

Managing Osteoarthritis in Dogs

Don Hulse, DVM, DACVS
Austin Veterinary Sports Medicine
College Station, TX

Sandra Hudson, BS, MBA, CCRP
Canine Rehabilitation and Conditioning Center
Austin, TX

Osteoarthritis is the most common cause of chronic pain in dogs with approximately one in five adult dogs having OA. OA (sometimes referred to as degenerative joint disease) is a slowly progressive degenerative disease involving the entire joint: articular cartilage, subchondral bone, synovial lining, joint fluid, ligaments, and muscles. Osteoarthritis is commonly classified as primary OA or secondary OA. Primary OA is associated with aging and chronic loading and wear of the articular surface. Secondary OA (the most common form seen in dogs) has many acquired and congenital etiologies including: ligamentous injury (CCL), abnormal joint conformation (elbow dysplasia), Osteochondrosis (OCD shoulder). In general, OA can develop in any joint where abnormal stresses are imposed on a normal joint or alternatively where normal stresses are imposed on an abnormal joint. Although more senior dogs exhibit clinical signs of OA as compared to their younger counterparts, younger dogs may also exhibit signs of OA. The most common example in younger dogs being OA associated with hip dysplasia. It becomes easy to understand why OA is painful when joint innervation and the role of inflammatory cytokines are considered.

Innervation of joints includes nociceptors which are free nerve endings found in all joint tissue except articular cartilage. They are found in the subsynovial layer only two to four cell layers beneath the synoviocytes lining the joint cavity. Dogs with OA have an ongoing synovitis the severity of which varies depending upon activity and joint trauma. The synovitis is accompanied by the accumulation of increased levels of eicosinoids (prostaglandins, leukotrienes) and pro-inflammatory cytokines (IL-1, TNF, NO) in joint fluid. Additionally, synovitis is accompanied by increased vascular flow in the subsynovial tissue. These two factors, increased inflammatory mediators in the joint fluid and increased blood flow in subsynovial tissue, increases the exposure of free nerve endings (nociceptors) to inflammatory mediators. The result is sensitization of free nerve endings, increased stimulation of free nerve endings, and transmission of pain to the CNS. Inflammatory mediators also up regulate the expression of harmful mediators which play a role in catabolism of articular cartilage.

The architect of cartilage is the chondrocyte which produces the extracellular matrix. The matrix is composed of glycosaminoglycans (hyaluronan and proteoglycan) and collagens (mainly type II). The collagen forms a dense network that retains the proteoglycan. The proteoglycan is highly charged and attracts water into the tissue. Thus cartilage is 75% water. In normal cartilage there is a very slow turnover of collagens but the proteoglycan is constantly being renewed. The proteoglycans are aggregated into large molecules ("aggrecan") with a protein core and many side chains of keratan sulphate and chondroitin sulphate. This core is in turn bound to hyaluronan chains with each chain containing many proteoglycan molecules. Aggrecan and water provide the compressive stiffness to the tissue whereas collagen provides the tensile strength. The morphological changes seen in OA include: 1. cartilage loss, especially in areas of increased load, 2. subchondral bone remodelling (loss of bone initially followed by sclerosis), 3. marginal osteophytosis, 4. variable synovial inflammation. The biochemical changes in the cartilage include: 1. loss of proteoglycan, 2. upregulation in the degradative and synthetic activities of chondrocytes, 3. disruption of the collagen network, 4. increase in water content. These changes reduce the elasticity of the cartilage leading to fibrillation and fissuring of the cartilage with eventual loss of tissue. If this continues eburnation of subchondral bone may result. It is proposed that the cytokines responsible for stimulating cartilage degradation in OA are interleukins 1 and 6 (IL-1 and IL-6) and tumor necrosis factor- α (TNF- α). However, whilst these cytokines have been shown to stimulate degradation in several species, their effect in the dog is less marked. Recent in vitro studies (Innes) on canine cartilage explants show the resistance of canine cartilage to rhIL-1, rhIL-6 and rhTNF- α . However, canine cartilage does respond readily to oncostatin M (OSM) and Leukaemia Inhibitory Factor (LIF). Catabolic cytokines can stimulate the chondrocyte to produce and release degradative enzymes. The enzymes studied in most detail in this respect are the matrix metalloproteinases (MMPs) and the new family of endopeptidases the ADAM-TS-4 and -5 (**A** disintegrin and **metal**loproteinase with a **thrombospondin** motif). ADAM-TS-4 and -5 are also known as aggrecanases. MMPs and aggrecanases can cleave the protein core of aggrecan so as to release the majority of the molecule from the matrix. Under normal circumstances the chondrocyte also produces a natural inhibitor of these enzymes known as tissue inhibitor of metalloproteinase (TIMP). TIMP production appears to be decreased in OA.

Osteoarthritis progresses slowly and has a gradual onset of clinical signs. Subsequently, the diagnosis of OA is often made in the later stages of the degenerative process after extensive bone and joint damage has occurred. Commonly the diagnosis of OA is made by radiographic changes characteristic of degenerative joint disease. However, by the time radiographic changes are apparent the condition has progressed considerably. Therefore, early intervention using alternative diagnostic modalities is essential for the well being of the animal. One recommendation is to establish an Osteoarthritis pain assessment screening protocol. Behaviors consistent

with OA in dogs include: limping, inactivity, difficulty rising, lagging behind on walks, stopping on walks, difficulty posturing to eliminate. Managing the osteoarthritic dog is multifocal; An accurate diagnosis is essential for the management of secondary osteoarthritis since surgical intervention may be necessary to correct the underlying problem to achieve optimal outcome. In addition to appropriate surgical intervention, successful treatment of osteoarthritis is a compilation of strategies including client education, behavior modification (both client and pet), appropriate exercise activities, rest, weight control, disease modifying agents and anti-inflammatory medications. Of these, controlled exercise activity coupled with adequate rest and weight control will benefit your pet as much or more than any other modality.

Regular physical activity and rest play a key role in wellness. Episodic physical activity may also be preferable to continuous exercise by avoiding injury due to overuse. Episodic activity refers to those activities that occur for a reasonable time period multiple times throughout the day. Of considerable harm to the process of osteoarthritis is your pet having a sedentary life throughout the week only to exercise strenuously on the weekend. This lifestyle exacerbates the osteoarthritis and is very likely to result in serious injury. Treatment regimes should include regularly scheduled rest. Exercise effectively squeezes the water out of the cartilage making it less compliant and more susceptible to injury. Rest allows fluids to seep back into the cartilage restoring its mechanical efficiency and lessening the incidence of injury due to overuse. Family members must learn to recognize their pet's body signals and know when to stop or slow down. Doing so prevents pain and injury caused by overexertion. Two types of exercise are important in osteoarthritis management. The first type, therapeutic exercises, keeps joints working as well as possible. Therapeutic exercises are low impact and designed to maintain or increase joint range of motion, proprioceptive feedback, muscle tendon unit and periarticular tissue elasticity. Examples of therapeutic exercises are passive range of motion activity, massage, aquatic therapy, and stretching. The other type of exercise, aerobic conditioning exercises, improves strength and fitness, and controls weight. Examples are brisk walking, brisk walking or trotting through high grass, cavaletti training, and aquatic therapy. Your veterinarian and/or a rehabilitation therapist can evaluate your pet and develop a safe, personalized exercise program to increase strength and flexibility. Each program will include a warm up period, exercise period, and cool down period. Weight and body condition are important in preventing Osteoarthritis as well as an important factor in the treatment of osteoarthritis. Heavy dogs are at increased risk of developing arthritis because their joints may be strained by excess weight. This is especially evident in weight-bearing joints such as the knees and hips, which often show the first signs of weight-related strain and injury. An investigation into the cause of cranial cruciate ligament injury and the development of secondary osteoarthritis showed a significant risk factor to be obesity. One study in man showed that an average of 10 pounds of weight loss over a 10-year period decreased the risk of osteoarthritis of the knee by 50%. Similarly, obesity accounts for up to 30% of knee OA in man, exacerbates symptoms, and is associated with more rapid progression of the disease. If your pet is overweight and you enforce a weight loss program, you will dramatically decrease the risk of your pet injuring its knee joint and developing osteoarthritis. In fact studies of dogs with hip osteoarthritis show that reaching target reduction weight increases a dogs' ability to move in a more normal fashion as assessed by gait analysis and owner observations.

Pain control medication allows the OA dog to engage in activity; this in turn helps control body weight and improve physical condition. The drugs of first choice for controlling arthritis are NSAIDs. NSAIDs function in part by inhibiting cyclooxygenase (COX) isoenzymes. COX-1 is the constitutive isoenzyme essential for the synthesis of homeostatic PGs in the GI tract, kidney, and platelets. COX-2 is for the most part induced and results in the production of PGs associated with pain and inflammation. However, COX-2 is also constitutive expressed and has a homeostatic role in canine brain, kidney, and vascular tissues. COX-3 is constitutively expressed and plays a role in brain tissue. NSAIDs approved for use in the dog include carprofen, deracoxib, etodolac, meloxicam, tepoxalin and others. All inhibit COX -1 and COX - 2 to varying degrees. The Coxib-class may exhibit less interference with the homeostatic functions of PGs associate with COX-1. However, the clinical effect of COX 1 vs COX -2 inhibition is largely unknown (Vioox!!)

Carprofen, a NSAID which is less ulcerogenic, is marketed by Pfizer Animal Health under their trade name Rimadyl™. Rimadyl relieves pain and clinical signs of osteoarthritis in dogs, while causing less gastrointestinal side effects. Plasma and serum concentrations of carprofen are consistent throughout the treatment period. Serum concentrations peak at 2 hours, while synovial concentrations peak between 3-6 hours. The synovial concentration of carprofen ranges between 1-10 µg/ml during the treatment period in both normal and osteoarthritic joints. A significant reduction of PGE₂ from chondrocytes occurs at all concentrations in this range. %). Recent studies have shown carprofen to have little effect on kidney and platelet function. Carprofen has been recently found to support cartilage metabolism and proteoglycan synthesis.

Etodolac (Etoogesic) is a Fort Dodge product used for treatment of osteoarthritis in dogs. The drug is available as a non-chewable tablet and is administered at a dose of 10-15 mg/kg every 24 hours. Etodolac has been found to be an effective treatment for ameliorating the clinical signs of osteoarthritis. Side effects with etodolac are typical of that seen with the NSAID class of drugs, gastrointestinal ulceration being the most common problem. Gastrointestinal ulceration can be severe at dosages above the labeled dose- this is well documented in their label claim during toxicity trials. Conflicting data has been found on etodolac's effect on proteoglycan synthesis and cartilage metabolism. The Cox 2:Cox 1 ratio appears to be less favorable as compared to carprofen.

Meloxicam was granted USDA approval in 2003, having been available in Europe since 1993. It is indicated for the control of pain and inflammation associated with OA in dogs. It is considered to have moderate COX-2 inhibition.

Deracoxib (Deramaxx) is a recently released NSAID from Novartis Animal Health approved for use in dogs for postoperative pain and inflammation. The recommended dose is 3-4 mg/kg, po, once daily for 7 days or 1-2 mg/kg, po, sid for chronic use. Like carprofen, deracoxib has a highly favorable Cox 1:Cox 2 ratio. The expected side effects are similar to other NSAIDS, primarily gastrointestinal disturbances.

The first dual-pathway (cyclooxygenase, lipooxygenase) canine NSAID, tepoxalin, has recently been approved. It has been suggested that the reduced ulcerogenic activity of tepoxalin is due to the ability to inhibit leukotriene production.

For many years, Aspirin was the most common NSAID used in the dog. Although effective in the majority of cases, aspirin is COX-1 selective causing platelet dysfunction and GI toxicity. Nevertheless, empirical observation would suggest that as many as 40% of pet owners administer aspirin to their pets. Even low dose aspirin causes GI lesions in dogs. However, dogs develop a tolerance to aspirin and lesions do not necessarily worsen. This has recently been explained by production of endothelial cell triggered lipoxin. Aspirin triggered lipoxin (APL) appears to be anti-inflammatory and decreases PMN migration to areas of ulceration. The production of APL is mediated through the COX-2 pathway. If aspirin is followed by or given concurrently with a COX-2 inhibitor, the APL pathway is blocked. Rather than APL production, a different pathway occurs giving rise to leukotriene B4 which is a very potent inflammatory cytokine. The result is a significant increase in GI ulceration. The clinical message is that one should not administer aspirin with a COX-2 inhibitor or administer a COX -2 inhibitor without adequate washout if aspirin has been used (10 -14 days).

Chondroprotective agents are emerging as a new class of drugs used to slow progression of and treat chronic DJD. These drugs not only should be antiinflammatory; but also should support anabolic (repair) processes in cartilage, bone and synovium essential for normalization of joint function. This class of drugs include the glycosaminoglycans. Examples of these drugs include glycosaminoglycan polysulfate ester, pentosen polysulfate and sodium hyaluronate. Cosequin (Nutramax Laboratories, Baltimore, MD) is marketed as a glycosaminoglycan enhancer, capable of providing raw materials needed for the synthesis of extracellular matrix of cartilage. Unlike most nutraceuticals, Cosequin has been evaluated in a variety of studies. Cosequin contains glucosamine which has been described as the building-block of the matrix of articular cartilage. It has been described as a preferential substrate and stimulant of proteoglycan biosynthesis, including hyaluronic acid and chondroitin sulfate. Cosequin also contains chondroitin sulfate, mixed glycosaminoglycans, and manganese ascorbate for the purpose of promoting glycosaminoglycan production. Orally administered glucosamine sulfate has been associated with relief of clinical signs of DJD and chondroprotection in clinical and experimental studies in man, horse and dog. Although glucosamine has a slower onset of relief of clinical signs associated with DJD as compared to ibuprofen, two clinical trials found it to have equal long term efficacy. No significant side effects have been reported with Cosequin.

Wrapping Your Head Around the Pericardium: A Review of Pericardial Disease

Barret Bulmer, DVM, MS, DACVIM
Tufts Veterinary Emergency Treatment and Specialties
Walpole, WA

Congenital and acquired pericardial disease may be encountered in a variety of situations ranging from the asymptomatic animal to the patient in acute shock. Therefore the possibility of pericardial disease should remain at the forefront of many different clinical presentations.

Pathophysiology

The most important pathophysiologic effect of pericardial disease is the reduction of diastolic filling of the heart. Diastolic dysfunction causes a reduction of ventricular stroke volume and cardiac output. The severity of clinical signs usually depends on the rate of fluid accumulation. It is important to realize that the pericardial pressure volume relationship is such that there is a progressively greater rise in pericardial pressure as pericardial volume increases.

History and clinical signs

Rapidly developing cardiac tamponade can cause acute hypotension, weakness, dyspnea, collapse, and sudden death. Animals with slowly developing and chronic pericardial effusion may present with signs of right-heart failure including abdominal distension, respiratory difficulty associated with pleural effusion, or exertional syncope. The heart sounds are usually muffled, careful examination will often reveal jugular venous distension or a positive hepatojugular reflux, and femoral arterial pulses are often reduced in strength or exhibit pulsus paradoxus.

Diagnostics

- 1) Electrocardiogram: ECG alterations are variable and non-specific but may often include low amplitude QRS complexes in all leads, sinus tachycardia, ventricular premature complexes (depending on the etiology of the effusion), nonspecific ST segment elevation or depression, and electrical alternans.
- 2) Thoracic radiographs: Although we often describe a large globular cardiac silhouette rounded in all views as the characteristic finding of pericardial effusion, most studies suggest there are no steadfast radiographic findings for distinguishing cardiac tamponade from various other cardiovascular diseases. With small effusions, changes may be minimal and animals with pleural effusion may have an obscured cardiac silhouette.
- 3) Echocardiography: Echocardiography is the most sensitive method of detecting pericardial effusion and it often permits visualization of neoplastic lesions that may serve as the etiology for cardiac tamponade.

Pericardiocentesis

Usually with the dog in left lateral recumbency, the right fifth intercostal space at the costochondral junction is clipped and surgically prepared. While monitoring the ECG, an over-the-needle catheter is advanced toward the heart and when fluid is obtained, the catheter is advanced into the pericardial sac. The stylet is withdrawn and most often the catheter is attached to an IV extension set, three-way stopcock and syringe for aspiration. The catheter may be fenestrated to make aspiration of fluid easier. Aspirated fluid can be compared to peripheral blood and monitored for clotting to make certain accidental cardiac catheterization has not occurred. Routine cytology and fluid analysis is generally performed to try and exclude bacterial, fungal, or obvious neoplastic etiologies. But with most hemorrhagic effusions it is impossible to distinguish the neoplastic effusates from idiopathic effusions.

Diseases of the pericardium

Congenital diseases of the pericardium are infrequently encountered but their recognition is gratifying because they are often amenable to surgical correction. These lesions include pericardial defects, peritoneopericardial diaphragmatic hernia and intrapericardial cysts. Acquired pericardial disease is typically manifest as pericardial effusion of neoplastic or idiopathic/inflammatory origin. Less common etiologies for pericardial effusion include uremia, left atrial tear, rodenticide toxicity/coagulopathy, infectious disease, heart failure, hypoalbuminemia, trauma or pericardial foreign bodies. The prognosis and treatment varies with the underlying etiology but in general hemangiosarcoma and mesothelioma carry poor prognoses, while idiopathic disease and effusion related to chemodectoma often carry a better prognosis depending on response to therapy.

