasma product, coagulation status, hematocrit and/or total solids should be measured before and after transfusion, to verify the effectiveness of the therapy (6).

"Administration of blood products can usually be done using only gravity flow, and infusion pumps should be generally avoided, especially with RBC products, since they may cause hemolysis."

Maria João Dourado

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Figure 8. An in-line filter should be used during the infusion to collect any clots and micro-aggregate particles.

Adverse reactions

Various possible adverse reactions to transfusion of blood products are recognized. These include:

Febrile non-hemolytic transfusion reactions (FNHTR)

This is an acute reaction which can be either immunologic or non-immunologic in nature. Patients develop a temperature above 39ºC (102.2ºF) or have an increase in temperature more than 1ºC (1.8ºF) from that registered at the physical exam pre-transfusion. To diagnose a FNHTR, underlying infection, acute hemolytic transfusion reaction, transfusion-related acute lung injury and transfusion transmitted infection have to be excluded (25).

Respiratory reactions

These include Transfusion Associated Dyspnea (TAD), Transfusion Associated Cardiac Overload (TACO), and Transfusion Related Acute Lung Injury (TRALI). TAD is again an acute transfusion reaction, with the patient developing severe respiratory distress within 24 hours following transfusion. For the correct diagnosis of TAD, transfusion circulatory overload and transfusion related acute lung injury must be ruled out (25). TACO is an acute, non-immunologic reaction secondary to increased blood volume, with the patient showing signs of respiratory stress and pulmonary edema within

6 hours of transfusion (25). TRALI is secondary to antigen-antibody interactions and is distinguished by acute hypoxemia and non-cardiogenic pulmonary edema, again within 6 hours of transfusion (25).

Allergic transfusions reactions

Acute and immunologic, these are secondary to a type I sensitivity response to an antigen. They are distinguished by an anaphylactic response (moderate to life-threatening) within 4 hours after transfusion. In the dog, clinical signs can include erythema, urticaria, pruritus, angioedema, gastrointestinal alterations and hemoabdomen with progression to collapse. In cats the signs are primarily respiratory, but pruritus and gastrointestinal signs are also reported (25).

Hemolytic reactions

These can be acute or delayed in nature. An AHTR is characterized by an acute hemolysis which can be immunologic or non-immunologic in nature; it is a non-infectious reaction occurring during or within 24 hours of the transfusion procedure (25). Delayed reactions (24 hours to 28 days afterwards) are also non-infectious, and again can be immunologic or non-immunologic; they are secondary to lysis or accelerated clearance of transfused RBCs (25).

CONCLUSION

Blood transfusions were originally a treatment option that only referral centers could offer, but with the ready availability of blood products and the ability to perform in-house blood typing and crossmatching, most clinics can now offer transfusions with good quality blood products. Since blood products are a valuable and finite resource, it is important to use them rationally and minimize wastage; a transfusion is often not the only and definitive treatment. Optimizing use of the different blood products is essential, meaning that whole blood is often not the "go-to" product, so a correct diagnosis is necessary to ensure a good outcome. Finally, it is fundamental that the blood donor's welfare is protected during the entire collection process.

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HOW I APPROACH... THE DOG IN RESPIRATORY DISTRESS

How do you deal with a dog in respiratory distress? This article reviews the optimal approach required to assess and stabilize the critically ill patient.

KEY POINTS

1. Dogs presenting in respiratory distress can decompensate quickly.
2. Initial stabilization involves oxygen supplementation, minimal handling, and – when appropriate – sedatives.
3. A rapid but thorough examination allows the clinician to characterize the respiratory pattern and then localize the abnormality.
4. There are 8 categories of possible localization of the respiratory distress that need to be investigated.

Introduction

There are many conditions that can cause respiratory distress or apparent dyspnea in veterinary patients. Strictly speaking, the word "dyspnea" refers to a feeling of being unable to catch one's breath; therefore, although animals are frequently described as being "dyspneic", the clinician is observing "apparent dyspnea" or increased respiratory effort. Regardless of the terminology used, rapid identification of the problem is critical for treatment, but as these patients tend to be fragile and can decompensate quickly, a thorough diagnostic work-up may be challenging. History and physical examination, and particularly characterization of the respiratory pattern, can help localize the area of concern, which can then inform the differentials and diagnostic and therapeutic strategy for the patient. This article will review the different sections of the respiratory tract that can be involved in cases of canine dyspnea, and discuss differentials, emergent diagnostics, and treatments for each.

The initial approach

Given that dyspneic patients are often critically ill, appropriate initial stabilization is important while a more tailored plan is formulated. In general, two key principles should be kept in mind for all animals presenting in respiratory distress, namely oxygen supplementation and minimal stress.

Oxygen supplementation, in the short term, is not harmful; this can be administered with a face mask or flow-by during examination and then transitioned to a nasal cannula if the animal tolerates it, or an oxygen cage if preferred. Oxygen cages allow for a quiet, low stress environment with a relatively high fraction of inspired oxygen (40-80%); however, if the patient is at risk of upper airway obstruction (as discussed below), they should be in a cage that allows people nearby to hear any change in their respiratory noises (*i.e.*, worsening obstruction). If an animal has severe airway obstruction, is fatiguing, or is unable to breathe on its own, intubation should be pursued. The general rule is that if the clinician is worried that intubation is necessary, intubation should be performed; this allows for delivery of 100% oxygen and also bypasses any upper airway obstruction and takes over the work of breathing. Occasionally, oral intubation is very challenging or not possible, and other methods are described below.

Minimizing stress frequently means minimal handling, and can be eased by use of sedatives. After a brief physical examination, venous access should be secured (if possible), and sedatives administered if needed. Butorphanol is typically preferred as a sedative over full-mu opioids as it causes less respiratory depression; however, in painful conditions, such as following trauma, full-mu opioids (*e.g.*, fentanyl for its short-acting nature) are preferred given the lack of analgesia from butorphanol (an opioid with mu-antagonist and

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kappa-agonist activity). Ideally, this is given intravenously to decrease time to efficacy, but if placement of an intravenous catheter risks causing the patient to decompensate, intramuscular injections are an alternative option. After sedatives are administered, the patient should be placed in a temperature and humidity-controlled cage to deliver supplemental oxygen and to provide a quiet environment to minimize hospital stress.

The full physical examination may need to be staged depending on the severity of the respiratory distress; part of the examination is hands-on and requires a stethoscope, but a visual examination, even from outside the oxygen cage, is also valuable. Examination should focus on:

1. a quick overview looking for external abnormalities (*e.g.*, evidence of trauma or abdominal distension),
2. the respiratory pattern (*e.g.*, looking for tachypnea, abnormal inspiratory or expiratory effort, stertor or stridor, a restrictive pattern, orthopnea, paradoxical breathing, or nasal flaring),
3. pulmonary auscultation (*e.g.*, checking for crackles, wheezes, increased or decreased respiratory sounds), and
4. cardiac auscultation (*e.g.*, to detect a murmur, gallop, or abnormal rhythm).

The abnormality is localized once the clinician has this information, and diagnostic and therapeutic plans can then be tailored to the most likely disease process; the owner can be given more information, and ultimately morbidity and mortality are minimized. Pulse-oximetry is often the first objective measurement of oxygenation status, given its non-invasive nature. Ultimately, it is a useful tool to assess severity of disease and track improvement/decompensation over time; however, some animals are stressed by this procedure, and the result must be correlated with the clinical picture as an animal that is struggling to breath but maintaining a normal pulse-ox should still be considered critical and in respiratory distress until proven otherwise. An arterial blood gas measurement is more reliable – and allows for calculation of an A-a (alveolar-arterial) gradient – but more technically challenging to obtain and can also cause the animal excessive stress. A venous blood gas assessment, when possible, can also give valuable information about acid/base and perfusion status (*e.g.*, lactate), but importantly can also demonstrate hypercarbia, which would raise concern for lack of appropriate ventilatory ability.

There are several ways to break down how to localize the cause of respiratory distress; we use eight categories of potential disease localization: upper airway, lower airway, pulmonary parenchymal, vascular, pleural space, chest wall, abdominal distension, and "look-alikes" **(Table 1)**.

Upper airway

Physiologically, the upper respiratory tract is from the nose and mouth to the trachea at the level of the thoracic inlet. If this section is affected, examination will typically reveal inspiratory dyspnea (although some animals have expiratory effort as well). Animals may also exhibit inspiratory stertor or stridor, have a honking cough, or they may be observed choking or gagging. History and signalment will be helpful; for example, an excited Bulldog, an older Labrador running around on the first warm day in spring, or a young Pitbull Terrier seen playing with a stick may make us concerned about brachycephalic airway disease, laryngeal paralysis, or an oral foreign body, respectively. Other differentials include obstruction anywhere along the airways (secondary to mass, foreign body, or abscess), tracheal collapse, laryngeal collapse, nasopharyngeal collapse/stenosis, trauma, coagulopathy, or swelling/edema secondary to envenomation or heat stroke.

These patients are typically very stressed because they are struggling to breathe, so sedation with butorphanol and/or acepromazine is recommended. Close monitoring after sedation is

Table 1. Causes, treatments, and diagnostics for types of respiratory distress by localization.

Localization	Examination findings	Differentials	Emergency treatments	Diagnostics
Upper airway	• Inspiratory dyspnea • +/- stertor/stridor • +/- honking cough, choking, gagging	• Brachycephalic airway disease • Tracheal collapse • Laryngeal collapse • Nasopharyngeal collapse/stenosis • Trauma • Coagulopathy • Swelling/edema secondary to envenomation or heat stroke • Obstruction secondary to mass, foreign body, or abscess	• Oxygen • Sedation (butorphanol, acepromazine) • +/- intubation • +/- corticosteroids	• Sedated airway examination • Cervical/thoracic radiographs • +/- fluoroscopy • +/- tracheoscopy • +/- thoracic CT
Lower airway	• Expiratory dyspnea • Expiratory wheeze	• Bronchitis • Lungworm • Smoke inhalation • Trauma • Obstruction secondary to mass, foreign body, or abscess	• Oxygen • +/- bronchodilators	• Thoracic radiographs • +/- endotracheal or transtracheal wash • +/- fluoroscopy • +/- bronchoscopy • +/- thoracic CT • +/- fenbendazole
Pulmonary parenchyma	• Increased effort (inspiratory and/or expiratory) • Crackles/harsh lung sounds • +/- decreased lung sounds if severe • +/- restrictive pattern	• Pneumonia • Pulmonary edema (cardiogenic vs. non-cardiogenic) • Interstitial lung disease • Neoplasia • Trauma/contusions	• Oxygen • +/- furosemide vs. antibiotics vs. corticosteroids vs. other	• POCUS • Thoracic radiographs • +/- echocardiogram • +/- thoracic CT • +/- endotracheal wash
Vascular	• Acute onset tachypnea with increased effort • +/- cough • +/- syncope • +/- harsh lung sounds • +/- crackles/wheezes • +/- dull lung sounds	• Pulmonary thromboembolism	• Oxygen • Heparin • Treatment of underlying cause • +/- thrombolysis	• Thoracic radiographs • Complete blood cell count • Chemistry panel • D-dimers • Echocardiogram • +/- abdominal ultrasound • +/- CT with angiography
Pleural space	• Inspiratory effort • Restrictive breathing pattern • +/- paradoxical breathing pattern • Decreased lung sounds	• Pleural effusion (pyothorax, chylothorax, hemothorax, neoplasia, other) • Pneumothorax • Mass effect (neoplasia vs. diaphragmatic hernia)	• Oxygen • +/- thoracocentesis	• POCUS • Thoracic radiographs • +/- fluid analysis
Chest wall	• Decreased chest wall excursion • +/- abdominal movement on inspiration • +/- external wounds	• Traumatic • Neurologic	• Oxygen • +/- intubation • +/- pain medication • +/- antibiotics	• Blood gases • Thoracic radiographs • +/- POCUS • +/- complete blood cell count • +/- chemistry panel • +/- MRI/CSF tap • +/- anti-acetylcholine receptor antibody testing • +/- botulinum toxin testing • +/- EMG
Abdominal distension	• Distended abdomen, possible tympanic or with a fluid wave	• Mass • Ascites • Organomegaly • Gastric dilatation (+/- volvulus) • Pregnancy	• +/- oxygen • +/- abdominocentesis, decompression, surgery if indicated	• +/- POCUS • Abdominal radiographs or ultrasound
"Look-alikes"	• Variable	• Hyperthermia • Excitement • Anxiety • Pain • Metabolic acidosis • Anemia • Shock • Hypoglycemia • Medications (steroids, opioids, stimulants) • Abdominal distension	• Variable • +/- pain medication • +/- anxiolytic • Treat underlying disease process	• Pulse-oximetry • Blood pressure • Bloodwork (PCV, blood gases, acid/base status) • Thoracic radiographs

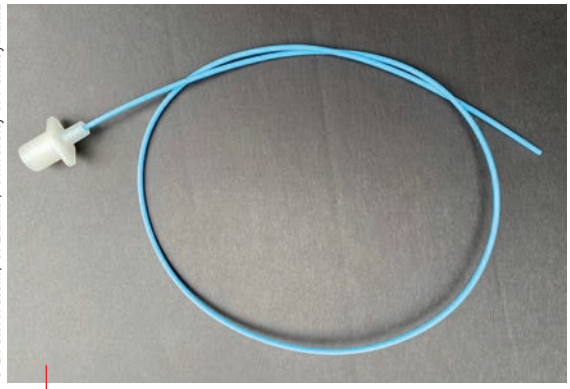

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Figure 1. An airway exchange catheter. This can be used for difficult intubations where the airway is narrow or partially obstructed. Note that the tip has holes to allow oxygen flow, and the top has a connector that can attach to an Ambu bag or a ventilator circuit. Once successfully placed, the connector can be detached and a larger endotracheal tube guided over the exchange catheter, which is then removed, leaving the more appropriately sized tube in place. Alternatively, if a larger tube cannot be placed, the airway exchange catheter can be used as a temporary measure to provide oxygen while an emergent tracheostomy is performed.