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Radiographic Review of Cardiovascular Disease

Barret Bulmer, DVM, MS, DACVIM
Tufts Veterinary Emergency Treatment and Specialties
Walpole, WA

Meaningful evaluation of the heart is predicated on a sound knowledge of normal anatomy, physiology, and breed variations and adherence to principles of standardized technique and positioning to eliminate non-pathologic variables. Digital radiography has helped improve radiographic technique but appropriate animal positioning remains critical. The ribs and spine should be penetrated well enough to show some bony detail (trabeculation) on the lateral view. On the VD or DV view, the thoracic vertebrae should be just visible but not show detail where they overlie the heart. One should also be able to trace the course of the descending aorta along the left side of the spine on the VD or DV view. Always consider the possibility of noncardiac anatomic or pathophysiologic factors that can alter the appearance of the heart including congenital anomalies of the spine, sternum, or rib cage, intrathoracic masses or fluid, megaesophagus, pneumothorax, lung collapse, a diaphragmatic hernia, trauma (including broken ribs, lung contusion), and pneumonia or other parenchymal lung densities overlying the heart. Chest radiographs are fairly accurate for identifying left atrial (lateral view), left ventricular and right ventricular enlargement (DV view). Right ventricular and right atrial enlargement are often over-interpreted. Left ventricular eccentric hypertrophy is more visible than concentric hypertrophy.

Lateral view

The normal heart occupies approximately 2.5 to 3.5 intercostal spaces, and the height of the heart is approximately 2/3rds the height of the chest. The trachea typically diverges ventrally from the spine at an angle of about 20°. The caudal waist should be distinctly visualized. The shape of the heart conforms to the general shape of the thoracic cavity. In brachycephalic and other barrel-chested dogs, the heart appears rounder and larger than in the "normal" dog. The trachea may run nearly parallel to the spine on the lateral view. In these dogs, the heart often occupies nearer to 3 1/2 intercostal spaces and it contacts more of the sternum ventrally. In narrow, deep-chested breeds, the heart is more "upright" and slender appearing on the lateral view. Cats have a slender conical-appearing heart that tends to be tipped slightly on the lateral view with the base of the heart lying more anteriorly. In older cats, the heart is less upright and may be inclined almost horizontal to the sternum. Older cats also often have an elongated, tortuous aorta on the lateral view.

An alternative method of evaluating heart size developed by James Buchanan may prove helpful. If the long and short axes of the heart are measured in the lateral views using the thoracic vertebrae as a scale (starting with the cranial margin of the 4th thoracic vertebra), the sum of these measurements (vertebral heart score = VHS) should not exceed 10.5 vertebrae. In 100 normal dogs the average measurement was 9.7 vertebrae. Most normal cats have a short axis dimension of 3.1 to 3.4 vertebrae, and a VHS of 7.2 to 7.8 vertebrae.

Dorsoventral or ventrodorsal view

The width of the heart is approximately 1/2 to 2/3rds the width of the thorax. The right and cranial borders are rounded and the left border nearly straight. The apex points to the left side of the thorax. On the DV view the heart occupies at least 2/3rds of the width of the thorax and the apex of the heart is sometimes directed more to the left. In narrow, deep-chested breeds the heart often appears small and round due to the upright position of the heart.

Radiographic signs of cardiac chamber enlargement

1) Right atrial enlargement

Right atrial enlargement is encountered rarely as an isolated abnormality in the form of congenital tricuspid valve stenosis. It is observed most often with RV enlargement as a result of acquired (valve degeneration) or congenital tricuspid valve insufficiency (tricuspid dysplasia). Right atrial enlargement also develops in dogs with right heart failure due to heartworm disease or dilated cardiomyopathy.

2) Right ventricular enlargement

Right ventricular enlargement develops as a consequence of pressure overload - pulmonic stenosis, tetralogy of Fallot, pulmonary hypertension; as a consequence of volume overload -tricuspid valve insufficiency or an atrial septal defect; and it enlarges in concert with the left ventricle in dogs with dilated cardiomyopathy.

3) Main pulmonary artery enlargement

The main pulmonary artery segment is located between 1:00 and 2:00 o'clock using the clock-face analogy. It enlarges as a consequence of pulmonary hypertension, pulmonic valve stenosis (post-stenotic dilatation), and as a result of volume overload - left to right shunting defects (ASD, VSD, PDA), and pulmonic valve insufficiency.

4) Left atrial enlargement

Left atrial enlargement is usually seen together with LV enlargement as most acquired disorders, such as mitral regurgitation and dilated cardiomyopathy affect both chambers. LA enlargement with no or minimal LV enlargement may be seen with mitral valve stenosis and with those disorders causing concentric LV hypertrophy, e.g. aortic stenosis and hypertrophic cardiomyopathy. Cats frequently display solely left auricular enlargement, a finding that is often absent on the lateral radiograph because of the anatomic location of the left auricle.

5) Left ventricular enlargement

Left ventricular enlargement develops as a consequence of pressure overload (concentric hypertrophy) due to valvular or subvalvular aortic stenosis or systemic hypertension or as a consequence of volume overloading (eccentric hypertrophy) due to mitral valve insufficiency or a left to right shunting VSD or patent ductus arteriosus. Concentric LV hypertrophy also occurs due to hypertrophic cardiomyopathy. The LV undergoes eccentric hypertrophy in concert with the right ventricle in dogs with dilated cardiomyopathy. Some cases of severe concentric hypertrophy have minimal radiographic changes because the sarcomeres are in parallel, thereby increasing the wall thickness but decreasing the radius of the left ventricle.

6) Aortic arch enlargement

The aorta is located between 11:00 and 1:00 o'clock using the clock-face analogy. It enlarges as a consequence of subvalvular aortic stenosis (post-stenotic dilatation), as a result of aortic valve insufficiency, and, more rarely as an idiopathic disorder or secondary to systemic hypertension. The aortic arch is also enlarged in dogs with a patent ductus arteriosus or tetralogy of Fallot.

Radiographic evaluation of the pulmonary arteries and veins

On the lateral view, the pulmonary arteries lie dorsal to the bronchus while the veins are located ventral to the bronchus. In the lateral view, vessels in the cranial and middle lung lobes are most easily seen. The arteries and veins should be approximately the same size. On the dorsoventral view, the pulmonary arteries lie lateral to the bronchus while the pulmonary veins are medial to the bronchus.

The vessels in the cranial and caudal lung lobes are usually easily seen in this view.

1) Enlarged pulmonary arteries and veins

Left to right shunts cause enlargement of both the pulmonary arteries and the pulmonary veins together with an overall increase in pulmonary density. Expiratory radiographs can accentuate the size of the pulmonary vessels and can falsely suggest pulmonary edema.

2) Diminutive pulmonary arteries and veins

Right to left shunts cause a decrease in the size of the pulmonary arteries and veins and a generalized decrease in pulmonary density. Also consider the possibility of hypovolemia.

3) Enlarged pulmonary veins with normal arteries

This finding usually indicates left heart failure or iatrogenic over-hydration. This sign is more reliable in dogs than in cats.

4) Enlarged pulmonary arteries with normal veins

With pulmonary hypertension (heartworms), the proximal branches of the pulmonary arteries are often noticeably larger than the veins. The arteries are also often more tortuous and truncated in appearance.

Comprehending Common Congenital Cardiac Disorders: Examination Findings, Diagnostics, and Treatment

Barret Bulmer, DVM, MS, DACVIM
Tufts Veterinary Emergency Treatment and Specialties
Walpole, WA

The primary objectives of the cardiovascular evaluation for animals with congenital heart disease are to define the nature and severity of the anatomic defect present. Familiarity with the available therapeutic options, their efficacy and limitations is necessary before an accurate prognosis can be offered to the owner.

Acyanotic congenital heart defects: Left to right shunts

Patent ductus arteriosus (PDA) including right to left shunting lesions

In the fetus the ductus arteriosus serves to shunt the majority of the right ventricular output away from the non-functioning lungs. Expansion of the lungs, increased oxygen concentrations and removal of the umbilical circulation at the time of birth promotes ductal closure. Failure of ductal closure usually results in a left to right shunt from the descending aorta to the pulmonary artery with an excess volume load placed on the pulmonary arteries and veins, left atrium, left ventricle and aortic arch. Histology of the patent ductus reveals a wall structure resembling that of the aorta rather than that of a normal ductus. In the presence of a very large, wide PDA the magnitude and direction of shunted blood is determined by the relative resistance of the pulmonary and systemic circulations. In these dogs the elevated pulmonary vascular resistance present at birth does not fall normally and results in right to left shunting or bidirectional shunting. On rare occasion pulmonary hypertension develops later in life thereby truly reversing the direction of the shunt (Eisenmenger's physiology).

Clinical features

1. Historically the most common congenital heart defect in dogs although the recent popularity of large breed dogs has resulted in increased prevalence of SAS. PDA is much less common in cats.
2. Females are over-represented.
3. Physical examination findings include:
 - a. A continuous "machinery" murmur that is heard best at the left heart base. The continuous murmur may be confined to the heart base while a systolic murmur of mitral insufficiency is ausculted over the left apical region.
 - b. Bounding (or waterhammer) pulses are frequently identified because of the increased systolic and decreased diastolic aortic pressures (widened pulse pressure).
 - c. Common clinical signs include stunted growth or evidence of left sided heart failure (dyspnea, tachypnea, coughing, exercise intolerance.)
 - d. PDA with pulmonary hypertension has no murmur but may have a split S2, differential cyanosis, and hindleg weakness. These dogs often display "differential cyanosis" where the hindlimbs are affected while the forelimbs are normal. This develops because of the communication of the pulmonary artery with the descending aorta.
4. Electrocardiographic findings:
 - a. Variable but often marked left ventricular enlargement pattern, possible left atrial enlargement and secondary ST segment changes associated with hypoxia.
 - b. Advanced cases may show supraventricular tachyarrhythmias (APCs, A fib) or less frequently ventricular arrhythmias.
 - c. A right ventricular enlargement pattern is almost always evident in cases of right to left shunting with pulmonary hypertension.
5. Thoracic radiography:
 - a. Enlargement of the left atrium, left ventricle, aortic arch, main pulmonary artery along with pulmonary vascular overcirculation (enlargement of both pulmonary arteries and veins).
 - b. Evidence of left sided heart failure may be present.
 - c. Dogs with right to left shunting often display pulmonary vascular undercirculation (hypovascularity of pulmonary arteries and veins), a prominent right heart pattern, dilation of the main pulmonary artery and localized dilation of the proximal aorta.
6. Echocardiography: Serves to evaluate the severity of volume overload as reflected by changes in the left heart chamber dimensions, detect other coexisting congenital heart defects, and assess myocardial function.

7. Prognosis:
 - a. In dogs with left to right shunts the prognosis is excellent with surgical or transcatheter closure of the defect prior to the development of left-sided heart failure. Without correction puppies with large shunts may die before four weeks of age, dogs with intermediate sized shunts may live for several years although the majority will be dead by 2 years of age. Dogs with small shunts (uncommon) may live normal lives.
 - b. In dogs with right to left shunts the prognosis is guarded. Some dogs may survive for long periods of time with exercise restriction and periodic phlebotomy or agents utilized to decrease red blood cell production.
8. Treatment: Ideally involves surgical correction of left to right shunts via thoracotomy or less invasive embolization procedures prior to the development of clinical signs. In cases of left to right shunts with congestive heart failure stabilization is achieved with standard medical therapy followed by closure. Surgery is contraindicated in dogs with right to left PDAs and instead efforts are aimed at preventing hyperviscosity via periodic phlebotomy.

Acyanotic congenital heart defects: Obstructive malformations

Obstructive lesions produce their effects by impeding normal blood flow and causing an increased pressure proximal to the obstruction. The two clinical syndromes identified in small animals include pulmonic stenosis and aortic stenosis. Four anatomic types of obstruction can occur at each location and include: supra-ventricular, sub-ventricular, valvular and infundibular. All result in similar degrees of functional impairment but their distinction is important if surgical correction is contemplated.

Pulmonic stenosis

Pathology of the pulmonic valves typically includes variable thickening of cusps and fusion of the cusps at their commissures. Pulmonic stenosis may occur as an isolated lesion or may be combined with other complex defects of the conotruncal septum (Tetralogy of Fallot). The resistance to ejection of blood from the right ventricle induced by the stenotic valve produces elevated RV systolic pressures, right ventricular concentric hypertrophy and in some cases increased right atrial pressure. A post-stenotic dilatation is usually present in the main pulmonary artery.

Clinical features

1. The second or third (because of the increased prevalence of SAS) most commonly diagnosed congenital heart defect in dogs. Uncommon in cats.
2. Physical examination findings include:
 - a. Systolic, ejection (crescendo-decrescendo) murmur heard best over the left heart base. A split second heart sound may be obscured by the murmur.
 - b. Arterial pulses are usually normal unless severe heart failure is present.
 - c. Dogs may be asymptomatic, exhibit exercise intolerance, or in severe cases may exhibit dyspnea and cyanosis from low cardiac output. Syncopal episodes with exercise are occasionally reported. Signs of right-sided heart failure may be present in severe cases.
3. Electrocardiographic findings:
 - a. A right ventricular enlargement pattern is usually evident while the rhythm is usually normal. In severe cases complicated by tricuspid dysplasia/insufficiency supra-ventricular tachyarrhythmias may be identified.
4. Thoracic radiography: Characteristic findings include right ventricular enlargement and dilation of the main pulmonary arterial segment. The pulmonary vasculature is usually normal.
5. Echocardiography: Serves to evaluate the extent of hypertrophy of the papillary muscles, septum and ventricular free wall of the right ventricle. The site of obstruction (valvular, subvalvular, etc.) may be identified via two-dimensional echocardiography and Doppler studies can evaluate the integrity of the tricuspid valve. Spectral Doppler can measure the peak blood flow velocity through the stenotic area and the modified Bernoulli equation ($4V^2$) can estimate the pressure gradient and hence the severity of the stenosis.
6. Prognosis: Many dogs with mild disease appear to do well without therapy while most agree that dogs with a pressure gradient over 80 - 100 mm Hg have a more guarded prognosis without therapy. Dogs with gradients between 40 and 80 mm Hg are more difficult to characterize.
7. Therapy: Balloon valvuloplasty is effective at reducing the pressure gradient significantly in approximately 70% - 85% of cases. In the presence of congestive heart failure exercise restriction and medical therapy are employed followed by consideration for surgery.

Subvalvular aortic stenosis (SAS)

SAS may be the most commonly identified congenital lesion in some regions because of the vast popularity of Golden Retrievers and other large breed dogs predisposed to SAS. In dogs a subvalvular fibrous ring or band partially or completely encircles the left ventricular outflow tract. Small nodules may also occur on the aortic valve cusps. Valvular obstruction results in elevated left ventricular systolic pressures, concentric hypertrophy of the left ventricle and post-stenotic dilatation of the ascending aorta. Increased oxygen requirements of the concentrically hypertrophied left ventricle and disturbances in coronary blood flow may lead to

myocardial ischemia. Histologically, arteriosclerosis of the small coronary arteries, fibrosis, necrosis, and calcification of the myocardium may be observed. SAS usually occurs as an isolated lesion although mitral valve dysplasia has been reported to occur concurrently.

Clinical features

1. A common defect in dogs although it is infrequently recognized in other species.
2. Physical examination findings:
 - a. A systolic ejection murmur (crescendo-decrescendo) at the left heart base. It frequently radiates to the carotid arteries at the thoracic inlet and may radiate to the right hemithorax.
 - b. Pulses may be weak and late rising due to retarded ventricular ejection.
 - c. Young dogs are frequently asymptomatic but may have history of fatigue, dyspnea, or syncope. Sudden death (presumably from ventricular arrhythmias) is one of the most commonly reported events in young dogs with severe SAS.
 - d. Arrhythmias (usually ventricular) may be present.
3. Electrocardiographic findings: The ECG may be normal in mild cases or it may display a left ventricular enlargement pattern in more severe cases. ST segment depression may be present due to myocardial hypoxia and arrhythmias (usually ventricular) are common.
4. Thoracic radiography: frequently unremarkable because the left ventricle hypertrophies concentrically. Findings may include left ventricular enlargement, post-stenotic dilatation of the aorta with variable left atrial enlargement. The pulmonary vasculature is normal unless left sided heart failure has developed.
5. Echocardiography: Serves to evaluate the severity of the left ventricular hypertrophy, the area of the obstruction may be directly visualized by two-dimensional echocardiography, and Doppler evaluation can categorize the severity of the stenosis via the modified Bernoulli equation. Myocardial fibrosis, presumably due to ischemia, may be identified as hyperechoic areas within the myocardium. Echocardiography also helps to evaluate for the presence of combined congenital defects. Differentiating normal dogs from dogs with very mild SAS can be difficult even with echocardiography because the subvalvular lesion may be so discrete.
6. Prognosis: The prognosis is guarded in cases of severe SAS (pressure gradient over 80 mm Hg). Owners should be made aware of the possibility of sudden death. SAS appears to be the one cardiac malformation that predisposes dogs to the development of bacterial endocarditis and standard antibiotic administration should be instituted whenever dogs with SAS undergo elective surgical procedures. Congestive heart failure may occur when mitral dysplasia is concurrently present or if myocardial failure develops after long-standing SAS.
7. Treatment: To date surgical resection of the stenotic lesion has not decreased the incidence of sudden death. Balloon valvuloplasty has also proved unrewarding in most cases as the obstruction tends to recur shortly after the valvuloplasty. A cutting balloon technique has started to be employed more recently. Current medical management may include administration of beta-blocking drugs to decrease the heart rate and cardiac contractility thereby decreasing myocardial oxygen demands and hopefully the risk of sudden death. The effectiveness of this therapy is unknown. Arrhythmias should be appropriately treated if present.

The Latest on Managing Mitral Valve Disease

Barret Bulmer, DVM, MS, DACVIM
Tufts Veterinary Emergency Treatment and Specialties
Walpole, WA

Chronic degenerative valvular disease (CDVD) is the most common cause of cardiac disability in dogs, accounting for as many as 75% of all dogs with signs of congestive heart failure. The disease process is best described as myxomatous degeneration of the heart valves wherein the integrity of the valves is compromised often resulting in valvular insufficiencies. During the initial stages of the disease there is no valvular insufficiency so there is no hemodynamic change or murmur ausculted, and the patients are entirely asymptomatic. As the lesions progress and the valves become incompetent, a systolic murmur results at the affected valve site and atrial pressure begins to rise. Left atrial enlargement and eccentric hypertrophy of the left ventricle maintain normal cardiac output for an indefinite period of time, often months to years. Eventually, left atrial and pulmonary venous pressures rise resulting in pulmonary venous congestion and ultimately pulmonary edema. The two primary determinants of the volume of valvular regurgitation include the size of the regurgitant orifice and the ventricular to atrial pressure gradient.

Most of the early signs of mitral regurgitation result from pulmonary congestion and most owners seek treatment for their dog after noticing some degree of respiratory distress. Coughing is a common but nonspecific sign of developing heart failure in dogs. When due to heart failure, coughing is usually accompanied by an elevated respiratory rate (tachypnea) and increased respiratory effort (dyspnea). Some dogs with valvular disease develop signs of right-heart failure due to degeneration of the tricuspid valve, as a consequence of pulmonary hypertension, or a combination of these disorders. Generalized muscle weakness and progressive exercise intolerance become evident when forward output is impaired by severe valvular regurgitation, pulmonary hypertension, and/or declining myocardial contractility.

Cardiac auscultation is the most practical and economical diagnostic method for detecting mitral regurgitation. There is a strong relationship between murmur intensity, heart size, the severity of regurgitation, and class of heart failure. The murmur of mitral regurgitation is usually best heard at the left fifth intercostal space, but dorsal, cranial, caudal, or rightward radiation of the murmur is common. It is particularly difficult to determine whether murmurs heard over the tricuspid valve area originate from that valve or if they are referred from an incompetent mitral valve. Cardiac arrhythmias can be readily identified as they interrupt the predominating cadence of the heart, create abnormal pauses in the rhythm, and alter the intensity of both murmurs and transient heart sounds.

Therapy

At this time early institution of therapy, in the asymptomatic patient and prior to the onset of heart failure, has been unable to demonstrate significant reduction in the time to development of congestive heart failure. Diuretics, vasodilators, angiotensin converting-enzyme inhibitors, and positive inotropic drugs all have demonstrated the capacity to lessen the severity of clinical signs associated with mitral regurgitation under certain conditions. Therapeutic recommendations should be based on a complete cardiovascular evaluation to identify the specific requirements of each dog. Many cardiologists consider the use of furosemide, an ACE inhibitor, and pimobendan standard therapy for dogs with valvular disease and heart failure. Dogs requiring medical therapy to control the signs of heart failure should avoid strenuous exercise and may achieve benefit from a low sodium diet.

Diuretics are the most effective drugs available for the symptomatic short-term treatment of congestive heart failure in animals. They are administered to reduce blood volume and, thereby, to lower filling pressures and alleviate congestion and associated clinical signs. With judicious use of diuretics, indirect improvement in cardiac output may result from improved oxygenation as pulmonary function returns towards normal. Diuretics tend to decrease preload and can aggravate low cardiac output signs if used overzealously. Always use the lowest dose necessary to control signs. In chronic, refractory cases of congestive heart failure, subcutaneous or intramuscular furosemide may be effective even if the animal is refractory to oral therapy. Alternatively, a combination of different types of diuretics can be used in this circumstance. The angiotensin-converting enzyme (ACE) inhibitors are the most important class of neurohormonal antagonists currently available for treating congestive heart failure. ACE inhibiting drugs are believed to palliate the deleterious consequences of vasoconstriction and sodium retention in patients with heart failure by blocking formation of angiotensin II and aldosterone. Overall, ACE inhibitors appear to be safe and well tolerated in dogs with congestive heart failure. Some of the specific adverse effects of ACE inhibiting drugs include systemic hypotension, hyperkalemia, and renal dysfunction/failure. When appropriate dosages are adhered to, systemic hypotension is an infrequently observed complication of ACE inhibitor treatment in dogs. Hyperkalemia is also occasionally observed in dogs receiving ACE-inhibiting drugs. Hyperkalemia appears to result from reduced glomerular filtration and diminished release of aldosterone. The degree of hyperkalemia is usually mild and few dogs develop clinical signs of hyperkalemia. Evidence of mild to moderate renal dysfunction is common in a substantial percentage of dogs with congestive heart failure, regardless of the form of treatment selected. Azotemia is usually interpreted in this population of dogs as evidence of decreased renal perfusion (prerenal azotemia) combined with an age-related decline in renal functional capacity. Angiotensin converting enzyme inhibitors are known to decrease glomerular filtration pressure by virtue of their vasodilating effects

on the renal efferent arterioles. As a result, treatment with an ACE inhibitor can result in mild azotemia and slightly increased serum creatinine concentrations. In most dogs treated with an ACE inhibitor renal function soon normalizes or stabilizes at a new steady state. In some circumstances, severe renal failure is observed shortly after initiating ACE inhibitor therapy. This consequence may be more common in dogs with serious preexisting renal disease, in dogs that are dehydrated, and in dogs experiencing systemic hypotension. It is prudent to evaluate renal function prior to and about 5 to 7 days after initiating an ACE-inhibiting drug. Most dogs that display intolerance can be adequately managed by decreasing either the dose of the ACE inhibitor or diuretic. On rare occasion, ACE inhibitor therapy may have to be abandoned.

Calcium sensitizers, combined with phosphodiesterase (PDE) inhibition in the form of pimobendan, are an additional drug class used in the management of congestive heart failure in dogs with valvular heart disease. Pimobendan has the ability to augment systolic performance by enhancing calcium-binding to troponin C and/or by affecting the cross-bridge turnover kinetics without increasing cytosolic calcium levels. Because pimobendan displays both calcium sensitization and PDE inhibition it becomes difficult to identify if the positive inotropic action stems from enhanced reactivity of troponin C and Ca^{2+} , cAMP-mediated phosphorylation of phosphoproteins, or a combination of the two. Pimobendan combined with furosemide has shown to improve outcome in dogs with valvular disease and heart failure in comparison to furosemide and an ACE inhibitor. The most common reported sided effects tend to be GI in nature. There are reports of development of ventricular concentric hypertrophy and worsening of the histologic grade of valve lesions in asymptomatic dogs with mitral valve disease, however the frequency of these adverse effects is uncertain and seem rare.

Complications of valvular heart disease

Cardiac arrhythmias

Atrial fibrillation occurs uncommonly but is hemodynamically one of the most serious rhythm disturbances observed. As a result of the loss of the atrial transport, clinical signs usually dramatically worsen with the onset of this rhythm disturbance.

Ruptured chordae tendinea

Rupture of the first-order chordae tendineae results in eversion of the valve leaflet into the atrium, severe mitral insufficiency, and the likelihood of rapid decompensation and acute, severe pulmonary edema. Rupture of second or third order chordae is better tolerated and may not result in rapid decompensation or any clinically recognizable signs.

Left-atrial tears

Endocardial splitting of the left atrial wall may complicate chronic mitral insufficiency. Nonperforating splits are often found at necropsy and are usually observed in the same areas as jet lesions on the posterior wall of the left atrium. Perforating myocardial splits most often produce hemopericardium or more rarely atrial septal defects. The sudden development of cardiac tamponade or signs of right heart failure in a previously compensated patient should alert the astute clinician to this possibility.

Bronchial collapse

Collapse of the left mainstem bronchus due to compression from a greatly enlarged left atrium may result in a chronic cough resistant to therapeutic efforts designed to abolish it.

Prognosis

The prognosis for dogs with asymptomatic mitral valve disease is good for survival although the disease is invariably progressive and may ultimately lead to congestive heart failure. Currently it is impossible to predict the rate of progression for an individual patient. In general, dogs with asymptomatic mitral valve disease carry a favorable prognosis. A large retrospective study by Borgarelli, et al. identified a median survival time of 28 months for dogs with ISACHC 2 and a median survival time of 9 months for dogs with ISACHC 3.

Dilated Cardiomyopathy: Boxers and Dobies, Oh My!

Barret Bulmer, DVM, MS, DACVIM
Tufts Veterinary Emergency Treatment and Specialties
Walpole, WA

The cause(s) of dilated cardiomyopathy (DCM) in dogs is (are) unknown. Some of the proposed causes of DCM include: genetic defect(s), viral infection, microvascular spasm, chemical toxin(s), dietary deficiency, and immune-mediated processes. There appears to be a familial predisposition to the development of DCM in some breeds of dogs, and many investigators suspect a heritable defect in the metabolic processes of myocardial cells. It is quite possible that DCM is not a single disease, and that there are many etiologies. Taurine deficiency has been convincingly shown to be a reversible cause of DCM in cats and is also a suspected cause of DCM in foxes, but is not an important cause of DCM in dogs—except in Cocker spaniels. A number of chemical toxins (anthracycline antibiotics, gossypol, monensin) have been shown to cause myocardial failure. There is evidence that Adriamycin exerts at least some of its toxic myocardial effects by inducing histamine and catecholamine-mediated microvascular spasm.

One of the most frustrating aspects of attempts to identify the etiology behind DCM is determining if changes in protein expression are primary or secondary in nature. Up-regulation and down-regulation of proteins responsible for cardiac contraction (β_1 , β_2 , and α receptors), ventricular relaxation (SERCA2, phospholamban) and energy production (carnitine transport, creatine kinase) occur to equivalent degrees in volume overload, pressure overload, and cardiomyopathy. “In this respect the intracellular biochemical specificity of the response of the myocyte to a chronic insult appears to be relatively restricted. The foremost question remains, which, if any, are the true pathogenic alterations and which are cellular adaptations.”

Dilated cardiomyopathy is a diagnosis arrived at by a process of exclusion. Causes such as infectious myocarditis, chronic volume overload (A-V fistula, valvular insufficiency), heartworm disease (and other causes of cor pulmonale), pericardial disorders, and toxic cardiomyopathy (doxorubicin) must be ruled out before a diagnosis of dilated cardiomyopathy is offered. A provisional diagnosis can be based on the history, physical findings, and typical radiographic and electrocardiographic changes, but echocardiographic evaluation is necessary to establish the diagnosis with certainty.

Most dogs with DCM have an abnormal electrocardiogram, although the changes may be subtle. Dogs may display criteria for left ventricular or left atrial enlargement. There is also a high prevalence of cardiac rhythm disturbances in dogs with DCM. Atrial fibrillation, ventricular premature complexes (VPCs) and ventricular tachycardia are commonly identified. Ventricular rhythm disturbances are most common in Boxer dogs and Doberman pinschers, both of which suffer a high rate of sudden death associated with the development of DCM. Using 24-hour ambulatory ECG (Holter) recordings, 81 percent of asymptomatic Doberman Pinschers with DCM had complex ventricular arrhythmias and almost 30 percent had sustained or non-sustained ventricular tachycardia. The prevalence of ventricular tachycardia and VPCs in Boxer dogs is similar to or greater than that observed in Dobermans.

Radiographic changes in dogs with moderate to severe disease almost always include biventricular or left ventricular and left atrial enlargement as well as evidence of right or left sided heart failure. Pleural effusion is common in dogs with biventricular failure, obscuring thoracic detail and preventing critical evaluation of heart size. Pulmonary edema is present in many dogs with DCM, and is often particularly severe in Boxers and Doberman Pinschers.

Echocardiographic alterations often include larger than normal end-systolic and end-diastolic dimensions of the left ventricle. The interventricular septum and ventricular free walls are hypokinetic, often thinner than normal in diastole, and they fail to thicken normally in systole. The left atrial dimension is increased, and the left atrial to aortic dimension ratio is increased. Fractional shortening, the percent change in short-axis diameter of the contracting left ventricle, is usually markedly decreased. The distance between the interventricular septum and the mitral valve at its maximal opening point in early diastole (EPSS) is increased as a reflection of a reduced ejection fraction.

Breed-specific idiosyncrasies.

Most dogs with dilated cardiomyopathy (classic cardiomyopathy) present with signs of right, left, or biventricular failure, in atrial fibrillation, and with marked weight loss and muscle wasting. In affected Boxers, approximately 20% are presented in predominately left-sided failure, 40% are presented for syncope or collapse secondary to a rhythm disturbance, and 40% are asymptomatic but have rhythm disturbances (primarily ventricular arrhythmias). Doberman pinschers usually present in severe left-sided heart failure, have a slightly lower incidence of atrial fibrillation than other breeds, have a higher incidence of ventricular arrhythmia, and experience a higher incidence of syncope and collapse.

Therapy

Treatment of heart failure in dogs with dilated cardiomyopathy often mimics that of dogs with valvular heart disease and heart failure. Diuretics help control congestion, angiotensin converting enzyme inhibitors are used to blunt activation of the renin angiotensin system, and positive inotropes (pimobendan) are used to enhance systolic performance. Dogs with dilated cardiomyopathy often

require antiarrhythmics to manage ventricular or supraventricular arrhythmias. Caution must be exercised with many of the antiarrhythmics because of their negative inotropic properties.

Prognosis

Dogs with echocardiographic evidence of dilated cardiomyopathy, but with no clinical signs of congestive heart failure, may live for a very long period of time. However, most affected dogs with congestive heart failure die within 6 months. Some very ill dogs improve to a remarkable degree with treatment and live comfortably for months or years. Others dogs do not survive the initial 48 hours of hospitalization.

A Unified Perspective on Managing Congestive Heart Disease

Barret Bulmer, DVM, MS, DACVIM
Tufts Veterinary Emergency Treatment and Specialties
Walpole, WA

Myocardial disease is the most frequently diagnosed heart disease in the cat. A study from southwestern Virginia published in 2009 identified 16% of apparently healthy cats (16/103) had echocardiographically demonstrable cardiomyopathy. The prevalence of DCM in cats has drastically declined with identification that most cases were attributable to taurine deficiency. Therefore hypertrophic cardiomyopathy (HCM) is now the most commonly identified feline myocardial disease. Cats with HCM may range from one to 16 years of age, with a large percentage ranging from 4 to 7 years. A genetic alteration in cardiac myosin binding protein C has been identified as a cause of familial HCM in some Maine Coon cats. Similarly an alteration in cardiac myosin binding protein C has been found in Ragdolls with familial hypertrophic cardiomyopathy. There are mutations in 11 or more genes producing >1,400 variants in humans with familial HCM, therefore it is likely there are many additional genetic modifications responsible for feline HCM. Other forms of endomyocardial disease described in cats include arrhythmogenic right ventricular cardiomyopathy, restrictive cardiomyopathy, and endocardial fibroelastosis. Many of these forms of myocardial disease in cats are difficult to distinguish from one another clinically or therapeutically and many cases do not fit neatly into any category. Therefore in many instances the objectives of therapy are uniform across myocardial disease and include (1) to treat the underlying cause, if one can be established, (2) to medically manage congestive heart failure, (3) to control arrhythmias, and (4) to treat or prevent thromboembolic complications.

Treatment of asymptomatic cats

Treatment of any form of cardiomyopathy in the asymptomatic patient is controversial and often depends on the severity of underlying echocardiographic changes, the presence and severity of left ventricular outflow tract obstruction, the rate of disease progression (if known), the presence and severity of other underlying systemic diseases, and the likelihood that medications can be administered easily and with good compliance. 1) Atenolol may be administered to try and resolve significant left ventricular outflow tract obstruction. 2) ACE inhibitors may be used in an effort to blunt the rennin-angiotensin-aldosterone system. 3) Anticoagulant therapy may be administered in an effort to prevent thromboembolism.

Treatment of cats with congestive heart failure

Independent of the form of myocardial disease, many of the priorities and agents used to treat heart failure in cats are similar. These often include: 1) Thoracocentesis is performed to remove large volumes of pleural fluid. 2) Furosemide is used to control edema. Additional diuretics may ultimately be required. 3) ACE inhibitors are used to blunt the activation of the renin-angiotensin-aldosterone system. 4) Anticoagulant therapy is administered in an effort to prevent thromboembolism. 5) Depending on the circumstances atenolol may be used to slow the heart rate and to reduce or eliminate dynamic obstruction in cats with hypertrophic obstructive cardiomyopathy. However caution should be exercised in cats that have active congestive heart failure. 6) Alternatively, diltiazem has been suggested to improve filling (positive lusitropic effect) and to decrease the heart rate in cats with HCM. 7) Pimobendan should be considered experimental therapy at this time but in some cases with myocardial dysfunction, presumed low output, and/or significant renal dysfunction we may use it in cats with HCM and heart failure. Contraindications may include significant left ventricular outflow tract obstruction. But interestingly one potential benefit is the PDE inhibitor action of pimobendan may enhance diastolic function.

Treatment of cats with aortic thromboembolism

Many approaches to this difficult problem have been suggested and none is very satisfactory. The site of thrombosis and duration of the event is critical in determining the clinical outcome. Cats with thrombi occluding the renal arteries or with gastrointestinal infarction have an extremely poor prognosis. Although surgical removal of the clot sounds ideal many cats die when surgery is attempted because of underlying heart disease, from anesthetic depression of the heart, or during the washout phase (of toxins, potassium, etc.) if perfusion is reestablished. Thrombolytic therapy may be accomplished with streptokinase or recombinant tissue plasminogen activator (TPA). Aggressive attempts to dissolve emboli using thrombolytic drugs should be reserved for cats with more serious thromboembolic events. Pion, et. al. reported successful thrombolysis, defined as evidence of reperfusion within 36 hours of TPA (Activase, Genentech) treatment, in 50 per cent of cats with spontaneous aortic thromboembolism that were treated with tissue plasminogen activator. Forty-three percent of the cats walked within 48 hours of presentation. However, 50 per cent of the cats died from either reperfusion syndrome, heart failure, or suddenly.