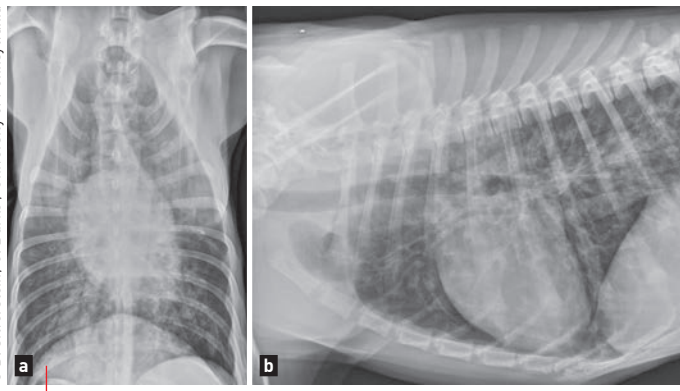

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Figure 2. DV **(a)** and lateral **(b)** thoracic radiographs from a dog with end-stage bronchitis. Note the severe diffuse bronchial pattern.

required in case the animal becomes excessively relaxed and is unable to ventilate, or if the upper airway further narrows as muscle tone decreases. When upper airway obstruction is suspected, preparation for imminent intubation is recommended. When a dog's airway becomes obstructed, the quality of noise produced may change, or the animal may suddenly make no sound despite significantly increased respiratory effort; at this point intubation will be required, but may be challenging depending on the cause of obstruction (*e.g.*, mass, inflammation, etc.). Oral intubation with a smaller endotracheal tube is recommended, but if the airway is compromised, a red rubber catheter or airway exchange device can be used to provide oxygen **(Figure 1)**. Certain functional diseases such as laryngeal paralysis are easily diagnosed with an airway examination at intubation, so if required emergently, the upper airway (laryngeal tissues, soft palate, oropharynx) should be evaluated, but this should not delay expedient intubation and delivery of oxygen. If intubation with anything larger than a catheter or airway exchanger is not possible, an emergent temporary tracheostomy may be required (ideally once the smaller tube is in place, to allow for even some degree of oxygenation during this procedure). Tracheostomy can be performed with an endotracheal tube if transtracheal (ideally cannulated) tubes are unavailable, and the technique is described elsewhere (1).

Some of these patients may present with an elevated body temperature (*e.g.*, heatstroke) or they may start to overheat in hospital if they continue to struggle and cannot lose heat through their respiratory tract. If this is the case, cooling may be required (wetting the fur with tepid water, fans, cool environment, etc.) to reduce the body temperature to 39.4°C/103°F; however, aggressive cooling below this point is not recommended, as this can lead to rebound hypothermia. Many of these dogs develop airway inflammation because of trauma to the tissues while breathing against an obstruction; an anti-inflammatory dose of steroids can be considered (*e.g.*, dexamethasone sodium phosphate, 0.1 mg/kg IV once). Some animals will also develop post-obstructive pulmonary edema; close monitoring of oxygenation levels, and auscultation and/or chest radiographs may be helpful in detecting this complication.

Once stabilized, diagnostics should be directed at determining the cause of the upper airway obstruction. A sedated airway examination is indicated to look for abnormalities of the oropharynx and larynx, such as brachycephalic airway disease, laryngeal paralysis or collapse, or any masses or foreign bodies. Cervical and thoracic radiographs, followed by fluoroscopy, may be considered if looking for tracheal collapse or mass effect. Advanced diagnostics, such as CT and

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scoping (*e.g.*, tracheoscopy, nasopharyngoscopy) may be required if the cause of obstruction cannot be easily identified with less invasive methods.

Lower airway

Lower respiratory tract disease encompasses the remainder of the conducting airways from the thoracic inlet to the alveoli. Patients with lower airway disease often have narrow bronchial lumens that are open at inhalation but have a tendency to close during expiration, thus causing an expiratory dyspnea, sometimes with an expiratory push. Expiratory wheezes may be heard on auscultation. In dogs this localization most frequently represents bronchomalacia seen in end-stage bronchitis, but trauma, lungworm, smoke or toxic substance inhalation, and obstructions (*e.g.*, secondary to stricture or foreign body) remain possible.

In addition to oxygen, these patients may benefit from bronchodilators such as terbutaline; however, caution should be used in dogs suspected of having significant heart disease, as terbutaline may increase the heart rate. Once stable, thoracic radiography to look for a bronchial or bronchointerstitial pattern is recommended **(Figure 2)**, although the diagnostic sensitivity of radiography for bronchial diseases in dogs is relatively poor (2). Thus, further diagnostics – such as an endotracheal or transtracheal wash and cytologic evaluation – should be considered. Fluoroscopy, bronchoscopy or CT could be considered to look for dynamic tracheal and/or mainstem bronchial collapse (if not observed on radiographs), tracheal masses or nodules, bronchiectasis, or excessive mucus production. The agreement between these tests can be relatively poor for lower airway disease, so ideally a combination of modalities is performed (3,4). Finally, a Baermann fecal test can be considered to diagnose lungworm infection, although empirical treatment with fenbendazole is often elected. If bronchitis is suspected, a corticosteroid taper may be recommended; some clinicians prefer inhaled fluticasone if required long term to decrease systemic absorption and side-effects.

Pulmonary parenchymal

Pulmonary parenchymal diseases incorporate abnormalities of the interstitium. Typical examination findings include crackles or loud breath sounds, although lung sounds can be decreased in dogs with severe disease that causes fluid accumulation and collapse of a portion of the lungs and thus lack of airflow. These dogs may have inspiratory effort, expiratory effort, or both, and may exhibit restrictive respiratory patterns, with short shallow breaths with or without abdominal effort.

Differentials are quite broad, and include pneumonia, pulmonary edema, interstitial lung disease, neoplasia (primary or metastatic), or traumatic injury (contusions), or ARDS (acute respiratory distress syndrome). Pneumonia may be secondary to infectious causes (bacterial, viral or parasitic) or aspiration events. Pulmonary edema can be cardiogenic or non-cardiogenic in origin. Interstitial lung disease includes idiopathic pulmonary fibrosis, heartworm disease, and (uncommonly) eosinophilic bronchopneumopathy. If detected, more specific clinical signs may help increase suspicion of the underlying cause; for example, murmurs or arrhythmias may be seen in dogs with cardiogenic pulmonary edema, while coughing, mucopurulent nasal discharge, and occasionally a fever may be seen in dogs with pneumonia, and hemoptysis can occur in cases with hemorrhage/contusions. Dogs that are suspected to have ARDS typically develop respiratory distress within 3-7 days of an underlying trigger or risk factor (*e.g.*, sepsis, pneumonia, surgery) and have evidence of edema on imaging that is not secondary fluid overload or cardiac dysfunction. These patients should be referred to a specialty hospital for work-up and aggressive supportive care. Signalment can also be used to narrow differential diagnoses (*e.g.*, West Highland White Terriers and idiopathic pulmonary fibrosis, or Huskies with eosinophilic bronchopneumopathy).

Given the many differentials, diagnostics are generally necessary to determine definitive treatment recommendations; however, until the animal is stable enough to safely perform tests, empirical treatment can be initiated, since oxygen therapy alone may not improve their respiratory status. For example, the index of suspicion for congestive heart failure may be higher in a small dog with localizable pulmonary disease, a loud murmur, and tachycardia, therefore empiric furosemide may be administered. Ideally, if ultrasound is available, it is worthwhile measuring the diameters of the left atrium and the aortic root in order to calculate the ratio and thus assess the size of the cardiac chamber; if the value is greater than 1.6, left atrial enlargement due to possible

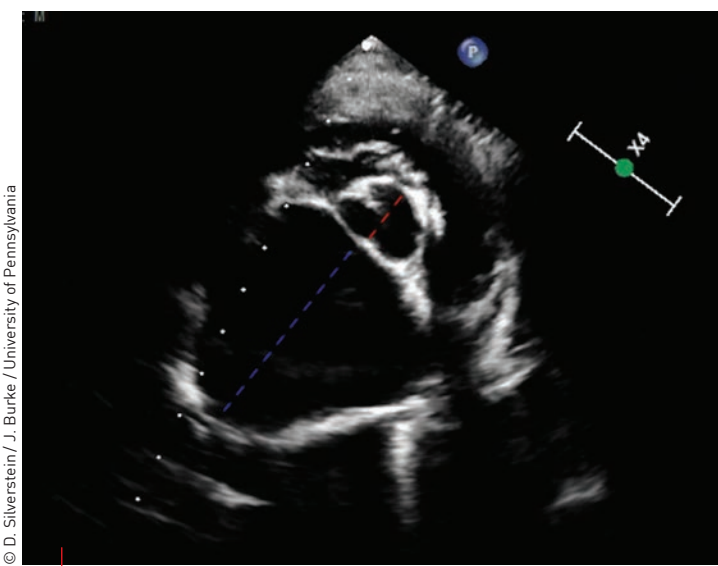

Figure 3. Point-of-care ultrasound (POCUS) evaluating the left atrium to aortic root ratio. The red dashed line represents the diameter of the aortic root, while the blue dashed line is the left atrium. This patient had a ratio of 3:1, consistent with left atrial enlargement.

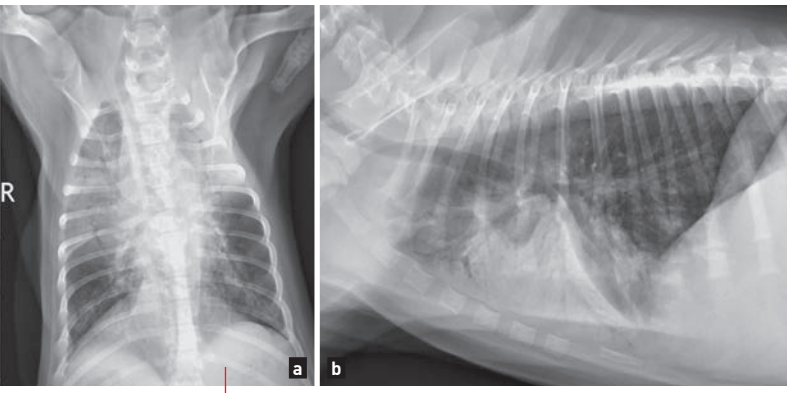

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Figure 4. DV **(a)** and lateral **(b)** thoracic radiographs from a dog with infectious pneumonia. Note the alveolar pattern in the right cranial, right middle, and left cranial lung lobes.

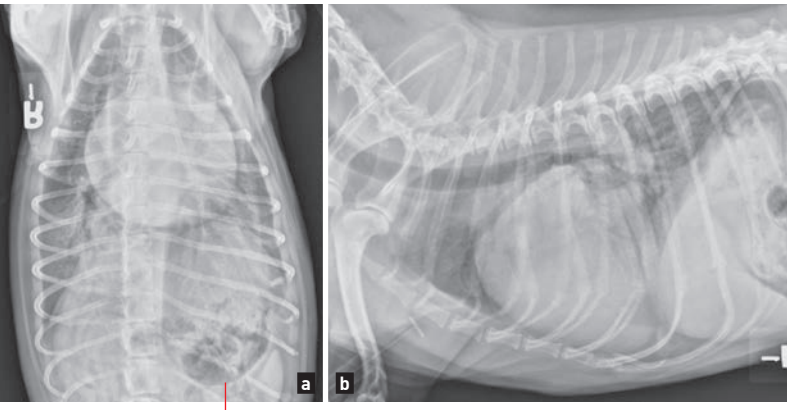

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Figure 5. DV **(a)** and lateral **(b)** thoracic radiographs from a dog with congestive heart failure. Note the left-sided cardiomegaly, perihilar to diffuse interstitial to alveolar pattern, and moderate pulmonary venous distension.

heart disease would be considered more likely **(Figure 3)** (5). A dog with dyspnea, an elevated temperature and mucopurulent nasal discharge would be concerning for pneumonia, and empirical antibiotics should be started.

Thoracic radiographs are the primary diagnostic for dogs with pulmonary parenchymal disease **(Figure 4)**, along with point-of-care ultrasound (POCUS) if possible, and an echocardiogram if cardiac disease is high on the differential list **(Figure 5)**. Pending initial diagnostic work-up, a thoracic CT and endotracheal wash may be recommended. Findings will help determine if treatment should consist of antibiotics, diuretics, steroids, bronchodilators, or oxygen alone.

Vascular

Some clinicians classify vascular disease (*i.e.*, pulmonary thromboembolic disease) as a subcategory of pulmonary disease; however, as it does not involve the parenchyma, we distinguish it from other causes. Pulmonary thromboembolism (PTE) is a challenging diagnosis to make and requires a full work-up to identify the underlying cause of hypercoagulability, as animals will be at risk of continued embolic disease without identification and correction of the primary source. Many disorders can cause hypercoagulability that may then lead to PTE, including protein-losing nephropathies or enteropathies, hyperadrenocorticism, immune-mediated hemolytic anemia, neoplasia, sepsis, and trauma. Examination findings vary, but typically include acute onset tachypnea and increased respiratory effort, and possibly coughing, syncope, or abnormal mentation. Auscultation may be normal or reveal loud lung sounds, crackles or wheezes. If concurrent pleural effusion is present, lung sounds may be decreased.

As with other conditions discussed, initial supportive care includes oxygen supplementation and intravenous catheter placement while diagnostics are pursued. Thoracic radiographs may reveal a variety of changes, including main pulmonary artery enlargement, interstitial or alveolar infiltrates, hyperlucent areas of peripheral parenchyma secondary to oligemia ("Westermark sign"), cardiomegaly, pleural effusion, or no abnormalities at all. In fact, PTE should be a differential in a patient with tachypnea and apparent dyspnea but with normal radiographs, especially if concurrent risk factors exist.
A complete blood count and biochemistry panel should be performed to look for underlying causes; thrombocytopenia and/or schistocytes may be present. A coagulation panel (looking specifically at D-dimers) may be helpful to increase the index of suspicion, but normal D-dimers do not exclude PTE, and elevated D-dimers are not specific for the condition (6,7). Abdominal ultrasound should be performed to rule out neoplasia or a source of sepsis if clinically indicated. Echocardiography occasionally reveals evidence of thrombi, or can show changes in cardiac structure and function associated with thromboembolic disease (*e.g.*, pulmonary hypertension) (8). A CT with angiography can be offered to identify emboli, but this may require general anesthesia; additionally, a negative scan does not exclude thromboembolic disease. Ultimately, the underlying cause should be treated, and if there is a high index of suspicion, anti-coagulants such as heparin are recommended. Thrombolytic therapy could also be considered, but must be weighed against the potential risk of hemorrhage.

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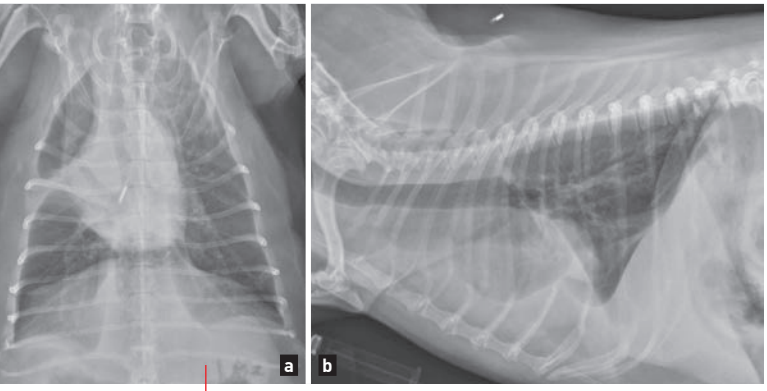

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Figure 6. DV **(a)** and lateral **(b)** thoracic radiographs from a dog with pleural effusion. This patient also had focal alveolar changes in the right middle lung lobe, potentially secondary to pleural effusion or concurrent pneumonia.

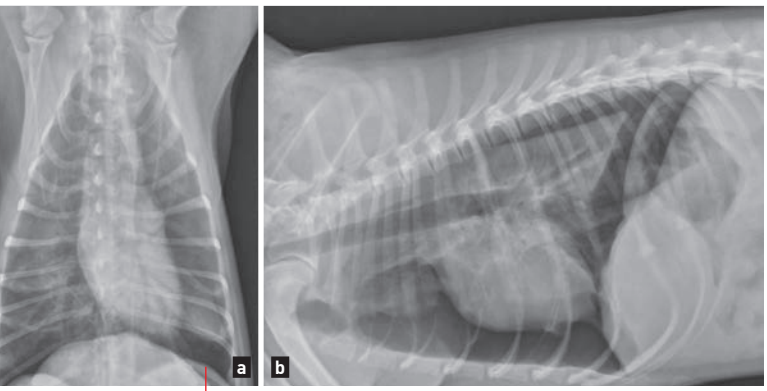

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Figure 7. DV **(a)** and lateral **(b)** thoracic radiographs from a dog with a pneumothorax. This patient had been hit by a car and had concurrent subcutaneous emphysema and peritoneal effusion (hemoabdomen).

Pleural space

Diseases of the pleural space result in a build-up of substance between the lungs and the chest wall, which compresses the lungs and prevents expansion. The substance can be fluid (as in pleural effusion), air (pneumothorax), or a mass effect (neoplasia or diaphragmatic hernia). Typically, these animals have a restrictive breathing pattern, with short shallow breaths, an inspiratory effort with abdominal effort, and decreased lung sounds (ventrally for fluid, dorsally for air). Animals may also have a paradoxical breathing pattern as the diaphragm moves caudally during inspiration, with the abdomen rising while the chest falls. In these cases, POCUS is useful to confirm effusion or pneumothorax (*i.e.*, absence of a glide sign), but thoracic radiographs can also be confirmatory. If examination is consistent with pleural space disease, ultrasound is not available, and the patient is too unstable for radiography, a therapeutic thoracocentesis is recommended to relieve the patient's distress. If effusion is obtained, it should be analyzed, and culture/susceptibility testing considered, as differentials are variable and include neoplasia, pyothorax, chylothorax, heart failure, hemothorax, lung lobe torsion, and diaphragmatic hernia. Packed cell volume, total solids, glucose, lactate, and in-house cytology of the effusion are recommended to look for hemothorax, transudate vs. exudate, or a septic effusion. Following thoracocentesis, radiographs are recommended to identify a possible underlying cause, such as a pulmonary bulla, pulmonary mass, or cardiomegaly **(Figures 6 and 7)**. A CT scan may also be indicated pending initial work-up. If the patient requires multiple thoracocenteses, placement of a chest tube should certainly be considered while further diagnostics are followed and/or until definitive treatment can be performed (*e.g.*, surgery for spontaneous pneumothorax secondary to a bulla).

Chest wall

Diseases of the chest wall refer to abnormalities of the skeleton, musculature, and nerves related to the wall of the thorax. These animals typically hypoventilate, with decreased chest wall excursions and sometimes increased abdominal movement during inspiration. Differentials are most commonly trauma and neuromuscular etiologies. With traumatic injuries, the history or external examination will frequently give clues as to what is going on. In addition to any external wounds, a flail segment may be present: a flail chest is a two or more adjacent ribs that are each fractured in at least two places, dorsally and ventrally, causing a section of the chest wall to become unstable and therefore move inwards during spontaneous inspiration. In these cases, pain medication (ideally full-mu opioids, *e.g.*, fentanyl or methadone) should be given, wounds should be covered, and the dog placed in lateral recumbency with the flail segment side to the table to stabilize the chest wall and allow for better ventilation with the less damaged side of the chest. These cases may also have pulmonary and/or pleural space disease (*e.g.*, pulmonary contusions or pneumothorax), so auscultation changes are variable; POCUS may be useful to identify some of these changes (*e.g.*, pleural effusion, pulmonary edema, or absence of a glide sign). If not immediately obvious, thoracic radiographs may be helpful to look for evidence of intrathoracic penetration, as that will warrant surgical intervention **(Figure 8)**. Ultimately, all external wounds should be explored and the surgeon prepared for a thoracic exploration, regardless of the imaging findings. This is because external wounds often do not reveal the entire extent of the damage.

Neurologic etiologies include central causes such as intracranial (*e.g.*, neoplasia, infectious, inflammatory, vascular), cervical spinal (*e.g.*, intervertebral disc herniation, neoplasia, infectious, inflammatory, vascular), or phrenic nerve abnormalities, as well as peripheral causes such as myasthenia gravis, botulism, tick paralysis, polyradiculoneuritis, or tetanus. Neurologic and musculoskeletal examination will help differentiate these causes; animals with intracranial disease may have abnormal mentation, while those with cervical spinal disease may have normal mentation but be tetraplegic, and peripheral causes may have either flaccid or stiff paralysis depending on the cause. In these cases, the chest wall muscles and diaphragm may not work effectively, so very shallow

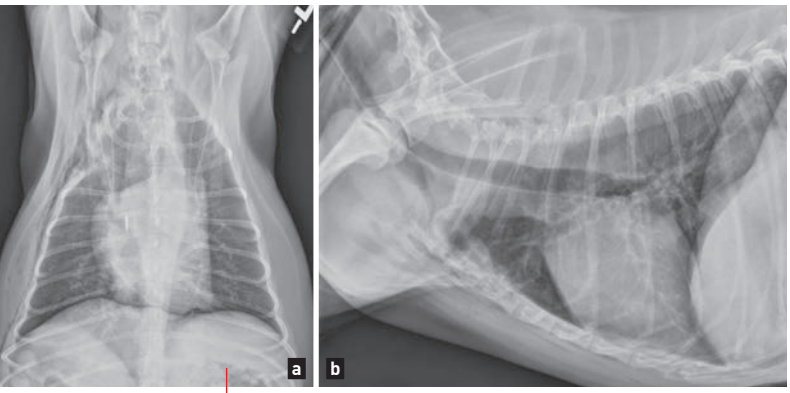

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Figure 8. DV **(a)** and lateral **(b)** thoracic radiographs from a dog with a penetrating chest wound secondary to a bite wound. Note the disruption of the right cranial thoracic wall around the level of the third intercostal space. This patient also sustained a displaced fracture of the right third rib.

breaths, along with open-mouth ("fish-mouth") breathing, may be seen. These patients are likely to require intubation and manual or mechanical ventilation. In less obviously severe cases, venous blood gases may be helpful to determine if the patient is hypercarbic, which would also be an indication for intubation and assisted ventilation. More specific treatments will depend on the diagnostic work-up and cause of hypoventilation. Dogs suspected of having intracranial or cervical spinal disease may ultimately require an MRI, but initial work-up should include bloodwork (complete blood cell count, chemistry panel), and thoracic radiographs (and cervical, in the case of cervical myelopathy). Those with peripheral causes may benefit from a thorough examination to look for ticks (as well as one dose of topical tick preventative), anti-acetylcholine receptor antibody testing for diagnosis of myasthenia gravis, and/or neostigmine response assessment, testing of serum or feces for botulinum toxin, and electromyography once stabilized.

Abdominal distension

Diseases causing abdominal distension can lead to respiratory distress by preventing caudal movement of the diaphragm and therefore inhibiting lung expansion. This can be due to a variety of etiologies, including masses, ascites, organomegaly, gastric dilatation (+/- volvulus), and pregnancy. Physical examination will usually reveal an obvious distension, which may include a palpable fluid wave or tympanic abdomen that will prompt abdominal imaging (radiographs, ultrasound, or even POCUS where available). Oxygen supplementation will not harm these patients, but ultimately treatment of the abdominal disease is required to relieve the pressure on the diaphragm.

"Look-alikes"

A number of other disease processes can mimic apparent dyspnea – hyperthermia, anxiety, excitement, pain, metabolic acidosis (*e.g.*, Kussmaul respiration associated with severe acidemia), anemia, shock, hypoglycemia, and various medications (including stimulants, opioids, or corticosteroids) can all mimic dyspnea. History, physical examination, and other diagnostics such as pulse-oximetry (normal), bloodwork (*e.g.*, arterial blood gases to ensure normal oxygenation, or a venous blood gas test for assessment of acid base-status, PCV, anion gap, etc.), and thoracic radiographs can help differentiate these from true distress. A trial of pain medication or an anxiolytic may also be useful, but ultimately treatment of the underlying cause is necessary to resolve respiratory changes on examination.

CONCLUSION

Treating dogs that present in respiratory distress can be stressful; they are fragile and require the clinician to work efficiently with minimal handling to prevent decompensation. Initial assessment includes stabilization with oxygen supplementation and possibly sedation, along with intravenous access if possible, and blood gas results may help. A brief examination focusing on auscultation and characterization of respiratory pattern will assist in localizing the disease process. Once this is achieved, systematic and appropriate diagnostics can help find and treat the cause, although empiric therapy is occasionally indicated based on the history and physical examination in animals that are too unstable for additional diagnostics.

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ARTERIAL THROMBOEMBOLISM IN CATS

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Feline thromboembolism is a condition which can strike without warning, and where the clinician's assessment and decisions can make the difference between life and death, as discussed in this article by Michael Aherne.