Many cats with saddle thrombi will regain function of the hind limbs, albeit slowly, with conservative therapy. Recovery takes several weeks to months and residual deficits (peripheral neuropathy, muscle contracture) are common. Conservative management consists of pain management, anticoagulant therapy to prevent additional clot formation and therapies aimed at resolving concurrent heart failure. Pain management is one of the most important goals of treating cats with systemic thromboembolism. Butorphanol,

buprenorphine and oxymorphone are used frequently but more aggressive measures, e.g. morphine epidurals, may be required in some cases.

Prognosis

The prognosis for cats with HCM is variable often depending on the stage of disease. Cats with minimal hypertrophy and normal left atrial size may live asymptotically for many years without institution of medications. However once myocardial disease of any form has progressed to congestive heart failure there is overall a guarded to poor long-term prognosis. Some cats respond favorably to drug administration and may live several years, however most others die within 6 to 12 months following development of heart failure.

Reacquainting Yourself with the ECG and Treatment of Arrhythmias

Barret Bulmer, DVM, MS, DACVIM
Tufts Veterinary Emergency Treatment and Specialties
Walpole, WA

A systematic approach to the evaluation of the ECG will prevent overlooking important abnormalities. The following characteristics should be evaluated in every ECG. Familiarity with the normal parameters for the ECGs of the various species is, of course, essential for accurate interpretation.

1) Determine the heart rate

If the heart rate is regular, the number of small boxes (mm) between QRS complexes can be divided into 3,000 (at 50 mm/sec) or 1,500 (at 25 mm/sec) to find the instantaneous heart rate. The heart rhythm in animals, especially in dogs, is frequently irregular. In this circumstance the more accurate average heart rate is found by counting the number of beats in a known time interval and multiplying appropriately. Single channel ECG paper on analog recorders is usually marked by a vertical line at the top of the paper at 75 mm (1 mm = 1 small box) intervals. At a paper speed of 50 mm/sec, 75 small boxes (equivalent to 15 large boxes) represent 1.5 seconds so the heart rate per minute can be calculated by counting the number of QRS complexes in 1.5 seconds and multiplying by 40. At a paper speed of 25 mm/sec, 75 small boxes (15 large boxes) represent 3.0 seconds and the number of QRS complexes in 3.0 seconds is multiplied by 20. Many of the newer digital ECG machines calculate heart rate automatically.

2) Determine the cardiac rhythm

The heart's rhythm is evaluated by inspection of the ECG and the findings are correlated with the physical findings. Analysis of the heart's underlying rhythm should include the following steps.

- A. What is the rhythm (including the regularity and the relationship among complexes)?
 - a. Regular?
 - b. Regularly irregular with a consistent and repeating pattern to the variation in the rate?
 - c. Irregularly irregular where the rhythm is chaotic and there is no pattern to the irregular nature of the rhythm?
 - d. Paroxysmal (which is defined as a sudden outburst)? When applied to the ECG, a paroxysm refers to a series of rapid ectopic beats, which begins and ends abruptly. The series may be as short as 3 beats or may last for minutes to hours.
 - e. What is the relationship between the P and QRS complex? Is there a P wave for every QRS complex? Is there a QRS complex for every P wave? Is the duration of time between the various components (P-R interval, Q-T interval) normal? Is the duration of time between the various complexes consistent?
- B. Where do the cardiac impulses originate (site of origin)? The four possible choices include:
 - a. The sinoatrial (SA) node
 - b. The atria
 - c. The atrioventricular (AV) node/junctional
 - d. The ventricles and His-Purkinje system

Impulses originating from the SA node, atria or AV node are grouped together under the heading *supraventricular* while impulses from the ventricles or His-Purkinje system are termed *ventricular*. Supraventricular beats should maintain a relatively tall, upright and narrow QRS complex because the impulse must utilize the His-Purkinje system to transmit the impulse to the ventricles. Therefore the ventricular muscle depolarizes uniformly with a set activation sequence. But when impulses arise from the ventricles or terminal branches of the His-Purkinje system they are slowly transmitted from individual myocardial cell to myocardial cell. This produces a relatively wide and bizarre QRS-T complex.

- C. What are the ventricular and atrial rates?
 - a. Too fast (tachycardia)
 - b. Too slow (bradycardia)
- D. What is the temporal relationship between any ectopic beats and the underlying heart rhythm?
 - c. Premature beats are defined as ectopic beats that occur early in the sequence of normal beats, meaning the R-R interval from the preceding normal beat to the ectopic beat is shorter than the prevailing R-R interval. Premature beats are formed when the ectopic focus depolarizes more rapidly than normal, overrides the sinus node and assumes control of the heart rate for one or more beats.
 - d. Escape beats are defined as ectopic beats that occur after a pause in the sequence of normal beats, meaning the R-R interval from the preceding normal beat to the ectopic beat is longer than the prevailing R-R interval. The ectopic site assumes control of the electrical activity of the heart by default because the SA node fails to discharge or the sinus impulse is not properly conducted to the rest of the heart.

3) Calculate the mean electrical axis (MEA).

One of the most useful applications of vector principles is the calculation of the MEA for the QRS complex in the frontal plane. The MEA is the average of all the instantaneous vectors recorded during the QRS complex. Each species has a range of normal values, for example the MEA of normal dogs is between $+40^\circ$ and $+103^\circ$. When the MEA is greater than $+103^\circ$ right ventricular enlargement is suggested. The mean electrical axis may be derived in two ways:

- Method 1: Using any two leads in the frontal plane, take the difference between the height of all positive QRS deflections and all negative QRS deflections in the two chosen leads. This calculates the vector for each lead. Plot the appropriate number of units, either positive or negative, on the lead axes. Draw perpendicular lines to the axes at these two points and then draw a vector from the origin of the figure to the point of intersection of these lines. The direction of this vector is the mean electrical axis.
- Method 2: Since the line of the mean electrical axis should have half of the total forces of ventricular depolarization on either side of it, a reasonable estimate of the MEA can be obtained by finding the limb lead which is the most isoelectric (i.e. the difference between the positive and negative QRS deflections in that lead is near 0). The MEA must then be perpendicular to that lead. To determine which direction the MEA takes, look at the lead whose axis is perpendicular to the isoelectric lead. If the lead has mainly positive QRS deflections, the MEA points toward the positive pole of that lead axis, just the opposite if the lead is mostly negative. Occasionally all of the limb leads are equally isoelectric and the MEA is said to be *indeterminate* in the frontal plane.

4) Measure the ECG waves and intervals.

The duration and amplitudes of the waves of the ECG are important in determining whether chamber enlargement is present. When one or more of the cardiac chambers enlarge, the processes of depolarization and/or repolarization may be altered in 1) magnitude of the vectors, 2) direction of the vectors, 3) rate of activation (duration), and 4) sequence of activation. These changes are reflected in the surface electrocardiogram as alterations in 1) the amplitude in the various leads, 2) the direction of the deflections in the various leads (i.e. change in MEA), 3) the width (duration) of the waves in various leads, and 4) the development of certain abnormal patterns of activation (i.e. S waves with RVH). The duration of the various intervals is important to determine if conduction or electrolyte disturbances are present. By convention the first negative deflection, preceding a positive deflection is termed a Q wave and the first positive deflection is called the R wave. A negative deflection occurring after a positive deflection is called an S wave. A second R wave is termed an r' wave, etc.

Management of arrhythmias

Arrhythmias are clinically important because of their ability to compromise cardiac output and oxygen delivery to the body. The level of cardiac performance during an arrhythmia is dependent on the rate, site of origin, and duration of the arrhythmia, as well as the presence of underlying cardiac or systemic diseases that may adversely affect the patient. Thus, the consequences of an arrhythmia may be clinically undetectable, may produce signs of inadequate cardiac output (weakness, fainting, shock), or may lead to the complete collapse of the circulatory system and sudden death.

Depending on the underlying cause of the arrhythmia, administration of antiarrhythmic drugs may not be needed. Metabolic abnormalities (acid/base or electrolyte disturbances, hypoxia) can contribute to arrhythmia formation and should be corrected. Arrhythmias in patients with concurrent congestive heart failure will often resolve spontaneously once the heart failure is successfully treated. Finally, the clinician must be familiar with the actions and potential side effects of the antiarrhythmic drugs, and must carefully weigh the risks and benefits of treatment. Administration of antiarrhythmics is not a benign procedure. Every agent has the possibility to induce further and perhaps more dangerous arrhythmias (pro-arrhythmia).

Ventricular tachyarrhythmias (VPCs, ventricular tachycardia)

- 1) No therapy may be required if the VPCs are infrequent and the patient is asymptomatic. However Holter monitoring is often required to confirm the true frequency of the arrhythmia.
- 2) Withdraw or adjust offending drugs (digitalis) if toxicity is suspected.
- 3) When associated with congestive heart failure, therapy with positive inotropes under close supervision is indicated along with other measures to treat the CHF.
- 4) Antiarrhythmic therapy is indicated when VPCs are frequent, multifocal, or occur in rapid groups (ventricular tachycardia). The most commonly employed oral antiarrhythmics include mexiletine and sotalol. Amiodarone may be used in select cases.
- 5) If life threatening ventricular tachycardia develops, intravenous therapy with lidocaine or procainamide is most often used.

Supraventricular tachyarrhythmias (frequent APCs, atrial tach, atrial fib)

- 1) No therapy may be required if the APCs are infrequent and the patient is asymptomatic. However Holter monitoring is often required to confirm the true frequency of the arrhythmia.
- 2) When frequent APCs are observed in patients with congestive heart failure, digitalis or diltiazem therapy can be considered (may be a precursor for atrial fibrillation).
- 3) Termination of atrial tachycardia may be accomplished by vagal maneuvers, precordial (chest) thump, or control of the ventricular response rate utilizing digoxin, atenolol, diltiazem, or sotalol. The same agents may be useful for preventing recurrence.
- 4) Atrial fibrillation.
 - a. The usual goal in patients with heart disease is to slow the ventricular response rate. This is often achieved by digitalization +/- the addition of diltiazem, atenolol or sotalol if appropriate rate control is not achieved with digoxin alone. Amiodarone may be used in select cases.
 - b. Conversion to sinus rhythm is usually only attempted in patients with a reasonable probability of remaining converted (those with minimal underlying heart disease). Oral quinidine, IV procainamide, or electrical defibrillation have been employed. Intravenous administration of diltiazem, amiodarone or sotalol is occasionally effective.

Getting the MOST out of your Serum Chemistry Panel and Urinalysis

Casey LeBlanc, DVM, PhD, DACVP

KDL VetPath

Springfield, VA

Proteins

Hemorrhage	↓ Albumin and globulins Anemia
Protein losing enteropathy	↓ Albumin and globulins
Protein losing nephropathy	↓ Albumin and proteinuria
Chronic inflammation	↑ Globulins +/- ↓ albumin Polyclonal gammopathy (SPE)
Multiple myeloma	↑ Globulins +/- ↓ albumin Monoclonal gammopathy (SPE)

Hepatic/pancreatic

Hepatocellular damage	↑ AST, ALT
Cholestasis	↑ ALP, T. Bili, Cholesterol
Hepatic Dysfunction	↓ Albumin, Cholesterol, BUN, Glucose ↑ PT / PTT, Bile acids, Ammonia
Sepsis/Endotoxemia	↑ T. Bili, ↓ Glucose
Acute Pancreatitis	↑ ALP, T. Bili, Cholesterol +/- ALT, AST ↑ c/f Pancreatic Lipase Immunoreactivity Inflammatory leukogram
Exocrine pancreatic insufficiency	↓ TLI, cobalamin, ↑ folate

Renal

Pre-renal azotemia	↑ BUN/creatinine, phosphorus, anion gap, USG >1.030 (dog), >1.040 (cat)
Acute renal failure	↑ BUN/creatinine, phosphorus, anion gap, potassium, USG commonly 1.008-1.012 but can be a little higher, Anuric to oliguric
Chronic renal failure	↑ BUN/creatinine, phosphorus, anion gap USG commonly 1.008-1.020 ↓ to normal potassium Commonly polyuric Non-regenerative anemia
Urinary blockage or rupture	↑ BUN/creatinine, phosphorus, anion gap, potassium, USG commonly 1.015-1.025

Pyelonephritis	<ul style="list-style-type: none"> ↓ Sodium and chloride ↑ BUN/creatinine, phosphorus, anion gap, Inflammatory leukogram, Pyuria, cylinduria, bacteriuria
Glomerulonephritis	<ul style="list-style-type: none"> ↓ Albumin, ↑ Cholesterol (nephrotic syndrome) Proteinuria, inactive sediment

Extra-renal causes for less than optimal concentration of USG

Osmotic diuresis	Glucosuria secondary to Diabetes mellitus
Decreased ADH production	Central diabetes insipidus Glucocorticoid excess
Inhibition of ADH	Endotoxemia Hypercalcemia
Medullary washout	Decreased medullary sodium: Addison's disease, psychogenic water drinker Decreased medullary urea: Liver failure

Endocrine

Hyperthyroid	<ul style="list-style-type: none"> ↑ RBCs +/- Heinz bodies ↑ ALT, ALP
Hypothyroid	↑ Cholesterol
Addison's disease	<ul style="list-style-type: none"> ↑ BUN/creatinine, phosphorus, anion gap, potassium, USG commonly dilute due to medullary washout ↓ Sodium and chloride Reversed stress leukogram (lymphocytosis, no neutrophilia)
Cushing's disease / Glucocorticoid excess	<ul style="list-style-type: none"> ↑ ALP, Cholesterol, ↑ ALT, AST if steroid hepatopathy

Acid/base

Upper gastrointestinal obstruction

↓ Chloride (without or disproportionate to sodium)
↑ $\text{TCO}_2 / \text{HCO}_3$

Renal tubular acidosis

↑ Chloride (without or disproportionate to sodium)
↓ $\text{TCO}_2 / \text{HCO}_3$
Normal anion gap

Retention of renal acids (SO_3/PO_4)

↑ Anion gap

Lactic acidosis

↓ $\text{TCO}_2 / \text{HCO}_3$

Ketoacidosis

Ingestion of exogenous acids (ie ethylene glycol)

Getting the MOST out of your Serum Hematology Data

Casey LeBlanc, DVM, PhD, DACVP
KDL VetPath
Springfield, VA

HCT, RBC, Hgb

These three analytes represent RBC mass. Hematocrit

- (HCT) is calculated using the concentration (RBC) and size
- (MCV) of red blood cells. HCT will accurately reflect RBC if MCV is normal. HCT will accurately reflect Hgb if MCHC is normal. Hgb can be falsely elevated by lipemia, Heinz bodies, and oxyglobin therapy.

Retic count, Retic percent

Retic conc. or absolute count is the preferred method for evaluating marrow response to anemia. >80,000/uL in dogs, >60,000 in cats is considered a regenerative response. Reticulocytosis does not occur until 2-3 days after occurrence of anemia. Maximum response in 5-7 days. Hemolytic anemias are typically the most regenerative. Machine calculated retic percent must be corrected for the patient's anemia to accurately evaluate marrow response.

MCV, RDW

Mean cell volume is expressed in femtoliters and is determined directly by most automated cell counters. Reticulocytosis is the most common cause of macrocytosis; however, a normocytic anemia may also be regenerative. Red cell distribution width (RDW) is an index of the degree of anisocytosis/variation of red cell size. RDW may increase prior to development of macrocytosis or macrocytosis.

MCHC, MCH

MCHC is the cellular Hgb concentration per average RBC and MCH is the quantity of Hgb per average RBC. MCH is not generally used to classify anemias. If MCHC and MCH differ, MCHC should be used because it corrects for cell volume.

↑ MCHC	↑ MCV Artifact*	Normal MCV Artifact*	↓ MCV Artifact*
Normal MCHC	Regenerative anemia FeLV Toy/mini poodles Agglutination	Normal (not anemic) Early regeneration Non-regenerative anemia	Asian dog breeds PSS Iron deficiency
↓ MCHC	Markedly reg. anemia	-----	Iron deficiency

* ↑MCHC is most commonly artifactual (lipemia, hemolysis, Heinz bodies, marked leukocytosis, cell shrinkage related to hyponatremia), however pathologic conditions such as eccentrocytosis or spherocytosis can rarely be associated with ↑MCHC

PLT, MPV, PDW, PCT

Many analyzers offer platelet parameters beyond platelet count (PLT). MPV is the average volume of all particles counted as individual platelets. Because MPV is an average, population of both large and small platelets may result in a normal MPV. In these cases, the platelet distribution width (PDW – an assessment of platelet anisocytosis) would be expected to be increased. Also note, if large platelets are similar in size to RBCs, they will be counted as RBCs. PCT is the thrombocrit and is an assessment of circulating platelet mass. PCT is calculated using PLT and MPV. PCT may be better than PLT at representing the total platelet functional potential, especially in the Cavalier King Charles Spaniels.

Thrombocytopenia

Differentials include increased destruction (immune-mediated), increased consumption (DIC), decreased production (bone marrow disease), sequestration, hemorrhage

Thrombocytosis

Fairly uncommon, differentials include reactive (most common cause and usually associated with inflammation), regenerative (rebound from thrombocytopenia), decreased sequestration (splenic contraction), essential thrombocytosis (very rare leukemia)

WBC

Most analyzers are pretty accurate at counting the total number of nucleated cells (which includes nucleated RBCs). If there are 10 or more nRBCs per 100 leukocytes on a blood smear, then the total leukocyte count (and all absolute counts of all the leukocytes) needs to be corrected.