KEY POINTS

1. Appendicular arterial thromboembolism can be diagnosed based on classical physical exam findings.
2. Arterial thromboembolism is nearly always secondary to advanced cardiac disease, and ~ 50% of affected cats will have concurrent congestive heart failure at diagnosis.
3. Acute treatment is aimed at appropriate analgesia using full mu opioid agonists and antithrombotic drugs, with the latter being continued long term to reduce risk of recurrence.
4. Prognosis is guarded to poor in the early stages, with risk of reperfusion injury and high incidence of concurrent heart disease, but improves in patients surviving until discharge.

Introduction

Arterial thromboembolism (ATE) occurs when a thrombus embolizes within a peripheral artery and typically manifests acutely or peracutely, with severe clinical signs. The apparent propensity for cats to develop ATE (the reported prevalence is approximately 0.3-0.6% (1,2)) more than other species may be due to a variety of factors, with the most notable being the higher prevalence of myocardial disease and resultant left atrial enlargement. A large proportion of ATE cats are euthanized at initial presentation owing to the severity of clinical signs, but for those that undergo therapy and survive the initial stabilization, a significant number can regain motor function in affected limbs while maintaining a good quality of life. Unfortunately, the type and severity of any concurrent or underlying conditions may limit long-term prognosis in cats experiencing ATE.

Etiology and pathophysiology

Cats appear to have an increased propensity for intracardiac thrombus formation when compared to other species (3,4), which in most cases occurs as a result of advanced cardiac disease, leading to left atrial enlargement. Hypertrophic cardiomyopathy (HCM) is the most common cardiomyopathy encountered, but any cardiomyopathy or congenital defect (*e.g.*, mitral stenosis) affecting the left side of the heart may lead to ATE. Rarely, infective endocarditis can cause systemic embolization of septic thrombi. However, not all cases of ATE occur as a consequence of cardiac disease; pulmonary neoplasia with subsequent tumor embolism is the most common non-cardiac cause of feline ATE (2), and in a few cases the condition can occur spontaneously, with no apparent cause identified.

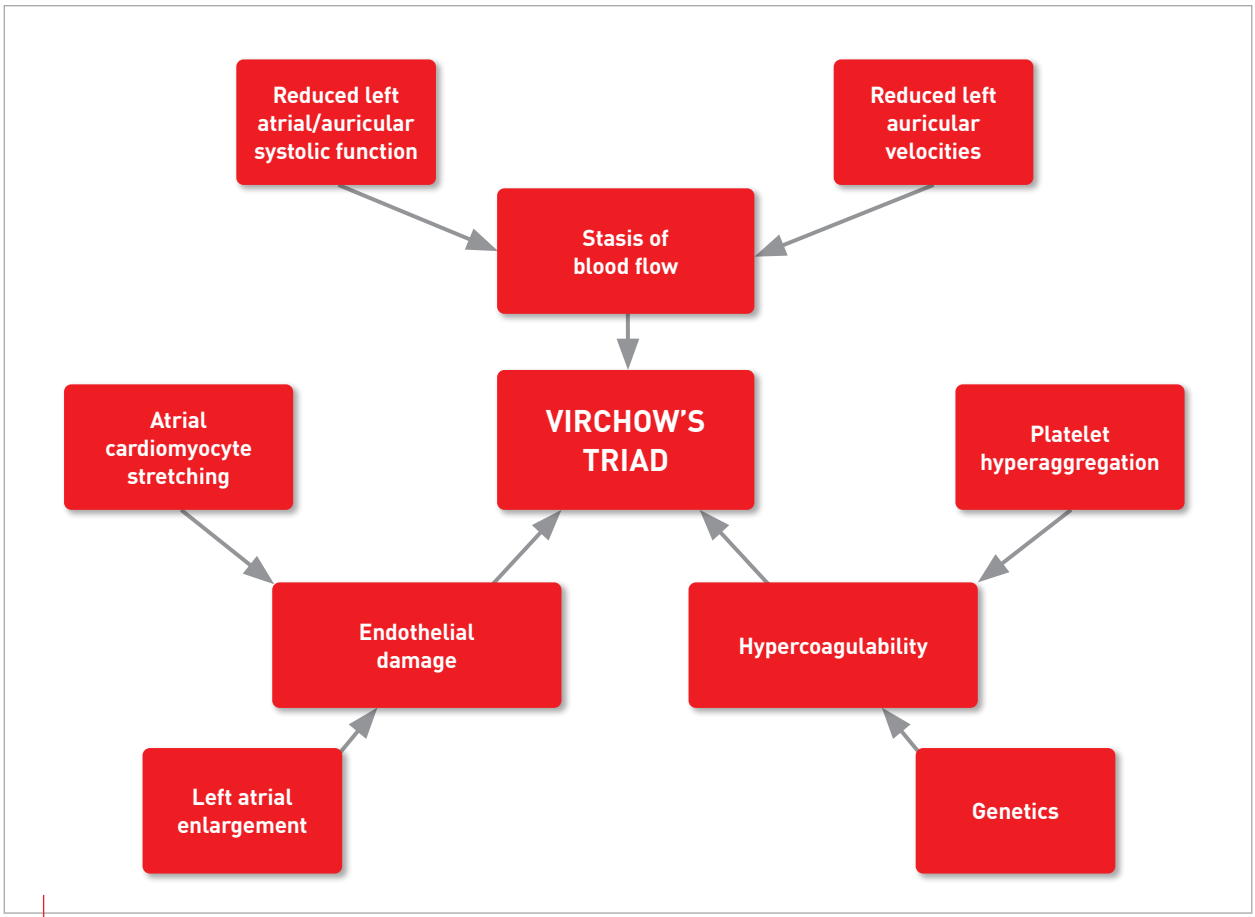

Figure 1. Factors influencing Virchow's triad of thrombosis.

Virchow's triad describes the predisposing factors for excessive thrombotic activity, namely hypercoagulability, stasis of blood flow and endothelial dysfunction **(Figure 1)**. Alterations to one or more points of the triad can lead to ATE, and in many cats with cardiogenic ATE all factors likely play a role. One significant factor identified as contributing to hypercoagulability in cats with ATE is platelet hyperaggregation (5,6), but hypercoagulability can be difficult to determine. The gold standard for assessment of feline platelet function is platelet aggregometry, but the test is very dependent on the operator's skill and experience (5,6). There can be significant overlap in the range of values for activated partial thromboplastin time (aPTT) and prothrombin time (PT) between hypercoagulable and normal patients and, as such, there is limited utility in identifying hypercoagulable states with these tests, which are better suited to identify hypocoagulable states. Calibrated automated thrombography is another option that has recently been shown to be more sensitive than PT, aPTT, and rotational elastography (7) and in future this may have a role in measuring hemostasis in cats. Left atrial and/or left auricular dilation can cause stasis of blood flow and endothelial damage, both of which may be exacerbated by concurrent left atrial systolic dysfunction.

As previously noted, initial thrombus formation in most ATE cats occurs in the left heart before either a fragment or the entirety of the thrombus dislodges. The thrombus then enters the systemic circulation, and eventually becomes lodged in an artery of smaller diameter than itself **(Figure 2)**. The formation and embolism of a thrombus does not only cause direct mechanical obstruction of the affected artery; it also leads to a cascade of vasoactive events resulting in vasoconstriction of

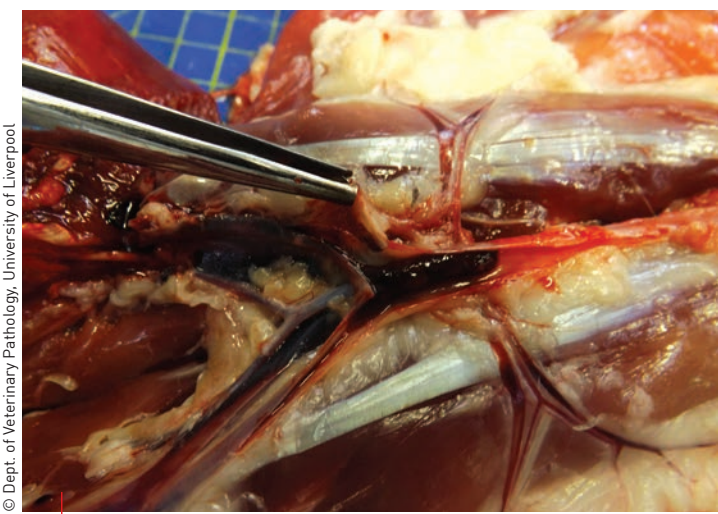

Figure 2. Post-mortem of a cat following euthanasia with a distal aortic thromboembolism (saddle thrombus). A large thrombus in the distal aorta can be seen, extending down both external iliac arteries.

the collateral circulation. Acute ischemia of the tissues supplied by the obstructed vessel(s) results from occlusion of the systemic circulation to the affected area, and clinical signs of ATE become apparent. In most cases, the outcome is systemic hypoperfusion and shock (either maldistributive shock, cardiogenic shock, or both).

Several studies support the role of vasoactive mediators in the pathogenesis of feline ATE (8). Studies also show that collateral circulation is preserved and paralysis is prevented by administrating cyproheptadine (a serotonin antagonist) or high-dose aspirin (which inhibits thromboxane A_2) prior to thrombus formation (9,10).

Clinical presentation

There is a higher incidence of ATE amongst male versus female cats (1,2,11-13), probably reflecting the higher prevalence of HCM in males (2,14). Affected cats typically present between 8-12 years of age (1,2,11,12), with over-represented breeds including the Abyssinian, Birman, and Ragdoll (2) as well as Maine Coon, Himalayan, Siamese, and Persian cats (1,2,11); however, most affected cats are domestic short- or longhair (1,2,11,12).

ATE typically has an acute or peracute onset, with little to no warning. Affected cats experience significant distress, which can be harrowing for owners to witness. There is severe pain to the affected limb(s), and the cat will often vocalize and display overt signs of distress and discomfort **(Figure 3)**. A variety of clinical signs may be observed, depending on the specific location of the thromboembolism within the peripheral circulation; this in turn is dependent on both embolus diameter and vessel diameter throughout the various levels of the arterial tree. Appendicular arteries are the most common sites for feline ATE, but non-appendicular arteries (*e.g.*, renal, mesenteric, or cerebral vessels) can also be involved.

Distal aortic thromboembolism (saddle thrombus) at the level of the aortic trifurcation, characterized by paralysis or paresis of one or both pelvic limbs, is the most common manifestation of feline ATE. If both hind limbs are affected, one may be affected to a greater extent than the other. The next most common presentation is that of embolization within either of the brachial arteries, which results in lower motor neuron signs to the affected forelimb. Of cats diagnosed with ATE in a general practice setting, 20.8% of cats had one limb affected, 77.6% of cats had two limbs affected, and 1.2% of cats had three or more limbs affected (1). The affected limbs have overt neurologic deficits, and the cat will often drag these limbs. The degree of vascular occlusion will determine the severity of clinical signs, with partial occlusion resulting in more subtle signs. Depending on the embolism location, other signs (including central nervous system abnormalities, vomiting, or abdominal pain) may be observed (2), and diagnosis can be challenging in non-appendicular cases.

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Figure 3. Cats with thromboembolism and associated ischemic neuromyopathy almost always present in severe pain, and effective analgesia is mandatory.

Affected cats are commonly hypothermic, primarily as a result of systemic hypoperfusion and shock resulting from the vasoactive cascade following tissue ischemia; however, direct occlusion of the arterial supply to the hindquarters may also have a contributary role.

Evidence of underlying cardiac disease (*e.g.*, murmur, gallop heart sounds, or arrhythmia) may be identified in some cats with ATE, but an absence of auscultatory abnormalities does not preclude the presence of underlying heart disease. The presence of gallop sounds in an affected cat has been associated with poor prognosis (14). Some cats may also exhibit signs of concurrent congestive heart failure (CHF), including tachypnea, dyspnea, orthopnea, lung crackles, and open-mouth breathing. 40-67% of feline ATE cases have concurrent CHF (2,12,13), but open-mouth breathing and tachypnea can also be a result of pain. The acute signs of ATE are often the first indicators of severe cardiac disease, with the majority of affected cats having no known history of heart disease prior to the ATE event.