Neutrophilia

Most commonly due to inflammation (+/- left shift and toxic change), glucocorticoid excess (associated with lymphopenia), or epinephrine response (associated with lymphocytosis). Blood smear evaluation is critical to determine presence of left shift.

Differentials for extreme neutrophilic leukocytosis (total WBC counts >50,000 leukocytes/uL): local sites of suppurative inflammation

(pyometra, pyothorax, acute pancreatitis), hemolytic anemias (esp. IMHA), *Hepatozoon americanum* infections (Gulf south, Texas, Oklahoma), malignant tumors secreting G-CSF, chronic myelogenous leukemia (CML), canine leukocyte adhesion deficiency (CLAD).

Neutropenia

Most commonly due to inflammation or BM disease. Differentials include: excess tissue demand, endotoxemia, bone marrow disease (commonly associated with other cytopenias), and immune-mediated destruction of peripheral neutrophils.

Eosinophilia

Differentials include parasitism, hypersensitivity/allergic disorders, idiopathic conditions (hypereosinophilic syndrome, eosinophilic gastroenteritis), Addison's disease, paraneoplastic syndrome, and eosinophilic leukemia (very rare).

Basophilia

Differentials include parasitism, hypersensitivity/allergic disorders, and hematopoietic neoplasias such as myeloproliferative disorders, essential thrombocytopenia, polycythemia vera, lymphomatoid granulomatosis, basophilic leukemia.

Monocytosis

Differentials include: Acute and chronic inflammation, and stress response (glucocorticoid response).

Lymphocytosis

Differentials include: chronic inflammation, physiologic response (epinephrine driven; cats, horses), Addison's disease, and leukemia (CLL, ALL).

Lymphopenia

Differentials include: stress response (glucocorticoid response), acute inflammation, depletion of lymph or normal lymph flow, and lymphoid hypoplasia or aplasia.

Why You Should ALWAYS Look at a Blood Smear

Casey LeBlanc, DVM, PhD, DACVP
KDL VetPath
Springfield, VA

Confirm the WBC differential and evaluate WBC morphology

Depending on the analyzer, WBC differentials can be accurate. However all differentials should be confirmed by evaluating a blood smear (30-60 seconds to confirm which leukocyte is in the majority, to confirm any increases or decreases in counts). Even the most accurate analyzers cannot differentiate segmented versus band neutrophils. Further, most, if not all, will not correctly characterize nucleated RBCs. Lastly, large, immature neoplastic cells will not be correctly characterized by any standard hematology analyzer. WBC morphology should always be evaluated. Two common abnormalities that should be detected are toxic change to neutrophils (Döhle bodies, basophilic cytoplasm, vacuolated cytoplasm) and reactive change to lymphocytes (basophilic cytoplasm). A more difficult challenge can be in differentiating reactive versus malignant lymphocytes, which are typically larger and may exhibit prominent nucleoli. Large lymphocytes or any other large cells are commonly pushed out to the feathered edge – the feathered edge should always be evaluated when looking at a smear.

Although far less common than RBC parasites, WBCs can also contain intracellular parasites (Ehrlichia, Histoplasma, Hepatozoon). These parasitized cells are also commonly pushed out to the feathered edge of the smear.

Confirm the platelet count (especially if low)

Take a quick look on the feathered edge to look for platelet clumps, especially in cats. Further, a platelet estimate can be obtained by looking at a blood smear (should look at 4-5 fields minimum). Platelet estimate = average # of platelets (within 100x field) x 20,000

Evaluate RBC morphology

A wealth of knowledge can be obtained by evaluating RBCs. Listed below are evidence of regeneration and the more common types of poikilocytosis, inclusions and other abnormalities, and RBC parasites.

Evidence of regeneration

Polychromasia - a polychromatophilic macrocyte is an anuclear, immature erythrocyte (reticulocyte) with enough cytoplasmic dispersed RNA to stain light blue with a Romanowsky stain (Diff-Quik, Wright's); Anisocytosis - variation of cell size – most commonly associated with macrocytosis and therefore regenerative anemias; Howell-Jolly bodies - a nuclear remnant; usually a single, small round deep purple inclusion found in more immature erythrocytes; number in blood increases with accelerated erythropoiesis or decrease splenic function; Basophilic stippling - presence of fine to coarse blue/purple dots of aggregated ribosomes within the erythrocyte cytoplasm; can be seen with regenerative anemias, esp. in cattle, but also in dogs and cats; Increased number of nRBCs – increased release from bone marrow during accelerated erythropoiesis (appropriate rubricytosis); increased circulating nRBCs without regeneration is inappropriate and usually associated with conditions such as endotoxemia, hyperthermia, bone marrow disease, splenic disease/contraction/removal, lead toxicity

Poikilocytosis

General term abnormally shaped erythrocytes; Spherocytes - spherical erythrocytes that usually result from a loss of cell membrane; they lack central pallor and have smaller diameters than normal erythrocytes; most frequently associated with IMHA; Schistocytes/schizocytes - erythrocyte fragments with pointed extremities; result when erythrocytes are forced through altered blood vessels or exposed to turbulent blood flow; commonly associated with DIC but can be associated with many other conditions; Acanthocytes (vs. Echinocytes/Crenated RBCs) - erythrocytes with multiple (3-6) club-shaped projections; associated with hemangiosarcoma, liver disease (alteration of membrane lipid composition), DIC, and glomerulonephritis – echinocytes are erythrocytes with many sharp to blunt spicules and are usually an artifact of excess EDTA, improper smear techniques, or prolonged storage; Eccentrocytes – erythrocytes with eccentric dense-staining area with adjacent clear space that is crescent-shaped – associated with ingestion of oxidants (see list below under Heinz bodies); Codocytes/Target cells – erythrocytes with a central area of Hgb surrounded by a ring of pallor – not pathognomonic for one disorder – typically associated with regenerative anemias, also seen with hepatic, renal, and lipid disorders

RBC inclusions and other abnormalities

Heinz bodies - round to irregular inclusions/protrusions attached to the internal surface of the erythrocyte membrane; large aggregate of oxidized, precipitated hemoglobin; stain clear/pale on Romanowsky stains; stain blue with NMB stain. Other findings can include mild to severe regenerative anemia, eccentrocytosis, hyperbilirubinemia/uria, hemoglobinemia/uria in acute severe cases, and possible methemoglobinemia (chocolate-colored blood). Heinz bodies do not disperse with in vitro lysis of erythrocytes (inside the hematology analyzer), so large numbers can artifactually increase the hemoglobin concentration and MCHC. Etiologies include: onions and garlic toxicity, acetaminophen (Tylenol), wilted red maple leaves, Brassica veggies (cabbage, cauliflower, kale, rape), phenothiazine, propylene glycol, skunk musk, and zinc toxicity. Clinically healthy, non-anemic cats and sick cats without hemolytic anemia

frequently have circulating Heinz bodies (sometimes >5% of erythrocytes). Feline disorders most commonly associated with circulating Heinz bodies are hyperthyroidism, diabetes mellitus, and lymphosarcoma (lymphoma). Hypochromic erythrocyte – erythrocyte with increased central pallor and more faintly stained cytoplasm due to decreased Hgb content – associated with iron deficiency. Rouleaux – linear aggregation of erythrocytes resembling a stack of coins – most commonly associated with hyperglobulinemia and hyperfibrinogenemia – rouleaux with disperse when blood is diluted with isotonic saline. Agglutination – grape-like clusters of erythrocytes held together by patient’s antibodies – associated with immune-mediated hemolytic anemias – clusters will not disperse when blood is diluted with isotonic saline

Parasites

Babesia canis/Babesia gibsoni - protozoan organism that may cause hemolytic and nonhemolytic anemia – Hemolysis may involve proteases produced by the parasite, immune reaction to parasitized cells, or oxidative damage to erythrocytes. *Mycoplasma hemofelis* - parasitemia is usually present during hemolysis and when HCT is falling, but it may suddenly disappear within hours; organisms will fall off in vitro, so blood smears should be made with fresh blood; organisms appear as little dit-dots on the periphery of the erythrocyte. *Cytauxzoon felis* – intracellular oval organism with an eccentric nucleus (very small signet ring appearance is most common – similar to *B. gibsoni*). Distemper inclusions – round to variably shaped, variably sized, reddish purple to pale blue (depending on stain) inclusions found in both erythrocytes and leukocytes.

Diagnostic Cytology of Cutaneous and Subcutaneous Lesions

Casey LeBlanc, DVM, PhD, DACVP
KDL VetPath
Springfield, VA

Abnormal cytologic specimens can usually be classified into one of three main categories: inflammatory, non-inflammatory/non-neoplastic, and neoplastic.

Inflammatory lesions

Can be characterized further based on the types and relative numbers of cells present.

Suppurative or neutrophilic

Septic

Many types of bacteria can cause abscessation or cellulitis characterized by a suppurative inflammatory response. Bacteria are monotonous in appearance, staining a deep blue with most Romanowsky type stains, and may be phagocytosed by neutrophils (definitive evidence of sepsis). Microbial organisms on a cytology slide may indicate a septic lesion, or may be contaminants (e.g., from skin, oro- or nasopharynx, inadvertent sampling of GI lumen).

In the absence of definitive evidence, a lesion may be characterized as probably septic on the basis of indirect evidence – such as extracellular bacteria and an inflammatory response consistent with sepsis, or degenerate neutrophil morphology (cells with swollen, poorly staining nuclei). In most cases where sepsis is diagnosed or suspected on the basis of cytology, culture is indicated.

Non-septic

There are many causes of non-septic inflammation in the skin or subcutaneous tissues. A partial list includes: foreign bodies, furunculosis, insect bites, lick granulomas, immune-mediated conditions (e.g., pemphigus foliaceus), trauma, and necrosis.

Pyogranulomatous

Characterized by increased numbers of macrophages, usually with high numbers of neutrophils [the “pyo” component], typically with low numbers of multinucleated giant cells, lymphocytes, and plasma cells, +/- other cell types such as eosinophils and fibroblasts

Fungal

Fungal pathogens in this part of the country that are commonly associated with pyogranulomatous inflammatory reactions include:

Blastomyces dermatitidis

10-15 µm in diameter, round to ovoid, thick-walled yeast forms that often have broad-based budding

Cryptococcus neoformans

5-20 µm diameter, round yeast forms that usually have a wide clear or poorly stained capsule and often have narrow-based budding

Histoplasma capsulatum

2-5 µm long, reddish-purple, eccentrically staining ovoid yeast form with a thin, clear capsule; most often found within macrophages

Sporothrix schenckii

3-5 µm long, oval to cigar-shaped yeast form with a thin capsule; often phagocytosed by macrophages; typically few organisms detected in dogs many in cats

Pythium insidiosum

An oomycete characterized by clear to poorly staining, branching hyphal elements typically outlined by large numbers of neutrophils and macrophages

Foreign body

Reactions caused by penetration of plant, animal, or inorganic material into the skin typically consist of a pyogranulomatous or mixed inflammatory infiltrate (macrophages, neutrophils, lymphocytes, possibly eosinophils and multinucleated giant cells).

Certain bacterial infections

Mycobacterium spp. typically elicit a pyogranulomatous or granulomatous inflammatory response. These organisms appear as non-staining, long rods that are usually contained within macrophages. Actinomyces and Nocardia spp. are filamentous rods that may form dense aggregates (“sulfur granules”), and typically elicit a pyogranulomatous or suppurative response. Actinomycosis is a common disease in hunting dogs that invariably appears as a mixed bacterial infection, whereas nocardiosis is an uncommon disease of younger dogs.

Eosinophilic

Parasitic bite reaction

Insects, ticks, and spiders may induce an erythemic swelling with cellular infiltrates consisting of neutrophils, macrophages, and an increased proportion of eosinophils (>5% of nucleated cell infiltrate)

Eosinophilic plaque

Predominately a feline lesion found on the face, neck, abdomen, and medial thighs. Cellular infiltrates are predominated by eosinophils and mast cells with fewer lymphocytes. Eosinophilic granuloma – Occurs in dogs and young cats in response to a

hypersensitivity reaction on the posterior legs, nose, ears, and feet. Cellular infiltrates consist of macrophages, lymphocytes, plasma cells, neutrophils, and an increased proportion of eosinophils and mast cells.

Lymphocytic

Vaccine reaction

Weeks to months following vaccination, aspirates of reactions typically consist of numerous small mature lymphocytes and fewer large, foamy macrophages. Many of these macrophages will contain an amorphous reddish- purple material representing vaccine adjuvant.

Non-inflammatory / Non-neoplastic lesions

Epidermal / Follicular cyst

Firm to fluctuant well-circumscribed lesions consist of numerous densely basophilic keratin bars, keratinized squamous epithelial cells, a large amount of amorphous, cellular debris, +/- cholesterol crystals which appear as negative-stained rectangular plates. Rupture of these cysts can induce a localized suppurative to pyogranulomatous inflammatory response. These cysts cannot be cytologically differentiated from keratoacanthomas or a few other keratinizing lesions.

Seroma

Consists of poorly cellular fluid that may require concentration prior to examination. The low number within seroma fluid is predominated by macrophages with rare lymphocytes and neutrophils.

Hematoma

Initially, hematomas consist of peripheral blood devoid of platelets. Shortly afterward, erythrocyte-containing macrophages are commonly found. With more time, hemoglobin will be broken down resulting in macrophages that contain hemosiderin (brown-black globular pigment) and/or hematoïdin crystals (rhomboid golden crystals).

Salivary mucoceles (sialoceles)

Cytologically consist of scattered aggregates of pale basophilic, globular material consistent with saliva, numerous red blood cells, and a nucleated cell population predominated by highly vacuolated macrophages. Erythrophagocytosis is common and occasional hemotoïdin crystals may be seen.

Neoplastic lesions

Neoplastic lesions are classified according to two main criteria: biologic behavior (benign or malignant) and cell of origin (epithelial, mesenchymal, or round cell).

The distinction between benign vs. malignant neoplasia is made on the basis of morphology and, in some cases, anatomic location. The outline below lists some of the classic morphologic features of malignancy, and most malignant tumors exhibit multiple such features. However, it is important to recognize that not all malignant tumors have striking morphologic features of malignancy and, by the same token, there are some benign conditions (including some non-neoplastic conditions) that can mimic malignant neoplasia. There are situations in which the distinction between benign and malignant cannot be made on the basis of cytology, but requires evaluation of tissue architecture (histopathology).

Primary criteria of malignancy include

- Anisokaryosis - variation in nuclear size - probably the most important characteristic
- Prominent, multiple, and/or pleomorphic nucleoli
- High N:C ratio
- Nuclear pleomorphism / nuclear molding
- Coarse or atypical chromatin pattern

Supportive criteria of malignancy

Supportive of malignancy if found concurrently with primary criteria; these characteristics should not be over interpreted if found alone; they include high mitotic index, multinucleation, and basophilic cytoplasm.

Epithelial neoplasms

Round, cuboidal, to polygonal-shaped cells most often exfoliate in clusters or sheets

Glandular or secretory epithelial tissues may be arranged in acinar or tubular structures. These cells may contain secretory vacuoles or display a “signet ring” appearance. These carcinomas are typically referred to as adenocarcinomas.

Neuroendocrine neoplasms/carcinomas (ex: thyroid carcinoma, chemodectoma) differ slightly from other epithelial tissues. These tumors exhibit indistinct cytoplasmic borders and the malignant changes (ex: anisokaryosis) are usually minimal.

There are a small number of certain tissues in which differentiating between hyperplasia/adenoma/carcinoma is difficult to impossible. Well-differentiated carcinomas of the mammary gland and perianal gland will commonly look very benign cytologically.

Benign epithelial tumors

- Sebaceous adenoma – mature sebocytes characterized by pale, foamy cytoplasm and a dense centrally located nucleus; cohesive clusters
- Basal cell tumor – small, uniform cells with high N:C ratio; cohesive clusters or row formation
- Perianal gland tumor – cohesive clusters of “hepatoid” cells

Malignant epithelial tumors (Carcinomas)

- Squamous cell carcinoma – may appear as individual cells or sheets of adherent cells; cells are round to tadpole-shaped with keratinizing blue-green hyalinized cytoplasm; nuclear size and N:C ratio is highly variable; perinuclear vacuolation is common
- Apocrine gland adenocarcinoma of anal sac – loose clusters or acinar structures of cells with poorly defined cell borders (similar to neuroendocrine tumors); although malignant, exhibit few morphologic criteria of malignancy
- Thyroid adenocarcinoma – loose clusters or acinar structures of cells with poorly defined cell borders, similar to other neuroendocrine tumors; cells commonly contain blue-black cytoplasmic granules thought to represent tyrosine; although malignant, exhibit few morphologic criteria of malignancy

Mesenchymal or connective tissue neoplasms

Oval, spindle, to stellate-shaped cells, usually low cellularity due to poor exfoliation, often exhibit a pink extracellular matrix (osteoid, chondroitin, ...)