Diagnostic findings

Stress hyperglycemia (from epinephrine and cortisol release) is commonly found, and prerenal or renal azotemia is also often noted; raised blood urea nitrogen (BUN) levels are more frequently reported, and are typically more severe, than elevations in creatinine (2,11). Prerenal azotemia results from poor systemic perfusion and shock; the BUN:creatinine ratio may be elevated. Renal azotemia occurs as a direct consequence of thromboembolism of the renal artery (although acute renal injury due to shock, or existing chronic kidney disease may also play a factor in some cases). Severe elevations in serum creatine kinase result from muscle ischemia, and hyperphosphatemia is also commonly observed. One of the most significant, and potentially life-threatening, complications in cats with ATE is hyperkalemia, which can be severe and often

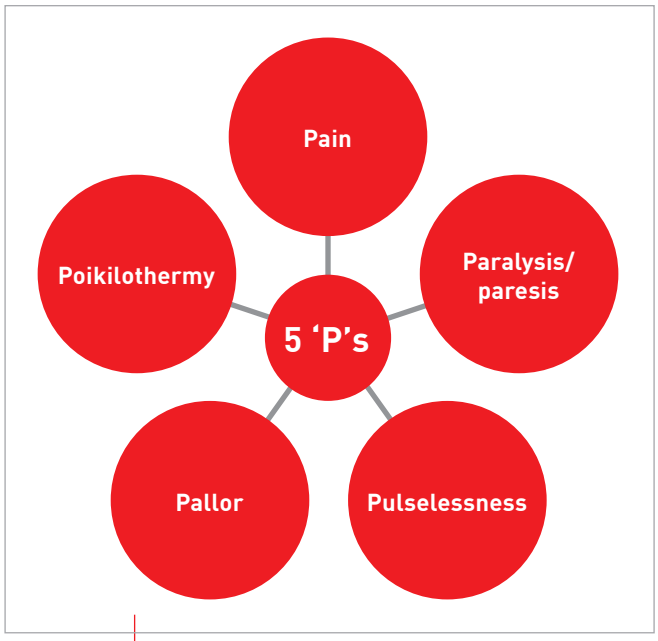

Figure 4. The 5 'P's: Classical clinical findings of appendicular arterial thromboembolism.

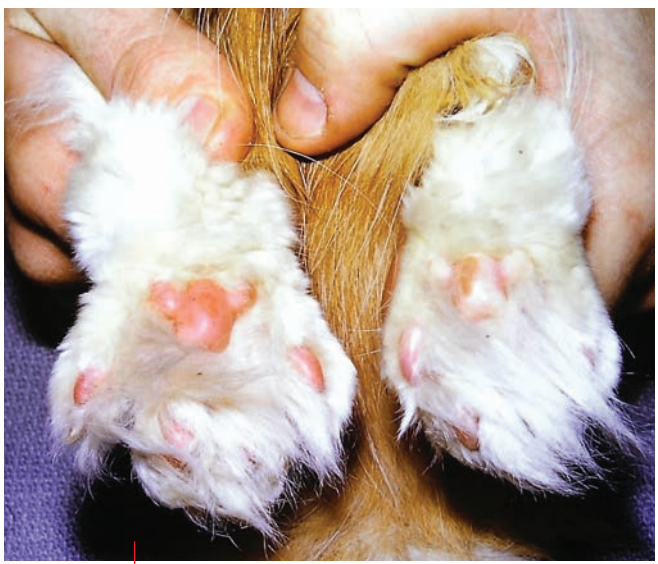

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Figure 5. In a cat with non-pigmented footpads, evidence of presence and severity of thromboembolism can be appreciated by pallor or cyanosis of the pads. In this cat only the right hindlimb was affected, as evidenced by the pallor of the pads. The pads of the unaffected contralateral hindlimb appear normal.

results from reperfusion injury once tissue perfusion is restored, although this abnormality can also be identified at presentation in some cases. Other electrolyte disturbances such as hypocalcemia and hyponatremia may also be noted. D-dimers may be elevated in affected cats, but as noted above, routine coagulation assays (such as PT and aPTT) are often within the normal reference range.

The diagnosis of appendicular ATE can typically be made on physical examination alone, with 5 cardinal signs associated with the condition, often referred to as the 5 P's: pain, paralysis/paresis, pulselessness, pallor, and poikilothermy **(Figure 4)**. On presentation, affected limbs are painful, often with firm muscles, and exhibit lower motor neuron signs, which may range from mild paresis to full paralysis. In one study, some motor function was retained in the affected limbs of approximately 34% of cats, and where an ATE event occurs in the forelimbs or in a single hindlimb there is a higher likelihood of motor function retention (2). In most cases, arterial pulses distal to the level of the embolism are absent or very weak, but remember that pulse quality may be difficult to determine in some cats that do not have ATE, especially forelimb pulses; detection can also be challenging in obese or uncooperative patients, especially in the face of acute pain. One method that may help in such circumstances is Doppler evaluation of the affected limb(s). The paw pads and nail beds of affected limbs should be examined; they are usually pale or even cyanotic, depending on the degree of tissue ischemia, and comparison to nonaffected limbs can be helpful **(Figure 5)**. Poikilothermy (*i.e.*, lower temperature in affected limbs compared to non-affected limbs) results from reduced or absent blood flow distal to the embolism. A 2.4°C (4.32°F) difference in temperature between ipsilateral affected and non-affected limbs on infrared thermography in cats has been shown to have excellent specificity (100%) and high sensitivity (80%) for ATE diagnosis (15). Further supportive evidence can be provided by differential measurements of blood glucose and serum lactate between affected and unaffected limbs. Glucose levels are lower and lactate is higher in peripheral venous samples from affected limbs distal to the embolism site when compared to that of samples from either central veins or non-affected limbs; a difference in absolute blood glucose concentration of ≥ 30 mg/dL between central and peripheral samples has been shown to have 100% sensitivity and 90% specificity in identifying feline ATE (16). Optimal cutoff values for identification of feline ATE using the serum lactate concentration difference between affected and unaffected limbs have not been determined.

Various diagnostic imaging modalities such as ultrasonography, angiography, computed tomography or magnetic resonance imaging of the implicated artery can be employed to confirm the diagnosis or investigate the presence of underlying causes, but these are rarely necessary.

Treatment and outcome

Acute stabilization and short-term management

Since the majority of cats with ATE present in severe pain and distress, a priority for initial therapy is prompt and effective analgesia, ideally with full mu opioid agonists (*e.g.*, methadone,

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Figure 6. Oxygen therapy and analgesia should be instituted as soon as a cat with suspected thromboembolism presents and a brief neurological assessment has been carried out.

fentanyl, oxymorphone, or hydromorphone). Oxygen therapy is recommended for any cat in respiratory distress **(Figure 6)**. However, a frank discussion should take place with the owners, explaining the various prognostic factors to consider when deciding to proceed with treatment versus euthanasia. Rectal temperature lower than 37°C (98.6°F) (1,2), bradycardia (2,11), absent motor function (2), having more than one limb affected (2) and confirmed concurrent CHF are all associated with reduced survival.

Following initial stabilization with analgesia and oxygen therapy, and without sacrificing patient stability, the cat should be assessed for evidence of CHF. Pulmonary edema may be identified on radiography, while the presence of pleural effusion may be determined using focused point-of-care ultrasound. Thoracocentesis should be performed in cats with significant pleural effusion. In cats with confirmed CHF (or when CHF is highly suspected) diuretic therapy (furosemide at 1-2 mg/kg IV or IM) should be administered and repeated at appropriate intervals until an effect is reached. The dosing interval may then be adjusted as necessary.

Signs of poor systemic perfusion and shock, which are present in most ATE cases, should be promptly addressed. Patients with severe decompensated cardiac disease may have cardiogenic shock, while tissue ischemia and release of vasoactive substances can lead to maldistributive shock; the specific approach to address the hypoperfusion will vary based on the nature of the shock, but this can be difficult to distinguish on presentation. Fluid therapy may be considered in dehydrated cats without evidence of CHF, but caution is emphasized with administering IV fluids to any animal with concurrent cardiac disease. Positive inotropes such as pimobendan (0.15 mg/kg IV or 0.3 mg/kg PO) may therefore be a more useful option for cats with decompensated cardiac disease and CHF, especially those with signs of systolic myocardial dysfunction; however, evidence of a definitive survival benefit with such agents is lacking. Poor systemic perfusion and shock results in low rectal temperatures and even generalized hypothermia in many cases, but active warming should be avoided until systemic perfusion is corrected, since it will only serve to worsen core perfusion and the clinical effects of shock as a result of peripheral vasodilation, which leads to more diversion of blood from essential organs.

Antithrombotic therapy should be started once the patient is stabilized in order to prevent propagation of existing thrombi and prevent new thrombi developing, but note these drugs do not cause lysis of existing thrombi. Either low-molecular weight heparin such as dalteparin (75-150 U/kg SC q6h) (17), or unfractionated heparin (250-300 U/kg q6h) (17,18) is recommended and is then typically discontinued 2-3 days after stabilization and the patient has been transitioned to oral antithrombotic medication.

Clopidogrel should be started as soon as the patient can tolerate oral medication. This drug antagonizes adenosine diphosphate, leading to reversible inhibition of platelet aggregation. An initial loading dose of 75 mg PO q24h per cat is recommended, followed by a maintenance dose of 18.75 mg PO per cat q24h (19). Many cats become aversive to clopidogrel owing to its apparent bitterness, and options to increase compliance such as formulations within gelatin capsules or flavored liquid should be considered. Clopidogrel is typically well-tolerated otherwise, although signs of excessive bleeding (*e.g.*, bruising) may be seen at the higher dosage. Peripheral veins should be used for blood sampling in patients receiving this therapy, and appropriate compression bandages used to ensure hemostasis following venipuncture.

Clopidogrel has been shown to be more efficacious than aspirin for the secondary prevention of ATE (20), but since the mechanisms of action of the two drugs differ, dual therapy may be a consideration in some patients, although studies on the efficacy of this combination are lacking. Aspirin inhibits platelet aggregation by irreversible inhibition of

"There are 5 cardinal signs associated with appendicular ATE, often referred to as the 5 P's: pain, paralysis/paresis, pulselessness, pallor, and poikilothermy."

Michael Aherne

thromboxane A_2 production on the platelet, and is usually administered at a dose of 20.25-81 mg per cat PO q72h. It should only be administered once the patient has resumed eating to reduce the risk of gastrointestinal ulceration.

Thrombolytic therapies, including tissue plasminogen activator (21,22), streptokinase (11), and urokinase (23) are not recommended in ATE cats; no survival benefit has been shown with these drugs when compared with standard-of-care antithrombotic therapies, and moreover significant complications have been observed with thrombolytic agents, in particular life-threatening hyperkalemia, most likely a manifestation of reperfusion injury.

The patient's pain levels should be routinely assessed, with effective analgesia continued for a minimum of 24-48 hours. After this point the need for full mu opioid agonist analgesics greatly diminishes, and buprenorphine (a partial mu opioid agonist) may be sufficient. In addition, further diagnostics to investigate possible underlying causes should be performed once the patient is stabilized. These may include a hemogram, serum biochemistry, echocardiography or ultrasonography of any implicated arteries as indicated based on the patient's initial assessment.

Reperfusion injury to ischemic tissues may lead to severe, life-threatening hyperkalemia and acidosis, and is one of the most significant complications encountered during therapy. All cases should be closely monitored for biochemical derangements, especially in the initial 48-72 hours following presentation. Reperfusion injury should be promptly addressed with appropriate therapies (*e.g.*, administration of dextrose, insulin and dextrose, calcium gluconate, or sodium bicarbonate) as necessary. Manipulation of affected limbs (including physiotherapy) should be avoided for at least 72 hours, as it may cause an acute influx of potassium and lactate into the circulation, increasing the risk of reperfusion injury,

Long-term management

Clopidogrel (18.75 mg/cat) should be continued long term and has been shown to be superior to aspirin for the secondary prevention of ATE (20). Oral factor Xa inhibitors (*e.g.*, rivaroxaban at 0.5-1 mg/kg/day) have been suggested as alternative antithrombotic agents for both short- and long-term management of ATE, but prospective data on their efficacy is limited. However, clinical studies of rivaroxaban are ongoing, and retrospective analysis of dual therapy using clopidogrel and rivaroxaban showed this combination was well tolerated with few adverse effects (24). It is currently recommended that such drugs should be administered in combination with, and not as a replacement for, standard clopidogrel therapy (19).

Low-molecular weight heparin or unfractionated heparin therapy can be continued at home long term in cats that have experienced severe ATE or those with recurrent ATE events, but these options are not routinely used for long-term management, and outcome data regarding this approach are limited.

Appropriate clinical therapy of cardiac disease is necessary in most cases of ATE due to the high prevalence of underlying heart disease. Cats with concurrent CHF require ongoing diuretic therapy with furosemide (0.5-2 mg/kg PO q8-12h). Renal function and electrolytes should be evaluated and, if normal, angiotensin-converting enzyme (ACE) inhibitors (either benazepril at 0.5-1 mg/kg or enalapril at 0.25-0.5 mg/kg, both PO q12-24h) should be considered, followed by close monitoring of renal function. Caution is required in cats with azotemia or known existing renal disease. Pimobendan (0.3 mg/kg PO q12h) may be used off-label in cats with evidence of systolic dysfunction. Antiarrhythmic therapies should be governed by the type and severity of any concurrent arrhythmias, and readers are directed to other resources for an in-depth review of long-term management of such cases (19).

Physiotherapy, including passive mobility exercises on affected limbs, is recommended as soon as the patient is stabilized, pain is well controlled and the risk for reperfusion injury has subsided. Owners should be educated on how to perform the exercises, and passive manipulation of the affected limbs should continue at home for at least several weeks until motor function improves and the risk for muscle contracture has reduced.