Most of the time, it is very difficult to differentiate various mesenchymal tumors cytologically. Here are a few tumors that may exhibit distinctive features to help us differentiate them:

Benign mesenchymal proliferations

- Fibroma / Fibroplasia / Granulation tissue – All consist of fairly uniform spindle or fusiform-shaped fibrocytes and/or fibroblasts with oval eccentrically placed nuclei; difficult to differentiate from a fibrosarcoma
- Lipoma – Aggregates of uniform, well differentiated adipocytes characterized by large round cells with clear cytoplasm and a small dense nucleus

Malignant mesenchymal tumors (sarcomas)

- Hemangiopericytoma – spindle to stellate-shaped cells with “veiling” cytoplasm; commonly highly cellular
- Osteosarcoma - malignant osteoblasts exhibit a perinuclear clearing indicative of Golgi (like plasma cells) - osteoclasts (large multinucleated cells) may also be present

Discrete round cell tumors

Round to oval-shaped cells with no cell to cell association

Lymphosarcoma (Lymphoma)

Most commonly associated with generalized lymphadenomegaly or visceral organ infiltration, but cutaneous lymphoma also occurs

Mast cell tumor

Round pale-stained nucleus with variable amounts of metachromatic (red-purple) granules within the cytoplasm; may be surrounded with variable numbers of eosinophils (orange-red granules); Diff-Quik commonly fails to stain mast cell granules

Histiocytoma

Common tumor of young dogs; moderate amount of pale gray cytoplasm and a round to oval shaped nucleus that is centrally located; “fried egg” appearance; tumor regression is associated with an infiltrate of small lymphocytes

Plasmacytoma (extramedullary)

Rarely associated with multiple myeloma; moderate amount of deeply basophilic cytoplasm with an eccentric nucleus; will commonly exhibit a perinuclear clearing indicative of the Golgi body; variable degree of anisokaryosis and occasional binucleation

Transmissible venereal tumor (TVT)

Nucleus has coarse, cord-like or “ropey” chromatin and prominent nucleoli; moderate amount of smoky blue cytoplasm with clear distinct vacuoles; most commonly found on genitalia or nasal passages; most common in tropical climates

Malignant and benign melanomas

most cutaneous melanomas are benign; found on the lips, oral cavity, or digits are frequently malignant; cells may be round, oval, stellate, or spindle-shaped; pigmented and amelanotic forms - brown to green-black pigment granules can almost always be found, even in amelanotic tumors

Cytopathology and Related Diagnostic Tests: Pitfalls, Myths, and Tips

Casey LeBlanc, DVM, PhD, DACVP
KDL VetPath
Springfield, VA

Tips for increasing your skill at cytology: Look at everything you can (aspirates, impression smears, washes/lavages), using one or more of the books available for reference. Recommended resources include: *Diagnostic Cytology and Hematology of the Dog and Cat*, 4th ed. Valenciano AC, Cowell RL (editors). Mosby Elsevier, 2014. and *Canine and Feline Cytology: A Color Atlas and Interpretation Guide*, 2nd ed. Raskin RE, Meyer D (editors). Saunders, 2010. Write down your observations and interpretation –this is a key part of the learning process, because writing it down forces you to commit yourself. If you’re unsure about what you’re seeing, send the sample to a board-certified clinical pathologist. Compare your findings to those of the pathologist, going back to look at the slide again if possible. Keep a collection of slides or digital images for your own reference.

Comparing cytology to histopathology

	Cytology	Histopathology
Turnaround time	Faster	Slower
Cost	Lower	Higher
Morphologic detail	Excellent	Fair
Tissue architecture	No	Yes

Indications for cytology include: characterizing a previously detected abnormality (mass/infiltrative area, organomegaly, ulcerated or exudative lesion, cavity effusion), cancer staging, and fishing (suspect occult infection, inflammation, or neoplasia).

It is a myth that histopathology is always better than cytology. In fact, they are often complementary. Histopathology is considered the “gold standard” for diagnosis of most solid tissue lesions, but *cytology is often better for evaluating*: fluids (cavity effusions, blood), organisms, round cell tumor lineage, and vacuolar change in hepatocytes (e.g., steroid hepatopathy, hepatic lipidosis) – especially in mild cases.

Some clinicians say “cytology is useless for liver lesions”. That is untrue. While a FNA sample certainly may fail to detect focal disease (e.g. “patchy” inflammation) or fibrosis, *it is nevertheless a good way to rule out other conditions, such as hepatic lipidosis or lymphoma, in a relatively inexpensive and non-invasive way.*

Indications for histology include: tumor grading, identification of tumor cell lineage (may require special staining), unable to obtain a good cytology sample – e.g., poorly exfoliative lesion, cytology findings are inconsistent with clinical impression – e.g., non-representative sample (FNA or impression smear missed the lesion), cytology results are inconclusive despite adequate cellularity – e.g., still uncertain if neoplastic vs. reactive, or benign vs. malignant, and refining cytologic diagnosis (e.g., cutaneous basilar epithelial tumors, benign keratinizing lesions).

Tip: As a rule of thumb, use the minimal amount of suction needed to get cells to exfoliate. To some extent, it is a matter of personal preference, and finding out what works best for you. The term “FNA” can be something of a misnomer, because aspiration (suction) with the syringe is not always required. In fact, overzealous aspiration can disrupt the cells being sampled and thus limit interpretation. Tissues that exfoliate readily (e.g., lymph node, spleen, liver, most epithelial tissues) usually do not require aspiration, and can be sampled instead with a “pincushion” technique.

Tip: Slide preparation should be done with minimal trauma to the cells, and air-dried as quickly as possible. For samples that are just too thick or “chunky” to use this method, you may employ the “squash prep” method, in which the two slides are compressed before drawing them apart, but you should understand that this method may crush enough cells to render the sample uninterpretable.

Once the slide has been prepared, it should be air-dried as quickly as possible and then stained. Unlike biopsy samples for histologic evaluation, no chemical fixation is necessary for cytology specimens. In fact, it is critical to keep the sample away from formalin fumes, which interfere with normal cytologic staining and almost always make the sample uninterpretable. Lastly, one should always label the slides (not the slide container) with the patient’s name and anatomic location of the sample.

Of course, other factors may also render a cytologic sample non-diagnostic – for example, if the tissue of interest was missed (e.g., perinodal fat v. lymph node) or did not exfoliate (e.g., fibrous lesions), if there is so much blood contamination that it obscures the morphology of other cells, or if the slide preparation is too dense.

Impression smears are used to prepare cytologic specimens from tissue biopsies and ulcerated cutaneous lesions. Before making an impression smear, the tissue should be blotted gently to remove excess tissue fluid. The impression smear is made by gently touching the tissue to the glass slide or by touching the cutaneous lesion with the glass slide.

Poor samples may result if the tissue is not blotted adequately, if too much pressure is applied when making the impression, or if the lesion is poorly exfoliative. In the latter case, a scalpel blade can be repeatedly scraped (in one direction) across the tissue and the accumulated cells along the edge of the blade can then be transferred to a glass slide for a squash prep.

Methods for further characterizing histopathology samples have been very routine for a long time (e.g., immunohistochemistry or IHC). Further characterizing cytology samples or samples derived from needle aspirates are now becoming very common. Needle aspirated samples can be submitted for PPAR (PCR test looking for clonal T-cell or B-cell receptor rearrangement), PCR tests looking for infections agents not apparent microscopically, flow cytometry looking for cell receptor/marker expression (these cells need to be submitted live in a fluid medium), and for immunocytochemistry (ICC), (also looking for cell receptor/marker expression).

Serum Chemistry Panel Discussions

Casey LeBlanc, DVM, PhD, DACVP

KDL VetPath

Springfield, VA

Case 1. Two year old female Pug presents with a history of inactivity and depression for last 1-2 weeks. No significant findings on physical examination.

Serum chemistry		Flag	Reference interval			
Glucose, mg/dL	80		80-115			
AST, U/L	97	H	0-50			
ALT, U/L	153	H	0-60			
ALP, U/L	98		0-100			
CK, U/L	154	H	0-150			
T. Bili, mg/dL	0.2		0.0-0.4			
T. Protein, g/dL	5.9		5.8-7.5			
Albumin, g/dL	2.5	L	2.6-4.2			
Globulin, g/dL	3.4		2.5-4.0			
Cholesterol, mg/dL	95	L	150-240			
BUN, mg/dL	4	L	8-22			
Creatinine, mg/dL	0.6		0.5-1.7			
CBC						
HCT, %	53.4		35-55			
MCV, fL	58.7	L	60-77			
MCHC, g/dL	32.3		32-36			
Plts, x10 ³ /uL	211		200-700			
Plasma Protein, g/dL	5.8	L	6-7.8			
T. Leukocytes, x10 ³ /uL	14.2		6-17			
Segs	11.8	H	3-11.5			
Bands	0.0		0-0.3			
Lymphs	0.9	L	1-4.8			
Monos	1.6	H	0.1-1.4			
UA: no findings on sediment						
Color	yellow					
Turbidity	clear					
Specific Gravity	1.008					
pH	7.5					
Protein	negative					
Glucose	negative					
Ketones	negative					
Bilirubin	negative					
Blood hemoglobin	negative					
				Bile Acids:		
				Fasting	25	H (0-8)
				Post-prandial	185	H (0-30)

Case 2. Five year old F/S mixed breed dog present with a history of lethargy for 2-3 days, pale mucous membranes and depression.

Serum chemistry		Flag	Reference interval
Glucose, mg/dL	187	H	80-115
AST, U/L	111	H	0-50
ALT, U/L	174	H	0-60
ALP, U/L	89		0-100
CK, U/L	72		0-150
T. Bili, mg/dL	1.2	H	0.0-0.4
T. Protein, g/dL	7.1		5.8-7.5
Albumin, g/dL	3.6		2.6-4.2
Globulin, g/dL	3.5		2.5-4.0
Cholesterol, mg/dL	220		150-240

BUN, mg/dL	252	H	8-22
Creatinine, mg/dL	7.1	H	0.5-1.7
Calcium, mg/dL	9.8		9.4-11.4
Phosphorus, mg/dL	24.8	H	3.4-6.3
Sodium, mmol/L	136	L	140-153
Potassium, mmol/L	6.2	H	3.8-5.5
Chloride, mmol/L	99	L	107-115
TCO ₂ , mmol/L	14.7	L	17-27
Anion Gap	28.5	H	7.4-19.8

CBC

HCT, %	17	L	35-55
MCV, fL	79	H	60-77
MCHC, g/dL	35		32-36
Plts, x10 ³ /uL	236		200-700
Retic, x10 ³ /uL	324	H	20-80
Plasma Protein, g/dL	7.4		6-7.8
T. Leukocytes, x10 ³ /uL	52.8	H	6-17
Segs	45.9	H	3-11.5
Bands	3.2	H	0-0.3
Lymphs	1.8		1-4.8
Monos	1.9	H	0.1-1.4

RBC morph: few spherocytes
moderate anisokaryosis and
polychromasia

WBC morph: 2+ toxic change

UA: cystocentesis; no findings on sediment

Color	brown
Turbidity	clear
Specific Gravity	1.017
pH	6.0
Protein	2+
Glucose	negative
Ketones	negative
Bilirubin	2+
Blood hemoglobin	3+

Case 3. Fifteen year old M/C Cock-a-poo presents with a 3-day history of vomiting and anorexia. Appears painful around the abdomen on physical examination.

Serum biochemistry		Flag	Reference interval
Glucose, mg/dL	468	H	80-115
AST, U/L	53		0-60
ALT, U/L	100		0-100
ALP, U/L	20530	H	0-135
CK, U/L	60		0-285
T. Bili, mg/dL	5.7	H	0.0-0.4
T. Protein, g/dL	7.5	H	5.7-7.4
Albumin, g/dL	3.0		2.1-4.1
Globulin, g/dL	4.5	H	2.5-4.0
Cholesterol, mg/dL	564	H	130-240
BUN, mg/dL	75	H	6-22
Creatinine, mg/dL	3.7	H	0.4-1.5
Calcium, mg/dL	8.7	L	9.4-11.4
Phosphorus, mg/dL	2.6	L	3.4-6.3
Sodium, mmol/L	142		140-153
Potassium, mmol/L	3.7		3.8-5.5
Chloride, mmol/L	105	L	107-115
TCO ₂ , mmol/L	5.9	L	17-27
Anion Gap	34.8	H	7.4-19.8

CBC

HCT, %	47.8		35-55
MCV, fL	70.2		60-77
MCHC, g/dL	33.5		32-36
Plts, x10 ³ /uL	134	L	200-700
Plasma Protein, g/dL	7.4	H	6-7
T. Leukocytes, x10 ³ /uL	40	H	6-17
Segs	35	H	3-11.5
Bands	2.8	H	0-0.3
Lymphs	0	L	1-4.8
Monos	2.2	H	0.1-1.4

UA: no findings on sediment

Color	yellow, clear
Specific Gravity	1.017
pH	7.0
Protein	neg
Glucose	3+ (1000mg/dL)
Ketones	1+
Bilirubin	3+
Blood hemoglobin	neg

Coag Panel:

PT (sec)	8.3	(5-8.5)
PTT (sec)	11.4	(9-14)
D-dimer	neg	(negative)

Case 4. Three year old female Rottweiler with history of chronic GI signs, weakness, and dehydrated on physical exam.**Serum chemistry**

		Flag	Reference interval
Glucose, mg/dL	57	L	80-115
AST, U/L	48		0-50
ALT, U/L	32		0-60
ALP, U/L	19		0-100
CK, U/L	128		0-150
T. Bili, mg/dL	0.2		0.0-0.4
T. Protein, g/dL	6.3		5.8-7.5
Albumin, g/dL	3.1		2.6-4.2
Globulin, g/dL	3.2		2.5-4.0
Cholesterol, mg/dL	205		150-240
BUN, mg/dL	130	H	8-22
Creatinine, mg/dL	6.6	H	0.5-1.7
Calcium, mg/dL	13.8	H	9.4-11.4
Phosphorus, mg/dL	9.3	H	3.4-6.3
Sodium, mmol/L	125	L	140-153
Potassium, mmol/L	7.9	H	3.8-5.5
Chloride, mmol/L	92	L	107-115
TCO2, mmol/L	12.1	L	17-27
Anion Gap	28.8	H	7.4-19.8

CBC

HCT, %	39		35-55
MCV, fL	65.5		60-77
MCHC, g/dL	34.2		32-36
Plts, x10 ³ /uL	238		200-700
Plasma Protein, g/dL	6.5		6-7.8
T. Leukocytes, x10 ³ /uL	17.6	H	6-17
Segs	7.0		3-11.5
Lymphs	9.3	H	1-4.8
Monos	0.2		0.1-1.4
Eosinos	1.1		0.1-1.2

UA: no findings on sediment

Color	pale yellow
Turbidity	clear
Specific Gravity	1.017
pH	6.0
Protein	neg
Glucose	neg
Ketones	neg
Bilirubin	1+
Blood hemoglobin	neg

Case 5. Six year old Fe Pekapoo presents for severe depression and vomiting.**Serum chemistry**

		Flag	Reference interval
Glucose, mg/dL	72	L	80-115
AST, U/L	111	H	0-50
ALT, U/L	29		0-60
ALP, U/L	87		0-100
CK, U/L	984	H	0-150
T. Bili, mg/dL	2.3	H	0.0-0.4
T. Protein, g/dL	8.1	H	5.8-7.5
Albumin, g/dL	3.3		2.6-4.2
Globulin, g/dL	4.8	H	2.5-4.0
Cholesterol, mg/dL	189		150-240
BUN, mg/dL	155	H	8-22
Creatinine, mg/dL	9.3	H	0.5-1.7
Calcium, mg/dL	9.4		9.4-11.4
Phosphorus, mg/dL	26.6	H	3.4-6.3
Sodium, mmol/L	146		140-153
Potassium, mmol/L	5.4		3.8-5.5
Chloride, mmol/L	86	L	107-115
TCO2, mmol/L	18.5		17-27
Anion Gap	46.9	H	7.4-19.8

CBC

HCT, %	46.6	H	35-55
MCV, fL	67		60-77
MCHC, g/dL	34		32-36
Plts, x10 ³ /uL	169	L	200-700
Plasma Protein, g/dL	8.3	H	6-7.8
T. Leukocytes, x10 ³ /uL	61.4	H	6-17
Segs	43.6	H	3-11.5
Bands	9.8	H	0-0.3
Lymphs	2.1		1-4.8
Monos	0.4		0.1-1.4
Eosinos	1.1		0.1-1.2

UA: cystocentesis

Color	orange	Sediment: 50-60 RBCs, TNTC WBCs, many cellular casts, many bacteria
Turbidity	cloudy	
Specific Gravity	1.020	
pH	6.5	
Protein	3+ (300 mg/dL)	
Glucose	negative	
Ketones	negative	
Bilirubin	2+	
Blood	3+	

Case 6. Nine year old male canine with an acute onset vomiting x 2 days.

Serum chemistry **Flag** **Reference interval**

Glucose, mg/dL	129	H	80-115
AST, U/L	122	H	0-50
ALT, U/L	36		0-60
ALP, U/L	459	H	0-100
CK, U/L	602	H	0-150
T. Bili, mg/dL	0.5	H	0.0-0.4
T. Protein, g/dL	7.9	H	5.8-7.5
Albumin, g/dL	3.7		2.6-4.2
Globulin, g/dL	4.2	H	2.5-4.0
Cholesterol, mg/dL	220		150-240
BUN, mg/dL	38	H	8-22
Creatinine, mg/dL	1.9	H	0.5-1.7
Calcium, mg/dL	11.2		9.4-11.4
Phosphorus, mg/dL	6.8	H	3.4-6.3
Sodium, mmol/L	149		140-153
Potassium, mmol/L	3.1	L	3.8-5.5
Chloride, mmol/L	92	L	107-115
TCO ₂ , mmol/L	32.6	H	17-27
Anion Gap	27.5	H	7.4-19.8

CBC

HCT, %	45		35-55
MCV, fL	70.5		60-77
MCHC, g/dL	35		32-36
Plts, x10 ³ /uL	468		200-700
Plasma Protein, g/dL	8.0	H	6-7.8
T. Leukocytes, x10 ³ /uL	31.8	H	6-17
Segs	27.9	H	3-11.5
Bands	1.9	H	0-0.3
Lymphs	0.9	L	1-4.8
Monos	0.9		0.1-1.4
Eos	0.2		0-1.3

Blood gas

pH	7.54	7.31-7.42
pCO ₂ , mmHg	35	29-42
HCO ₃ , mEq/L	29.5	17-24

UA

Color	yellow
Turbidity	cloudy
Specific Gravity	1.032
pH	6.0
Protein	neg
Glucose	neg
Ketones	neg
Bilirubin	2+
Blood hemoglobin	neg

Sediment: occasional ammonium biurate crystals

Evidence-Based Therapy: Truth or Consequences?