Prognosis

One study noted that only 12% of cats diagnosed with ATE in general practice survived at least 7 days after presentation (1); 61.2% of cats were euthanized at presentation, 8.8% were euthanized and 2.8% died within 24 hours of starting treatment, and overall only 27.2% survived beyond 24 hours (1). In contrast, survival rates of approximately 30-40% (and even up to 73%) have been reported in referral settings (2,11-13) although the influence of referral bias cannot be excluded as an explanation for these figures. The low overall survival rates in general practice may, conversely, reflect a perception of a hopeless prognosis and an inherent bias toward euthanizing affected cats on presentation. Moreover, survival rates in cats with only a single affected limb can be up to 70-80% (11,13) and can even be 90% if some motor function is retained at presentation (12). The clinical signs resulting from ATE often significantly improve after the first 24-48 hours of therapy, and many of the patients that survive longer than 48-72 hours will regain some or even all motor function within 1-2 months. Such outcomes suggest that consideration of therapy for at least the initial 72 hours is justified and

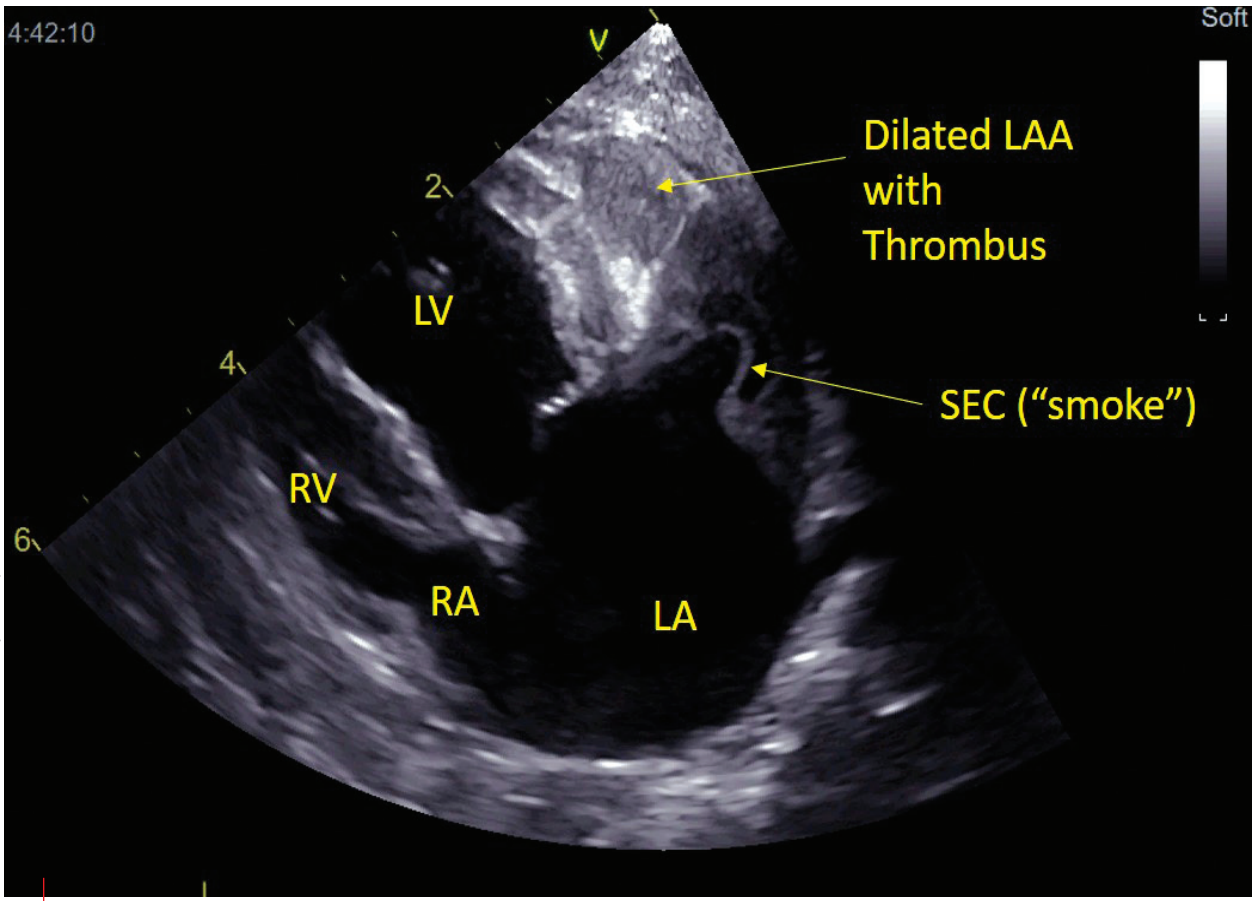

Figure 7. Echo findings can indicate a high risk of arterial thromboembolism, as shown in this scan from a 13-year-old cat with end-stage HCM and congestive heart failure. This is a left apical two chamber view, optimizing the left atrium and left atrial appendage, which are both enlarged. In the tip of the left atrial appendage (LAA), a thrombus can be seen. Proximal to that, at the junction of the left atrium and the LAA, spontaneous echo contrast (or "smoke") can be seen. **LA:** left atrium; **LAA:** left atrial appendage (or left auricle); **RA:** right atrium; **RV:** right ventricle; **SEC:** spontaneous echo contrast.

could potentially result in increased survival rates overall. However, having two or more limbs affected (1,2), a history of previous ATE events (14), bradycardia (2,11), presence of gallop heart sounds (14), and rectal temperature lower than 37°C (98.6°F) (1,2) are all significant negative prognostic indicators, with rectal temperature lower than 37.2°C (98.96°F) at presentation associated with a survival rate of less than 50% (2).

Long-term complications may also be observed in cats that survive an ATE event. The incidence of muscle contracture can be mitigated by performing physiotherapy during hospitalization and continuing it at home following discharge. Necrosis and skin sloughing may occur on affected limbs secondary to ATE-induced ischemia, and can take several days to become apparent. Such lesions may be localized to individual digits or may affect larger areas of skin, and surgical management may be necessary. Amputation of the affected limb may be necessary if perfusion is so poor as to result in entire limb necrosis (2). Paw excoriations due to dragging of limbs, and self-trauma of affected limbs due to neuropathic pain, are complications that may be encountered in cases with persistent neurologic deficits. Gabapentin therapy may be considered for managing neuropathic pain in these cats, but its utility in cats with ATE has not been investigated. The risks and warning signs of these complications should be clearly communicated to owners, ideally prior to any decision on treatment versus euthanasia.

Preventative measures

As with many diseases, prevention is better than cure, but despite this, studies evaluating the efficacy of any therapy for the primary prevention (*i.e.*, preventing a first ATE event in an at-risk patient) are lacking. Clopidogrel is currently recommended in at-risk cats for prevention of ATE (19) and is shown to have superior efficacy over aspirin in increasing time to ATE recurrence or cardiac death in cats following an initial ATE event (20). Identification of at-risk cats is probably the most significant barrier to prevention,

since there is a high prevalence of underlying subclinical cardiac disease, which owners may be oblivious to, and investigation for an underlying heart disease should be prompted whenever a murmur, gallop sound, or arrhythmia is detected in asymptomatic cats. Various echocardiographic parameters have been associated with increased risk for ATE in cats with known cardiac disease. These include the presence of spontaneous echo contrast (smoke) **(Figure 7)**, moderate-to-severe left atrial enlargement, reduced left auricular appendage velocities, reduced atrial fractional shortening, reduced left atrial ejection fraction, and increased left ventricular wall thickness, and are all considered indications for starting clopidogrel therapy in asymptomatic cats. Recently developed guidelines state that cats classified as having stage B2 cardiomyopathy (asymptomatic with moderate-to-severe left atrial enlargement) are considered at increased risk for the development of CHF or ATE, and recommend clopidogrel for all cats at this stage or beyond (19). The benefit of dual therapy with clopidogrel and either aspirin or a factor Xa inhibitor for prevention of ATE relative to therapy with clopidogrel alone is currently unknown.

Recommendations are currently limited for cats with non-cardiogenic causes of ATE or patients with no identifiable underlying cause, since most prevention strategies are directed towards factors associated with cardiogenic ATE.

CONCLUSION

Whilst arterial thromboembolism (ATE) can be a peracute and dramatic presentation, with a typically guarded to poor long-term outlook, by no means is it a death sentence for all cats. With rapid intervention, careful clinical decisions and intensive care, the overall prognosis is variable and is dependent on the cause and the severity of presenting signs. Given that many clinical signs will resolve within the first 72 hours after the onset of ATE, consideration of therapy for at least this initial period is justified for many cases.

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CANINE DIABETIC KETOACIDOSIS

What do you do when the critical diabetic patient arrives at the emergency clinic? This paper offers a step-by-step approach for optimal results.

KEY POINTS

1. Baseline blood glucose, electrolytes, acid-base balance and ketonemia/ketonuria analyses are crucial in the diagnosis of diabetic ketoacidosis (DKA).
2. Due to the high prevalence of concurrent disease in DKA, additional tests to rule out concomitant pathologies are essential after initial stabilization.
3. Fluid therapy requirements, electrolyte supplementation and insulin therapy will all dynamically change during DKA treatment.
4. Ketoacidosis resolution is the main goal of insulin therapy; once ketosis and acidemia normalize, transition to long-term subcutaneous insulin can be planned.

Introduction

Diabetes mellitus (DM) is characterized by the body's inability to utilize glucose, leading to cellular starvation and clinicopathological abnormalities. This may be secondary to lack of insulin secretion (DM type 1) or insulin resistance (DM type 2). DM type 1 is the more common scenario in dogs; its pathogenesis seems multifactorial, involving genetic predisposition, autoimmune mechanisms, environmental factors and concomitant insulin-resistant diseases (1).

When these mechanisms are exacerbated, severe hyperglycemia, ketonemia, electrolyte and acid-base balance abnormalities develop, causing a condition known as diabetic ketoacidosis (DKA). This, and hyperglycemic hyperosmolar syndrome (HHS), are complicated forms of DM, and are both diabetic emergencies, but they have different characteristics, underlying comorbidities and management. This article will focus on DKA in dogs, discussing its diagnosis, treatment and complications.

From diabetes to DKA

When glucose is unable to enter body tissues, cellular starvation and extra-cellular hyperglycemia develop; this is worsened by increased gluconeogenesis and glycogenolysis. In time, blood glucose (BG) can reach the renal threshold (180-220 mg/dL, 10.0-12.2 mmol/L), leading to glycosuria with subsequent fluid and electrolyte losses due to osmotic diuresis. As a consequence of the inefficient glucose utilization, cells use alternative energy pathways, mainly lipolysis **(Figure 1)**. The hormone-sensitive lipase stimulates hydrolysis of triglycerides into free fatty acids (FFA); these in turn undergo beta-oxidation in hepatocyte mitochondria into acetyl coenzyme A (Acetyl-CoA). In the presence of oxaloacetate, Acetyl-CoA can enter the Krebs cycle and produce energy, but during DKA oxaloacetate is preferentially directed toward gluconeogenesis; therefore, especially when Acetyl-CoA production is excessive, it accumulates and combines to form ketone bodies (KBs): acetoacetate (AcAc), beta-hydroxybutyrate (BHB), and acetone (2,3).

In small amounts, KBs are an important energy source, but an excess can be detrimental; as strong acids, their dissociation leads to metabolic acidosis. In order to maintain serum electrical neutrality, negatively charged KBs are excreted in the kidneys along with positive ions, causing osmotic diuresis and electrolyte deficiencies. Excessive KB production and severe hyperglycemia are further promoted by the insulin-resistance action of so-called counter-regulatory hormones (glucagon, cortisol, growth hormone, adrenaline), which increase with stressful conditions and comorbidities. They further stimulate gluconeogenesis, lipolysis and glycogenolysis (2,3). Moreover, hyperglycemia itself is recognized as a pro-inflammatory state that promotes cytokine release and development of reactive oxygen species, further promoting insulin resistance (4).

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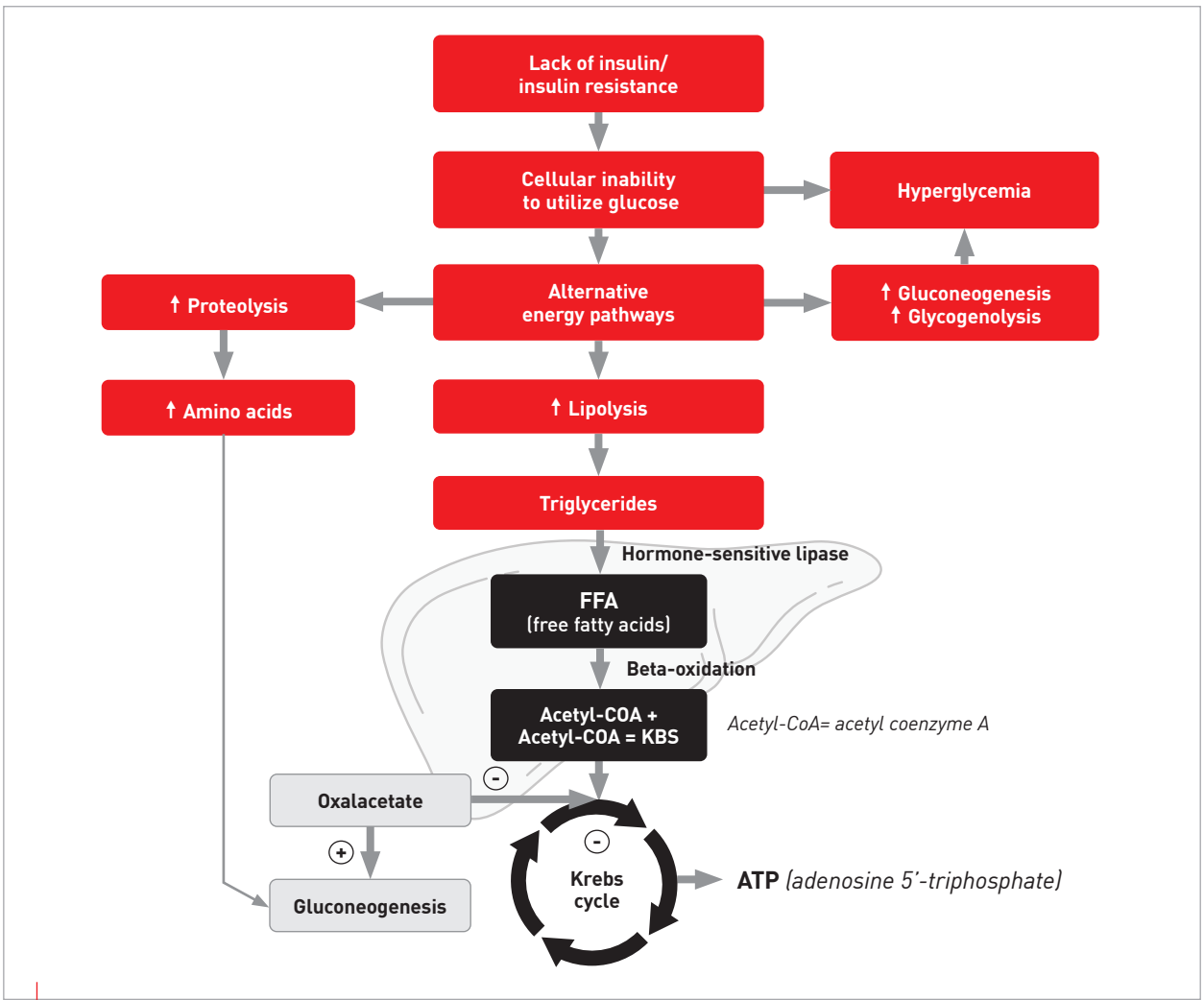

Figure 1. The metabolic pathways involved in DKA (3); alternative metabolic pathways (mainly lipolysis) are used in order to produce energy where there is intracellular glucose deficiency (*i.e.*, in DM/DKA).

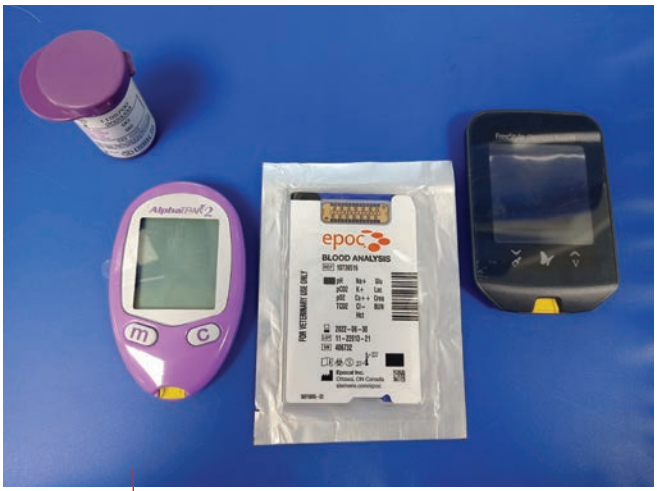

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Figure 2. To obtain a minimum database for DKA the clinician requires (L to R) a glucometer, a blood gas analyzer, and a ketonometer.

DKA diagnosis

The DKA acronym acts as a reminder that the condition is characterized by hyperglycemia (D) (as in diabetes mellitus), ketonemia/ketonuria (K), and metabolic acidosis (A) (2,5). DKA patients may present with a previous DM diagnosis, or a history consistent with DM (polyuria, polydipsia, polyphagia, weight loss) as well as signs indicative of an underlying pathology or DM decompensation (vomiting, anorexia, lethargy, hematuria). DKA is more common in middle-aged and older dogs, and some breed predisposition is reported (1,6).

Clinical findings may include dehydration, hypovolemic shock, abnormal respiratory rate or effort (from acidosis or lung pathology), abdominal pain, acetone breath, lethargy (or more severe neurologic deficits), or signs of other comorbidities (*e.g.*, dermatitis, alopecia, otitis) (6). If history and physical examination are indicative of decompensated DM, a minimum database evaluating BG, electrolytes, acid-base balance and ketonemia/ketonuria is essential **(Figure 2)**.

D. Persistent fasting hyperglycemia is characteristic of DM (normal BG: 80-120 mg/dL, 4.4-6.6 mmol/L). This can be rapidly measured via a validated point-of-care (POC) glucometer. If the glucose value is above the instrumental threshold, blood gas analysis or sample dilution should be considered. When whole blood is used for analysis, the patient's packed cell volume needs to be taken in consideration, as POC glucometers are inaccurate in hemodiluted and hemoconcentrated samples (7).

K. Ketonemia and ketonuria are indicative of an excessive KB production and therefore negative energy balance. KBs can be measured via a POC ketonometer or nitroprusside-reactive urine dipsticks (using either plasma or urine, plasma being considered more sensitive). The dipstick is a semi-quantitative test based on visual interpretation, and with a high risk of both false positive and negative results. Dipsticks primarily measure AcAc, so this may result in an underestimate of ketosis, as AcAc is less abundant than BHB in DKA. Furthermore, detection of DKA resolution is delayed using a urine dipstick because insulin promotes BHB conversion back to AcAc, such that a dipstick reading may still suggest high levels of KBs (3,8,9). Ketosis (BHB concentration > 0.1 mmol/L) may also develop with acute pancreatitis, starvation, low-carbohydrate diets, fever and pregnancy, but a BHB concentration above 3.5 mmol/L is suggestive of DKA, whereas with a value below 2.8 mmol/L DKA is considered unlikely (9).

A. Metabolic acidosis (pH < 7.3, bicarbonate < 15 mmol/L) in DKA is mainly secondary to KB accumulation, hypovolemia (lactic acidosis, volume-responsive azotemia), hyperchloremia and uremia. KB (unmeasured anions) accumulation causes a high anion gap (AG) acidosis (normal AG: 12-24 mEq/L).

This last letter of the DKA acronym can also be an *aide memoire* for the other two main "abnormalities" of these patients: electrolyte and osmolarity imbalances, as discussed below.

Up to 70% of DKA patients are in a state of decompensated DM because of concomitant pathologies responsible for increased insulin resistance – common comorbidities are acute pancreatitis, bacterial urinary tract infection and hyperadrenocorticism. Glucocorticoid use, bacterial pneumonia, uterine pathology, dermatitis, chronic kidney disease, pyelonephritis, diestrus and neoplasia have also been reported (6,8,9). Therefore, once the patient is stable, further investigations (*e.g.*, hematology, biochemistry, urine analysis with culture, pancreatic lipase serology, endocrine tests, imaging) are necessary in order to identify possible triggers. Impaired neutrophil adhesion, chemotaxis, phagocytosis and bactericidal activity may explain the higher predisposition of DM patients to secondary infection (10).

Electrolytes and DKA

The main electrolyte imbalances in DKA involve potassium, sodium, phosphate and magnesium (6,9).

Potassium

Total body potassium is generally depleted in DKA, but levels can vary between patients, and although not as frequent as in human medicine, hyperkalemia can be present. This can be a consequence of dehydration and/or hypovolemia, hyperosmolarity, hypoinsulinemia (potassium, like glucose, relies on insulin-dependent transporters to move intracellularly) or acidemia (as hydrogen ions move into the cells, potassium moves out to

maintain cellular electronegativity). After insulin treatment (potassium shift) and fluid therapy (dilutional effect, acidosis correction) true hypokalemia becomes evident. When potassium accumulates extracellularly, it can be easily lost as a consequence of osmotic diuresis. Hypokalemia may also be exacerbated by reduced food intake, vomiting and diarrhea. Muscular weakness, arrhythmias, gastrointestinal stasis, poor renal water retention, and respiratory failure may all develop secondary to hypokalemia (2,11a).

Phosphate

Total body phosphate is also reduced by previously discussed mechanisms, with insulin and fluid therapy further exacerbating the situation. Hypophosphatemia can cause hemolysis, neurological signs, muscle weakness and rhabdomyolysis (2,11a).

Magnesium

Hypomagnesemia is a common finding in human DKA patients, and whilst a high prevalence of hypomagnesemia has been reported in critically ill dogs, it was not a common finding in the subpopulation of dogs with DKA (6,12). Magnesium is an essential cofactor in energy production pathways; hypomagnesemia is linked to cardiovascular, immunological, neurological and platelet dysfunction, refractory hypokalemia and hypocalcemia. Moreover, hypomagnesemia is associated with insulin resistance and poor glycemic control, while magnesium supplementation improves insulin sensitivity (11b).

Sodium and osmolality

In DKA, hyperglycemia is the main contributor for dysnatremia. In biological fluids, glucose and sodium are defined as effective osmoles, as they have the ability to move water in relation to their concentration through a semi-permeable barrier (effective osmolality). Their importance is highlighted by the effective osmolality formula **(Table 1)**. In dogs, hyperosmolality is defined as an effective osmolality above 330 mOsm/kg (normal: 290-310 mOsm/Kg) (2,13). In DKA, glucose accumulates in the extracellular space and, as an effective osmole, is able to pull water from cells into the extracellular space, resulting in cellular dehydration and dilutional hyponatremia, with the main effects occurring in the brain. It is the sodium *concentration* (total body sodium content relative to extracellular water) rather than the total sodium *content* that decreases. In addition, osmotic diuresis, ketonuria and gastrointestinal losses may also contribute to dysnatremia, making the real sodium content difficult to estimate.

Blood gas analyzers yield the sodium concentration, which is misleading in DKA patients. Mathematical formulae have therefore been extrapolated in order to estimate the patient-corrected sodium in a normoglycemic state,

Table 1. Useful formulae (2,11c).

- Effective osmolality = $2(Na^+)$ + (glucose/18) if glucose is measured in mg/dL and Na^+ in mEq/L
- Effective osmolarity = $2(Na^+)$ + (glucose) if glucose is measured in mmol/L and Na^+ in mEq/L
- Anion gap = $(Na^+ + K^+) - (Cl^- + HCO_3^-)$
- Maintenance fluid rate (mL/h) = body weight $(kg)^{0.75}$ x 70/24h
- Estimated fluid deficit or dehydration (mL) = body weight (kg) × % dehydration × 1000*
- Total fluid rate = Maintenance (mL) + dehydration (mL) + estimated ongoing losses (mL)

*amount to be given over 6-24h

adjusting for the effect of fluid shift caused by hyperglycemia. These formulae establish that for every 100 mg/dL (5.5 mmol/L) increase in BG, there is an average decrease in serum sodium (by dilution) of 2.4 mmol/L; this correlation is not linear, so alternatively, a correction factor of 1.6 can be used for BG up to 400 mg/dL (22 mmol/L) and a factor of 4 for BG above 400 mg/dL (14).

Dysnatremia and hyperosmolarity can produce neurologic signs, which can occur at presentation or after treatment. Cerebral edema is a rare complication in veterinary medicine and its pathogenesis is unclear; although BG, sodium and osmolality may play a role, ischemic-reperfusion injury, inflammation and increase vascular permeability seem to be the main contributing factors (13,15).

Treatment: from DKA to DM

Insulin is obviously an essential treatment in diabetic patients, but correct management of electrolyte and acid-base imbalances is equally important, and treatment must be tailored to the individual patient **(Box 1)**.

"The DKA acronym acts as a reminder that the condition is characterized by hyperglycemia (as in diabetes mellitus (D)), ketonemia/ketonuria (K), and metabolic acidosis (A)."

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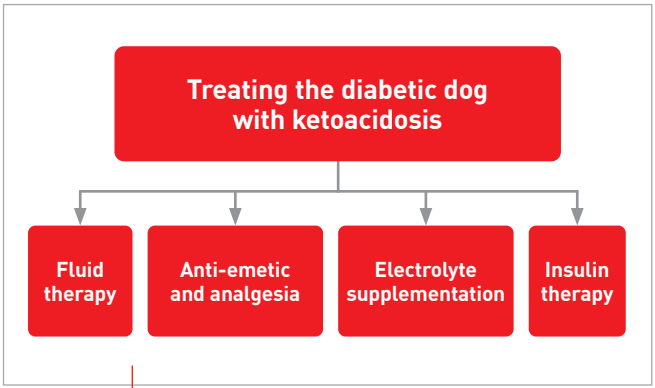

Box 1. Dogs with DKA require a balanced and multi-faceted treatment plan, which should be tailored to the patient's individual needs.