Duncan Ferguson, VMD, PhD, DACVIM, DACVCP
University of Illinois
Urbana, IL

Evidence-based decision-making in medical practice has seen greater emphasis in the “information” age, in part because information is now available in huge, but variable quantity via the Internet. It has become more incumbent on practitioners to use the discipline implied by evidence-based medicine (EBM) with regards to evaluating the quality of information they use to make diagnostic and therapeutic decisions. Over the last 2 decades, clients have started to share information via the Internet that makes it important for practitioners to begin to educate their clientele about the basic tenets of evidence-based medicine. The following discussion will highlight principles and strategies for structuring the approach to making a decision about a therapeutic choice. The presentation will reinforce the principles through a case example.

Goal of EBM

The goal EBM is to seek to clarify the parts of medical practice that are subject to scientific method, and then use the best available evidence gained from this method to medical decision making. What is the goal of EBM as it relates to therapeutics? It is to seek to assess the quality of evidence of the risks and benefits of treatments (including lack of treatment). To accomplish this, it is important to develop relevant questions related to therapy for a specific case which can be specifically answered by this process. Ultimately, the information cannot just be esoteric, but should be designed to impact successful choice and monitoring of therapy.

PACMAN - systematized approach to therapy

A strategy we have tried to apply with teaching veterinary students and residents clinical pharmacology at the University of Illinois has been to use the acronym “PACMAN” which stands for the following points about a therapy. The goal of this approach is to focus on key aspects of a drug’s action and safety, as well as practical aspects of administration.

- **Problem:** This is designed to connect the thought process to the problem-oriented medical record, with particular focus on problems or sets of problems, which may be addressed by therapy.
- **Approach:** Is the approach medical, surgical, palliative, curative, etc.?
- **Class of Drugs:** Most drug classes are associated with certain types of therapeutic indications and toxicities.
- **Mechanism of Action:** Understanding the mechanism of action in some cases down to the cellular level helps key the practitioner into potential drug interactions and toxicities
- **Absorption, Administration, Adverse Effects, Alternatives:** How well is the drug absorbed and by what routes as this will determine practicality of some medications. What are the main toxicities that may limit choice of a therapy? What therapy would be “Plan B?”
- **Note any problems (monitor):** Every therapy is an experiment and the animal should be monitored for success or failure of that therapy, so the practitioner can decide on when Plan B is necessary.

The pyramid of evidence

Ultimately, the practitioner needs to weigh the evidence available regarding a therapy. The list below describes first the information sources, which should carry the highest weight in clinical decision-making. However, largely because of the difference in funding for animal-disease based research, veterinary practitioners rarely have the luxury that physicians have of considering literature describing #1 or #2 on the following list. Most often the best evidence is rated as #3 or below, and commonly only a few studies may fit those criteria.

1. **Systematic Reviews:** This review examines the available literature on a given question and seeks to evaluate, select, and synthesize the highest quality evidence. In the review, the first step is to identify research articles by their titles and abstracts to qualify them for inclusion based upon pre-determined criteria for eligibility and relevance. This type of review uses an objective approach to synthesizing the data, seeking to minimize bias.
2. **Meta-analyses:** Also a statistical technique used to evaluate systematic reviews, when used to describe a review study and manuscript, it refers to the report on combined results of several published studies that address similar research hypotheses.
3. **Blinded Randomized Controlled Trials (RCT):** The “gold standard” for an individual clinical trial and usually the highest level of evidence available in veterinary medicine. In an RCT, bias of both the clinician, the owner, and any evaluator of an endpoint (for example, a pathologist reading histopathology or radiologist reading a radiograph) is designed to be eliminated by “blinding” them to the choice of an animal for the study, its assignment to a specific treatment, and evaluation of its outcome. In an RCT for a new drug, the control group may be a placebo, or if not ethically allowed to leave an animal untreated, it may be a currently approved or accepted treatment. In this design, there are completely separate groups of

animals (parallel design) that are subject to greater inter-individual animal variation, requiring larger numbers of animals to achieve similar statistical power. Another approach is the crossover study in which the animal goes through 2 or more “arms” of a study with one of them being the control. In this design, the animal serves as its own control, and may then be entered into one study “arm” or another based upon random assignment. This approach can only be used to evaluate therapy when the endpoint is not a cure, and so is more commonly used to evaluate therapy for chronic diseases (e.g. pain management for arthritis).

4. Open Uncontrolled Trial: This category includes trials, which only evaluate the test article and perhaps use a historical control from similar cases treated previously. Alternatively, the study might evaluate an animal’s improvement, without the appropriate control of knowing if the animal would improve without therapy.
5. Cohort Studies: Most often used as a retrospective design, cohort studies openly match animals in the control and treatment groups to control for similar factors that might impact outcome (age, breed, sex, duration of disease, etc.). The animals are then followed prospectively, or retrospectively via case records to determine their outcome, and then the groups are compared statistically. For example, the use of furosemide in managing a case of congestive heart failure in a dog could be evaluated in a selected control and study group to prospectively evaluate the extension of life span. The same study could be performed retrospectively via case records. The main disadvantage of retrospective studies that are not randomized and blinded are the potential for different standards of care, and for bias as to the patient selection outcome.
6. Case Control Studies: More commonly used in epidemiology, case control studies usually retrospective, and are used to identify factors that may contribute to a medical condition by comparing subjects having a condition (or treatment of a condition) with patients who do not have the condition.
7. Case Series: Clinical cases applying a specific therapy, perhaps by different clinicians, often with inconsistent data collected, is useful information that a therapy is feasible, but does not provide any statistical support for the practice.
8. Single Case Reports: Individual reports which document application of a therapy in at least one case.
9. Reports, Opinions, or non-peer-reviewed studies: Commonly found on veterinary exchanges between veterinarians on the Internet or in a practice, an obvious flaw to this level of evidence includes the bias of personal experience as this information is rarely controlled, and never blinded to outcome or evaluated by statistics.
10. Non-target species research: Research on a specific therapy conducted in other species should be used very cautiously until species-relevant data is available.
11. In vitro research: Drug companies identify potentially promising compounds using receptor and tissue targets, but many compounds are lost after this phase due to issues only predicted by in vivo application in the species of interest.

Bertone (2007) proposed an “Evidence Calculator” and used the example to rate types of evidence for equine therapeutics with a score from 0 to 10. The rating 10 was given to FDA-approved drugs used in their FDA-approved indication(s), at the approved dosage and frequency of administration. A clinical trial in horses not subject to FDA scrutiny was given a score of 8, an FDA approved drug for a non-equine mammalian species was given a score of 8, a compounded product which is not modeled after an approved drug a score of 6, unregulated herbs and homeopathic preparations a score of 0. For dosages, the level of evidence was scored as 5 when there was only a pharmacokinetic and not efficacy study available for horses. Pharmacokinetic studies in a species other than the horse was rated 0. Laboratory studies were rated 1, but only if the in vitro cells were equine. These numbers might be open to debate, but they clearly attempt to quantify many of the principles of EBM as related to therapy.

Statistical power: What number of animals is needed in a study to produce high-level evidence?

Although open to debate, it is clear that few humans would be happy to be taking a drug, which had been tested in less than 100 patients unless all therapeutic options had been already exhausted, and the prognosis was poor. Of course, the number of patients needed to test a therapeutic question depends upon the clinically relevant outcome sought, and the variation in outcomes between patients. For example, if a new therapy is dramatically superior to an old (control) therapy, high statistical significance might be achieved with a small number of patients in each group. However, Olivry and Mueller (2003) have suggested that veterinary clinical studies of types #3 through #7 above might be additionally rated based upon the number of subjects studied. Level 4 evidence would be provided by <10 subjects, Level 3 by 10-19, Level 2 by 20-50 and Level 1 is >50 subjects. The numbers associated with Level 3, 2 and 1 might be associated with an FDA-approved study by a drug company on Phase I, II or III trials. Suffice to say, it is also more common for small therapeutic differences to be detected in veterinary medicine.

Putting the data to test

All of the effort and evaluation should be brought back to impact therapy of the patient. At this point, pragmatism and common sense should be applied. For example, if the best evidence suggest that the best treatment for a deep pyoderma would suggest the use of an expensive 4th generation cephalosporin, and this medication was outside the range of the owner’s budget, the clinician needs to adjust his/her plan to fit the client’s circumstances. Above all, the clinician should not be paralyzed by the inevitable observation that the

data to answer some questions is often very weak. In the presentation, a specific case example will be provided to demonstrate these points.

Summary

EBM as applied to therapy requires the following steps:

1. Devise relevant, answerable clinical questions
2. Locate best evidence to answer question
3. Critically evaluate the evidence
4. Integrate appraisal with clinical expertise and patient's and client's circumstances

References and recommended reading

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Principles of Antimicrobial Usage in Small Animal Practice

Duncan Ferguson, VMD, PhD, DACVIM, DACVCP

University of Illinois

Urbana, IL

A veterinarian is often required to make the tentative diagnosis of a bacterial infection, and begin treatment without knowledge of culture results. For first-time infections, full courses of antimicrobial therapy may be prescribed without culture and sensitivity. Habitual use of a “broad spectrum” antimicrobial is to be discouraged. As a result, it is important to weigh all the evidence to make a rational decision for such empirical therapy. Empirical therapy is usually based upon:

- History and P.E.
- Clinical suspicion of microbes likely involved
- Gram stain

Certainly, this is the time to consider whether the severity of the animal’s illness merits an immediate culture and sensitivity (C & S), as previous unsuccessful empirical antimicrobial therapy may lead to resistance, and can occasionally confound interpretation of subsequent C & S results.

Questions to ask before empirical therapy

So, more specific questions the veterinarian might ask before empirical therapy include:

- What organ system is involved?
- Is the problem acute or chronic?
- What pathogen is most likely to be present in that organ system?
- What antimicrobial is most likely to be effective against that pathogen?

General considerations

General factors to consider about the antimicrobial options include:

- Antibacterial spectra: Gram- negative, gram -positive, anaerobic, rickettsial, and protozoal efficacy?
- Bactericidal or bacteriostatic at achieved concentrations?
 - Generally -static
 - tetracyclines, chloramphenicol, macrolides, lincosamides (lincomycin), sulfonamides, and nitrofurans.
 - Generally –cidal
 - penicillins, cephalosporins, aminoglycosides, quinolones, polymyxins, and trimethoprim-sulfonamide combinations
- Mechanism of action: Is there a post-antibiotic effect (PAE)? Are there synergisms or antagonisms with other drugs being used?
- Limiting toxicities
- Practicality of administration
- Availability and cost

Anaerobic therapy

Successful antimicrobial culture and sensitivity is often not possible, so empirical choices are more frequently seen when anaerobes are suspected. Options for anti-anaerobe therapy include:

- High doses of penicillin - resistance appears to be increasing
- Chloramphenicol
- Clindamycin
- Metronidazole
- Cefoxitin

Four-quadrant therapy

Serious systemic infections (bacteremia, septicemia, peritonitis) often call for immediate choice of “Four-Quadrant” therapy. The common choices are:

- Quinolone + amoxicillin
- Clindamycin + aminoglycoside
- Beta-lactam + aminoglycoside
- Penicillins + aminoglycosides

- Cephalosporins + aminoglycosides+ metronidazole
- Ticarcillin + carbenicillin and amikacin for resistant Pseudomonas

Prophylactic ("anticipatory") therapy

With increasing amounts of antimicrobial resistance developing in higher volume practices, it is worth considering that prophylactic antimicrobial therapy, that is, use of antimicrobials to prevent an infection, is not a rational or evidence-based approach except in certain high-risk patients, like diabetics and other immunosuppressed patients. The empirical use of antimicrobials (e.g. ampicillin) during intravenous or urinary catheterization has been shown to be unnecessary and has likely led to the fact that ampicillin is now only 37% effective against Staphylococcus species and only 55% effective against E. coli. Indeed, as a response to the increased incidence of multi-drug resistant (MDR) nosocomial infections, some human hospitals and tertiary care veterinary hospitals have found it necessary to resort to committees composed of infectious disease, epizootiology, and clinical pharmacology experts to approve the use of an antimicrobial within the institutional practice.

Guidelines for antimicrobial use according to organ system

The following are guidelines for "first-guess" empirical therapy of infections in selected organ systems. When available, information from culture and sensitivity tests should almost always take precedence.

Circulatory infections: Septicemia, bacteremia

- Try to identify the original site of infection
- Positive blood cultures in suspected bacteremia are rare. Culture several times for aerobic and anaerobic organisms timed with rise in temperature if hyperthermic
- If intestinal trauma, assume a mixed infection with gram-positive, gram-negative, and anaerobic organisms

Common aerobic organisms causing bacteremia

- Staphylococcus
- Streptococcus
- Escherichia coli
- Klebsiella
- Enterobacter
- Pseudomonas

Oropharyngeal, pleuropulmonary, and intra-abdominal infections

- 25% involve anaerobes: Bacteroides fragilis most common
- Rational first-line empirical choice of antimicrobials: Clavulanic acid-amoxicillin or clindamycin
- For procedures near the alimentary canal: gentamicin and cefazolin, or ceftiofur and cefotetan

Bite wounds and traumatic wounds or abscesses

- Streptococcus, Pasteurella, penicillinase-producing Staphylococcus are most common.
- Rational first-line empirical choice of antimicrobials: Clavulanic acid-amoxicillin
- Other drugs to consider include: oxacillin, dicloxacillin, cephalosporins, tetracyclines, quinolones, and trimethoprim-sulfadiazine/

Lower respiratory tract: Pneumonia

- No predictable bacterial pathogen in dogs: E. coli, Klebsiella species, Pasteurella spp., Pseudomonas species, Bordetella bronchiseptica, or Streptococcus zooepidemicus
- In cats, Bordetella and Pasteurella common
- 2/3 are gram-negative and may be resistant to commonly used antimicrobials; C & S of transtracheal wash recommended

While waiting for the results, trimethoprim-sulfa, chloramphenicol, or quinolones are also rational choices. If a gram-positive organism is suspected or identified by Gram stain, alpha- and beta-hemolytic Streptococci, Staphylococcus spp. are common pathogens. Rational first-line empirical choice of antimicrobials include cephalexin, trimethoprim-sulfa, clavulanic acid- amoxicillin, quinolones, amoxicillin, or ampicillin.

Bronchial infections

- More lipid-soluble drugs, such as chloramphenicol, quinolones, and larger drugs, such as macrolides, may be preferred owing to better tissue penetration
- When bronchial secretions are severe, gentamicin may be less effective because it penetrates secretions poorly
- Anaerobes: clindamycin and metronidazole
- Mycoplasma: clindamycin or a tetracycline

Urinary tract

- Entire urinary tract is at risk when one region of the tract is infected.
- Examination of the urine and of a Gram stain is always recommended prior to choosing antimicrobial therapy.
- Particularly in cats, it is important to distinguish inflammation from infection.
- 75% gram-negative: *E. coli*, *Proteus*, *Klebsiella*, *Pseudomonas*, and *Enterobacter*
- 25% due to beta-hemolytic *Streptococcus* or *Staphylococcus*.
- Two or more organisms may be found in about 20% of cases.
- In vitro sensitivity of microorganisms translates to >90% treatment success

Therefore, for empirical therapy of UTI's, broad-spectrum antimicrobials are recommended, but greatest consideration should be toward drugs which reach high concentrations in the urine: e.g. aminopenicillins, cephalosporins, and quinolones. For upper UTI infections (e.g. pyelonephritis), the agent should reach high concentrations in serum and, if possible, in urine.

The duration of treatment may require 4-6 weeks to achieve the goal of sterilization of the urine. Also, in some cases, after sterilization of the urine, preventive single evening doses of 50% to 70% of the daily dose of a urinary antiseptic or trimethoprim-sulfa may be required. In the case of pyelonephritis, greater than 6 weeks of therapy with an antimicrobial that has good tissue penetration (e.g., chloramphenicol, trimethoprim, or the fluoroquinolones) may be necessary.

Prostatitis

- Penetration of most drugs during early inflammation
- Penetration characteristics of an antimicrobial are critical – e.g. chloramphenicol
- Chronic prostatitis – entry of basic drugs favored
- Gram positive: chloramphenicol, erythromycin, clindamycin, oleandomycin, quinolones, trimethoprim
- Gram negative: chloramphenicol, trimethoprim-sulfa, quinolones

Pyometra and endometritis

- C & S should be performed on the uterine contents
- *E. coli* infection is observed in most cases
- *Proteus* and *Streptococcus* occasionally are found
- Chloramphenicol, trimethoprim-sulfa, quinolones

If medically managed, intrauterine infusion of antiseptic or antibiotic solutions is of little value.

Central nervous system

- High lipid solubility important: chloramphenicol, the sulfas, trimethoprim, metronidazole, and the quinolones
- Penicillins and cephalosporins may enter an inflamed site during acute infection, but are excluded by blood-brain barrier in chronic conditions.

Pyodermas

The most useful way to consider most dermatological infections is as microabscesses.