Fluid therapy

DKA patients normally require fluid therapy due to fluid losses secondary to osmotic diuresis, hypoinsulinemia, vomiting, diarrhea, reduced fluid intake and co-morbidities. The severity of fluid loss is variable; if the patient is volume-depleted and hemodynamically unstable, fluid resuscitation is required. If pathologies that predispose to fluid intolerance can be excluded, one or more boluses of 10-20 mL/kg over 15-20 minutes of an isotonic crystalloid are advised, guided by resuscitation endpoints. Once effective circulating volume is restored, the aim is to correct dehydration (over 6-24 hours) and to provide fluids for maintenance (increased because of osmotic diuresis) and ongoing losses. Frequent reassessment (every 4-6 hours) of losses, and any evidence of fluid deficit or overload, such as changes in bodyweight, is important in order to modify the fluid plan (11c).

Fluid therapy improves acidemia, hyperglycemia and ketonemia through dilution, improved glomerular filtration rate, increased blood flow and reduction of counter-regulatory hormones. Due to their ability to rehydrate interstitial and intracellular space, isotonic crystalloids are considered a good choice for DKA patients, however no clinical trials have yet indicated whether balanced isotonic crystalloids (such as Lactated Ringers) are superior to 0.9% saline (2). Chloride-rich fluids can cause hyperchloremic metabolic acidosis, which may worsen or delay acidemia resolution; in addition, some studies report an association between hyperchloremia and renal vasoconstriction that may translate into acute kidney injury (16). Correcting hyperglycemia along with natremia without significant changes in osmolarity is another important aim of the fluid therapy plan, and reduces the risk of cerebral edema and neurological deficits (13,15). Human studies lack good quality evidence to suggest a superiority amongst crystalloids in DKA treatment. However, due to the beneficial effects of buffered crystalloid vs. 0.9% saline in critically ill patients, alongside some evidence of a more rapid resolution of ketoacidosis in DKA, buffered solutions are now increasingly recommended as a first-line DKA replacement fluid (16,17).

Bicarbonate

Bicarbonate supplementation is controversial. Although it can transiently improve acidosis in DKA, most studies do not report improvements in outcome. As there is a lack of studies evaluating bicarbonate supplementation in human patients with pH < 6.9, several human guidelines consider its supplementation (over 2 hours, alongside potassium supplementation) in this subpopulation with a pH of 7 as the end-goal. However, other sources advise bicarbonate use only in case of persistent acidosis requiring inotropes (5,18).

A study of dogs with DKA found an association between bicarbonate supplementation and worse outcome, although an association between acidosis and worse outcome was also present (6). Bicarbonate replacement, especially in hypoventilating patients, is related to several complications: worsening hypokalemia and hypocalcemia, risk of volume overload, cerebral paradoxical acidosis, hyperosmolarity, right shift of oxyhemoglobin curve, cerebral edema and worsening of ketonemia (mainly via increased AcAc levels for augmented hepatic ketogenesis) (17).

In summary, because of the risks associated with its supplementation and the lack of benefits in this population, bicarbonate is rarely given.

Electrolyte supplementation

Total body electrolyte depletion, worsened by insulin treatment, is common in DKA. Therefore prior to starting insulin, these deficiencies should be corrected **(Table 2)**. Initially, electrolytes are monitored every 4-6 hours, however when values improve, intervals can be increased.

If hypokalemia is present, potassium supplementation via constant rate infusion (CRI) should be started with a maximum rate of 0.5 mEq/kg/h. Higher rates (with electrocardiography monitoring) may be indicated for severe hypokalemia, however evidence for this is scarce and it is rarely advised due to possible serious adverse effects. If hyperkalemia is present, potassium supplementation should be withheld until reassessment. A minimal supplementation is recommended if the patient is normokalemic (2,5,11a,18).

Routine phosphate supplementation has not been shown to improve outcome in human DKA patients, and guidelines advise it should only be done with severe hypophosphatemia (11c,17). This requires CRI of sodium or potassium phosphate;

Table 2. Electrolyte supplementation based on (11a,b).

Electrolytes (available supplementations)	Dosage		Notes
Potassium potassium chloride (KCl) potassium phosphate (KPO_4) (K → 1mEq = 1 mmol)	Serum potassium (mEq/L) < 2 2-2.4 2.5-2.9 3-3.4 3.5-5	Supplementation (mEq/kg/h) 0.5 0.4 0.3 0.2 0.1	• Via peripheral vein, potassium concentration should not exceed 40 mEq/L (risk of pain, phlebitis) • Do not exceed 0.5 mEq/kg/hr
Phosphate potassium phosphate (KPO_4) (P →1mEq = 1 mmol)	IV CRI = 0.03-0.12 mmol/kg/hr		• Incompatible with Lactated Ringer's solution • Potassium provided as potassium phosphate need to be taken into account in the total amount of potassium supplemented • Hyperphosphatemia may lead to hypocalcemia
Magnesium magnesium sulphate ($MgSO_4$) (Mg → 1mEq = 2 mmol)	IV CRI = 0.5-1 mEq/kg q24h		• Must be diluted to a concentration of 20% or less prior to IV infusion

the amount of potassium present in the latter needs to be considered alongside potassium supplementation. Note phosphate is incompatible with Lactated Ringer's solution. Magnesium supplementation, as magnesium sulphate or chloride, should be considered in cases of refractory hypokalemia.

Insulin therapy

Insulin is essential to decrease gluconeogenesis, improve glucose utilization and to both reduce KB production and increase KB metabolism. In reducing hyperglycemia (and therefore osmolality), insulin promotes fluid shift from the extra to intracellular space, worsening hypovolemia. It also causes electrolyte shifts, unmasking deficiencies, therefore insulin is started once these electrolyte deficiencies (particularly hypokalemia) and hypovolemia are corrected. Fluid therapy itself improves hyperglycemia, therefore starting insulin too soon may cause a rapid decline in BG. Human guidelines advise initiation of insulin therapy after at least an hour of fluid therapy, and with a potassium value of at least 3.3-3.5 mEq/L (5,18). A veterinary study showed that starting insulin within 6 hours of hospital admission reduces time for DKA resolution (based on ketonuria) and does not increase the complication rate (19). Although this study did not analyze outcome and complications in the 1-6-hour timeframe, it may be acceptable to start insulin sooner than previously believed, but certainly only when the patient is fluid-resuscitated and the main electrolyte abnormalities are improved, as per human guidelines.

A CRI of regular (short-acting) insulin is advised because of its rapid onset, short half-life and easy titration. Low doses are preferred, with an initial rate of 0.1 IU/kg/h (5,11c). However, intermittent intramuscular (IM) protocols may be considered, especially for uncomplicated cases with financial restrictions (20) **(Table 3)**. As an alternative to regular insulin, other type of short-acting insulins (lispro, insulin aspart) have been evaluated with promising results (21,22). Some human studies advise co-administration of long-acting subcutaneous insulin alongside regular insulin CRI in order to reduce insulin requirements and

Table 3. Insulin protocols.

CRI of regular insulin (adapted from 11c)

Blood glucose concentration	Rate regular insulin (mL/h)	Dextrose supplementation
> 250 mg/dL (14 mmol/L)	10	-
200-250 mg/dL (11-14 mmol/L)	7	2.5% dextrose
150-200 mg/dL (8-11 mmol/L)	5	2.5% dextrose
100-150 mg/dL (5.5-8 mmol/L)	3	5% dextrose
< 100 mg/dL (5.5 mmol/L)	stop	5% dextrose

- 2.2 U/kg of regular insulin is added to 250 mL of appropriate crystalloid solution (if chart is followed, rates are equal to 0.1 U/kg/h)
- Run 50 mL of the solution through the giving set before connecting to the patient (as insulin binds to plastic)

IM regular insulin (adapted from 20)

- 1st dose → 0.1-0.2 U/kg
- After 1 hour → 0.1 U/kg

Reassess BG drop (monitor BG every hour):

- > 75 mg/dL/h (4 mmol/L) → 0.05 U/kg/h
- 50-75 mg/dL/h (2.8-4 mmol/L) → 0.1 U/kg/h
- < 50 mg/dL/h (2.8 mmol/L) → 0.2 U/kg/h

When BG < 250 mg/dL (<14 mmol/L):

- 0.1-0.3 U/kg regular insulin IM q6-8h
- Supplement 2.5-5% dextrose to maintain BG 150 and 300 mg/dL (8 to 17 mmol/L)

"Insulin is obviously an essential treatment in diabetic patients, but correct management of electrolyte and acid-base imbalances is equally important, and treatment must be tailored to the patient."

Emma Donnelly

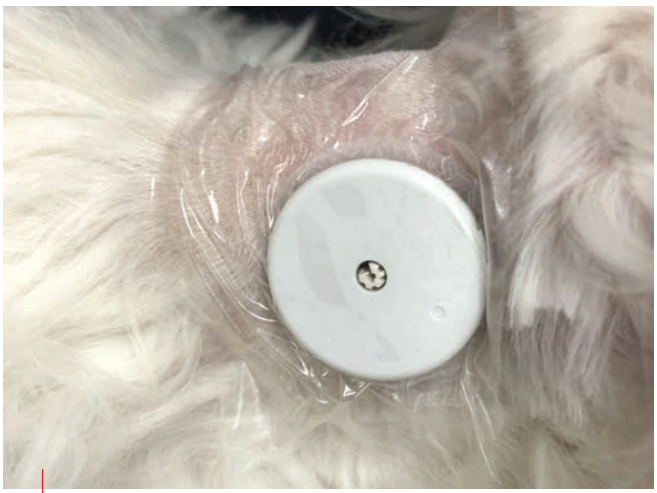

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Figure 3. A continuous (flash) glucose monitoring device on the dorsal neck of a dog; this allows continuous glucose measurement.

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Figure 4. A DKA patient with a naso-gastric tube receiving a liquid diet.

accelerate ketoacidosis resolution; it will also help avoid rebound hyperglycemia once regular insulin is stopped (23).

BG should be monitored every 1-2 hours during the IV protocol and initially hourly for the IM protocol. BG should drop by 50-75 mg/dL/h (3-4 mmol/L/h); human guidelines suggest to increase the insulin rate hourly by 1U if this goal is not achieved. Once BG reaches 200 mg/dL (11.1 mmol/L) insulin should be reduced and dextrose supplementation added **(Table 3)**. The goal is to maintain BG between 150-200 mg/dL (8-25 mmol/L), avoiding hypoglycemia but continuing insulin until ketosis resolution (5,11c). If the measured sodium does not increase concomitant with BG decline, fluid therapy needs to be modulated in order to reduce the risk for cerebral edema (15).

Once ketoacidosis is resolved (AG < 10-12 mEq/L, BHB < 0.6 mmol/L, pH > 7.3), glucose levels are well controlled, and patient is eating (or would eat at home) and drinking, long-acting insulin is started. This has a delayed onset, therefore an overlap between the two protocols is necessary to avoid rebound hyperglycemia. Porcine lente (intermediate-acting) insulin, at a starting dose of 0.25 IU/kg every 12 hours, is the gold standard for dogs; it has an onset of action of about 3 hours, with a nadir at 4-8 hours (24).

Monitoring and supportive care

Monitoring and treatment are intrinsically linked in managing DKA cases; frequent blood samples to assess BG, electrolytes and acid-base balance are necessary, so once the patient is hemodynamically stable, a central venous catheter is advisable. This reduces patient stress, allows for longer dwell time and safer administration of high osmolarity fluids.

Another useful tool, especially if a central line is contraindicated, is to use one of the continuous (flash) glucose monitoring devices which are now widely available **(Figure 3)**. These are small sensors that allow continuous monitoring via a subcutaneous filament that measures glucose levels in the interstitial fluid. They reduce patient stress, nurse workload and provide continuous glucose reading, although they seem less accurate in dehydrated patients (25).

The presence of ketosis, free fatty acids (FFA), abdominal pain, nausea or vomiting may cause reduced oral intake in DKA. After 3 days of anorexia, if the patient is hydrated, hemodynamically stable, with corrected electrolyte and acid-base imbalances, enteral or parenteral nutrition (the first being considered more physiological and safer) is advised. Early enteral nutrition is associated with a better outcome in critically ill patients, and a human study showed

shorter hospitalization in DKA patients in which enteral nutrition was started within 24 hours from hospital admission (26). If short-term nutritional support is expected, naso-esophageal or naso-gastric feeding tubes are chosen **(Figure 4)**. Although diabetic diets have high levels of fiber and complex carbohydrates, during DKA the main goal is to provide a good quality diet, and concomitant pathology requirements should be considered. As long as anorexia has not been prolonged, nutrition should start at 25-33% of resting energy requirements, with a gradual increase every 12-24h, taking into account the patient's tolerance to nutrition (11c).

CONCLUSION

70% of dogs treated for DKA are successfully discharged, with a median of 6 days of hospitalization. Complications include hypoglycemia, hypokalemia, hyperglycemia and (rarely) cerebral edema, and in addition, severe acidosis, pancreatitis or hyperadrenocorticism are associated with a worse outcome. It is therefore essential for the successful management of DKA patients to include strict monitoring of blood glucose, electrolyte and acid-base imbalances, together with diagnosis of comorbidities and a personalized treatment plan.

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