- Superficial: Coagulase-positive, penicillinase-producing *Staph*
- Consider methicillin-resistant *Staph aureus* (MRSA)
- Deep: gram-negative organisms, fungi, and *Mycoplasma*
- Most likely to be *S. pseudointermedius* in small animals rather than *S. aureus*
- Relatively predictable susceptibility to β -lactamase resistant antimicrobials agents with a beta-lactamase inhibitor (e.g. Clavamox[®])

Rational first-line empirical choice of antimicrobials: Dicloxacillin, oxacillin, high doses of amoxicillin and clavulanic acid, cephalosporins, erythromycin, lincomycin, trimethoprim-sulfa and the quinolones. Erythromycin and lincomycin should be used only as primary choices, because cross-resistance develops.

Orthopedics

- Sterile orthopedic surgery, particularly long procedures, generally is considered to be high-risk surgery that merits antimicrobial prophylaxis.
- With known infections, a culture of the wound or joint fluid is mandatory.
- Treat for no less than 4-6 weeks.

Osteomyelitis

- Most commonly involves *Staphylococcus*, *Streptococcus*, *E. coli*, *Proteus*, or *Pseudomonas* species.
- Gram-negative: gentamicin, amikacin, or the quinolones usually are effective.
- Gram-positive: cephalosporins, clavulanic acid-amoxicillin, and imipenem, a newer beta-lactam
- For penicillinase-producing *Staph*: oxacillin and cloxacillin

Highly suggested general references

Aucoin D (2011): Target: The Antimicrobial Reference Guide to Effective Treatment, 4th edition, North American Compendiums, Inc., Port Huron, MI
Blondeau JM (2009): STAT - Steps to Antimicrobial Therapy: Strategies to optimize therapy and minimize resistance when treating bacterial infections, North American Compendiums, Inc., Port Huron, MI

The Best Use of NSAIDs

Duncan Ferguson, VMD, PhD, DACVIM, DACVCP
University of Illinois
Urbana, IL

NSAIDs are a chemically diverse class of drugs that have anti-inflammatory, analgesic, and antipyretic properties. Aspirin, in addition, has antithrombotic effects. The purpose of this presentation is to review recent concepts of anti-inflammatory therapies and currently available products for anti-inflammatory therapy in dogs and cats. Nonsteroidal anti-inflammatory drugs (NSAIDs) and newer glucocorticoid preparations will be described.

Review of mechanism of action

Arachidonic acid (AA) may be released from cell membranes by physiological or pathological processes which stimulate phospholipase A2) in damaged tissues (pathological situations). The liberated AA may then serve as a substrate for cyclooxygenase enzymes producing prostaglandins and prostacyclins, and/or lipoxygenases (LOX) producing leukotrienes. LOX or dual LOX/COX inhibitors will be discussed later. Most NSAIDs act by decreasing prostaglandin synthesis by inhibiting the cyclooxygenase (COX) enzymes. There are 3 known subtypes of COX.

COX-1: constitutive enzyme in most tissues, including platelets, kidney, gastrointestinal tract, and seminal vesicles, and is involved in cell-cell signaling, tissue hemostasis and renal protection

COX-2: an induced enzyme in inflammatory cells when they are activated- endothelial cells, monocytes, macrophages, fibroblasts, synovial cells, chondrocytes, osteoblasts. COX-2 products may aid in ulcer healing, promote blood vessel formation, participate in bone remodeling and healing and maintain renal function.

COX-3: A splice variant of COX-1 that is expressed in the dog. The effects of some NSAIDs relative to fever and inflammation were not explained only on the basis of the COX-1/COX-2 model. COX-3 interaction has been used to explain the antipyretic effects of acetaminophen, because the enzyme isoform is expressed highly in the brain.

Anti-inflammatory effects of NSAIDs

COX inhibition results in decreases in prostaglandins E2 and prostacyclin, resulting in less vasodilation and edema. Importantly, the accumulation of inflammatory cells is not reduced (in contrast to glucocorticoids and LOX inhibitors). NSAIDs do NOT inhibit cell-mediated immunity and may even exacerbate tissue damage in chronic inflammatory conditions such as arthritis and vasculitis. Most of the beneficial effects are considered to be associated with COX-2 inhibition; however, recently COX-2 enzyme products have been associated with important physiological functions as well. COX-2 inhibitors certainly not been shown to be more effective than non-selective COX inhibitors. Mechanisms of NSAID-induced gastrointestinal mucosal injury include reduction in mucus and bicarbonate secretion, reduction in submucosal blood flow, and reduction in cell turnover.

Renal toxicity, most often associated with papillary necrosis, is caused by the reduction of PGE2 and PGI2, which are necessary for normal renal blood flow.

Adverse effects of NSAIDs

Most NSAIDs, regardless of purported selectivity, induce the following effects to some extent: gastritis, vomiting, diarrhea, gastrointestinal ulceration and hemorrhage, renal injury, hepatic injury, platelet inhibition (irreversibly by aspirin and reversibly by others) and allergic reactions. Most of the adverse effects have been associated with COX-1 inhibition but drug safety has not always correlated with selectivity of a drug for COX-2 over COX-1. However, newer NSAIDs do tend to cause less destruction to cartilage than older NSAIDs.

COX inhibition controversies

Despite the apparent certainty of some pharmaceutical marketing claims, it is not yet established whether COX-2 inhibitors are more effective and safer than other NSAIDs. It certainly doubtful that in vitro tests of selectivity against COX-1 vs. COX-2 are consistently predictive of clinical outcomes. It appears that both pharmacokinetic and pharmacodynamics factors in vivo may account for some of the discrepancy. Also, no NSAID is consistently more efficacious than another.

Common pharmacokinetic features of NSAIDs

All NSAIDs are weak acids and are highly protein bound in plasma. Therefore, they may compete for plasma binding by other drugs or endogenous hormones (e.g. thyroxine). They normally have a low volume of distribution but can accumulate at sites of inflammation.

Comparative oral dosages of aspirin in dogs and cats

Antithrombotic applications

Dogs: 3 mg/kg q1-6 days

Cats: 3 mg/kg q48h (1/4 baby aspirin=16 mg/cat)

Antipyretic, analgesic applications

Dogs: 10 mg/kg q12h

Cats: 10 mg/kg q48h

Anti-inflammatory applications

Dogs: 10-20 mg/kg q12h

Cats: 20 mg/kg q48h

NSAIDs for use in the dog

Approved drugs for the dog include Meloxicam (Metacam®), carprofen (Rimadyl®), etodolac (EtoGesic®), firocoxib (Previcox®), deracoxib (Deramaxx®), and phenylbutazone. Other NSAIDs used in this species include aspirin, flunixin (Banamine®), ketoprofen (Ketofen, Orudis), piroxicam (Feldene), tolfenamic acid (Tolfedine; not in U.S.), Vedaprofen (Quadrisol; not in U.S.).

NSAIDs for use in the cat

Meloxicam was the first NSAID approved for use in the cats in the U.S., and only for a single dose such as for postoperative pain management. In a trial of cats undergoing ovariohysterectomy, carprofen, ketoprofen, meloxicam, and tolfenamic acid have been compared. All showed similarly positive results with 9/10 cats responding.

	Dosage (mg/kg)	Dosage (mg/kg) ²
NSAID	DOG	CAT
Carprofen	4.4 q24h	NR
Deracoxib	3-4 q24h	NR
Etodolac	10-15 q24h	NR
Firocoxib	5 q24h	0.75-3 (1x)
Flunixin	1 q24h	NR
Ketoprofen	1-2 q24h	1 q24h (5x)
Meloxicam	0.1 q24h	0.3 (1x) or <0.05 q24h
Piroxicam	0.3 q48h	0.3 q48h
Robenacoxib	1-2 q24h	1 q24h (6x)

NR= not recommended; Max doses = 1x, 2x, etc

Absolute contraindications

Acetaminophen should not ever be used in cats. Cats are particularly susceptible due to a lack of glucuronyltransferase that leads to production of a toxic metabolite, which causes methemoglobinemia followed by hepatic necrosis. Most other NSAIDs should be dosed very carefully in the cat. Naproxen and Ibuprofen induce severe gastrointestinal bleeding in dogs.

Special characteristics of certain NSAIDs

Carprofen is probably the safest of the newer drugs in the dog. After 1 million uses, an incidence of 0.2% adverse was observed, with 10% of these being associated with hepatic damage. Early studies deemed Labrador retrievers to be more prone to hepatic damage, but did not correct for the high prevalence of this breed. Hepatic problems are not limited to this species, are more common in elderly animals, and should be anticipated by pre-screening animal for alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (SAP) and bilirubin. Most adverse reactions are observed within the first month of therapy.

Flunixin and ketoprofen (Ketofen®, Orudis® (human product)) demonstrate potent visceral analgesia through blockade of bradykinin receptors. Ketoprofen is a nonspecific COX inhibitor, but some reports have purported LOX inhibition. For similar reasons, flunixin has been employed for combatting vasodilation associated with endotoxic shock. Small animals appear exceptionally prone to the GI and renal toxicity of flunixin, and a maximum of 3 doses is recommended. Meloxicam and etodolac (EtoGesic®) are finding greater favor in small animal practice. Deracoxib (Deramaxx®), in theory, is COX-2 selective, but the specificity is lost at higher concentrations leading to toxicity as non-linear pharmacokinetics have been observed. Little published data

exists on piroxicam in the veterinary literature aside from reports of adverse reactions (GI ulceration, etc.). Robenacoxib (Onsior) was recently approved for dogs and cats (2nd approved NSAID for cats) and is approved for relief of musculoskeletal pain and inflammation and chronic osteoarthritis. The injectable form is used perioperatively in dogs and cats.

5-Lipoxygenase inhibitors, leukotriene receptor antagonists, and dual COX/LOX inhibitors

Zileuton (Zyflo®) is a 5-LOX inhibitor that suppresses leukotriene production. Montelukast (Singulair®) and zafirlukast (Accolate®) are leukotriene receptor (LTR) antagonists. A canine study of zileuton showed a reduction in erythema, but not pruritis in allergic skin disease. Indications of the LOX and LTR antagonists include asthma and allergic skin disease. In human medicine, dual COX/LOX inhibitors appear to slow the progression of arthritis. However, Tepoxalin (Zubrin®), a COX-1, COX-2, and 5-LOX inhibitor, which was marketed for canine drug for inflammation/ allergy, has now been removed from the market.

General recommendations on NSAID usage

It has been recommended by some to allow a washout period of 1-7 days before initiating a second NSAID, with the presumed purpose of eliminating the residual effect of the first drug. However, there is little data to support the need for this practice. Furthermore, while rarely necessary, the simultaneous administration of an NSAID and glucocorticoid is imprudent due to synergistic ulcerogenic potential.

In general, it is wise to become familiar with a limited number of drugs, use approved drugs, and for perioperative pain relief choose a COX-2 preferential drug.

Recommended reading

Boothe, DM (2012) Antiinflammatory Drugs, in Booth,DM (ed) Small Animal Clinical Pharmacology and Therapeutics, 2nd ed, Elsevier:1045-1118.

Papich, MG (2010) Saunders Handbook of Veterinary Drugs, 3rd ed.

Plumb D (2011) Veterinary Drug Handbook, 7th edition, Wiley-Blackwell, Ames, IA

Glucocorticoid Therapy in Small Animal Practice: What Do We Really Know?

Duncan Ferguson, VMD, PhD, DACVIM, DACVCP
University of Illinois
Urbana, IL

Glucocorticoids are among the most widely used (and misused) class of drugs in veterinary medicine. Despite this, scientific information on glucocorticoid therapy in most domestic species is difficult to identify, particularly with respect to optimal dosages and dosage intervals, physical and endocrine side effects, and efficacy in clinical applications. Therefore, therapeutic protocols are often the product of clinical experience, common sense, and information from human medicine.

Principles of rational glucocorticoid therapy

Because of their wide-ranging and nonspecific effects, reports of the clinical usage of glucocorticoids is replete with pragmatic recommendations regarding dosage, duration of therapy and severity of side effects. Much has been adopted from clinical use in man, and much more is known about the fine points of glucocorticoid therapy in dogs and cats than in other species. In the following discussion, most of the specific comments will apply to the use of glucocorticoids in the dog; however, when available, appropriate information for other species will be mentioned. It is important to recognize that glucocorticoids rarely cure disease, with the possible exception of spontaneous glucocorticoid deficiency; they suppress clinical signs hopefully long enough for a condition to run its natural course.

The following general principles should be considered when glucocorticoid therapy is employed:

1. Diagnose the disease first, if possible. Glucocorticoids are generally only palliative and do not provide a true cure for any disease. In addition, if used before all reasonable diagnostic tests have been completed, they may mask signs of underlying disease and complicate specific diagnosis and therapy. Though a definitive diagnosis is not always possible, a presumptive diagnosis should be proposed.
2. Classify the disorder into one of the following categories of glucocorticoid therapy, according to a definitive or presumptive diagnosis: physiologic replacement; intensive short-term; anti-inflammatory and antiallergic; immunosuppressive; and chronic palliative. Each of these usage classifications will be discussed in more detail. By using these classifications, the clinician clearly defines the goal of therapy and can choose a starting dose and formulation appropriate for the disorder.
2. Use glucocorticoids to accomplish specific objectives. It is important to decide on the therapeutic endpoint before therapy is started in order to objectively assess efficacy and determine the smallest effective dose. For example, in treatment of a dog with autoimmune hemolytic anemia, the goal for initial glucocorticoid therapy might be to raise the hematocrit from 10% to 25%. By defining a therapeutic objective, the clinician can then judge the efficacy of a treatment protocol and decide when the glucocorticoid dose should be altered or alternative therapy chosen.
3. The length of therapy should also be anticipated. For example, immunosuppressive therapy generally requires several months of glucocorticoid use. Accordingly, a plan for instituting and later decreasing the dose should be considered from the outset. In such a case, intermittent or alternate-day therapy would not be appropriate, and an intermediate- or long-acting glucocorticoid could be used.
4. Is the patient predisposed to any complications of glucocorticoid therapy? As many of the therapeutic effects of glucocorticoids are nonspecific, clinicians should anticipate the impact on the patient of the previously outlined complications of glucocorticoid use. In doing so, the risk/benefit ratio of using these potent agents is considered.
5. Dosages of glucocorticoids are derived by trial and error, and should be constantly reevaluated. It is important to understand the relative potency and, perhaps more important, the relative duration of action of a glucocorticoid preparation, as the duration of anti-inflammatory effects usually parallels the duration of effects on the hypothalamic-pituitary-adrenal axis. Success with alternate-day therapy, more commonly applied in small animal practice, depends on selecting a glucocorticoid preparation with slightly longer anti-inflammatory or immunosuppressive (beneficial) actions than HPA-axis-suppressive effects.

Classes of glucocorticoid usage

Physiologic replacement therapy

Replacement therapy involves use of glucocorticoids in amounts similar to those of the naturally occurring glucocorticoids (cortisol in virtually all domestic species) from the adrenal gland. Ideal replacement therapy should mimic the adrenal gland's hormonal output under basal conditions, with doses increasing if the animal is stressed by illness or surgery. Practically, this ideal is never achieved; however, the following regimens have been used successfully in adrenalectomized and Addisonian dogs or cats. As a general rule, animals produce approximately 1 mg/kg of cortisol (hydrocortisone) every day. It is not rational to employ alternate-day or

intermittent glucocorticoid replacement therapy in a glucocorticoid-deficient animal as the animal's metabolic wellbeing depends upon the presence of glucocorticoids every day. Therefore, physiological replacement therapy is aimed at providing a small daily amount of glucocorticoid. Physiological replacement therapy is rarely indicated or applied in large animals. In small animals, hydrocortisone or cortisone at 0.2-1 mg/kg/day, or more commonly, equipotent amounts of prednisolone or prednisone orally at 0.1-0.2 mg/kg/day once daily orally are indicated. There have been reports that the diurnal variation of cortisol results in a peak in the morning in dogs and evening in cats; however, more recent studies have not confirmed this pattern. Therefore, the timing of the single daily dosage would not appear to be critical, other than that it be provided approximately the same time each day. Because stress results in higher adrenal output of glucocorticoids, this pattern should be mimicked; in general, in moderate stress, give 2 to 5 times the physiological dosage, and in severe stress (e.g. surgery), administer 5 to 20 times this dosage until the stressful experience has ended.

Intensive short term and shock therapy

The effects of glucocorticoids in all forms of shock are still controversial; however, some evidence suggests that early treatment (probably about 4 hours post-induction in dogs) may lead to increased survival, particularly in hemorrhagic and septic shock. The nature of the formulation (particularly the ester) may affect the speed of cellular entry of glucocorticoids during shock; however, other conclusions have also been reached. Glucocorticoids improve hemodynamics and enhance survival in canine models of endotoxic and hemorrhagic shock. However, therapy for shock should also include aggressive fluid therapy. Septic (endotoxic) shock is the most responsive form to glucocorticoid therapy; however, human trials have shown improved short-term survival, but may succumb to chronic septicemia later. Suspected endotoxic shock should be treated with fluid therapy and a broad-spectrum antimicrobial, with or without glucocorticoids. Glucocorticoids and antibiotics were synergistic when given within 2 hours of induction of septic shock in baboons.

The potential detrimental effects of massive doses of glucocorticoids should always be considered. However, proponents of glucocorticoid therapy for shock point out that short-term (~48 hours) glucocorticoid therapy has few negative effects and the positive effects far outweigh the risks. Most human patients with sepsis survive beyond the acute stages of endotoxemia but succumb later to chronic septicemia. Certainly, the immunosuppressive effects of glucocorticoids make their use contraindicated during chronic sepsis, and those supporting glucocorticoid use in septic shock do not generally advocate use other than during the early acute hypotensive state.

Antiinflammatory and antiallergy therapy

A large proportion of glucocorticoid use in veterinary practice is designed to combat inflammation or allergy. Unfortunately, many such diseases are difficult to definitively diagnose. Therefore, misuse of glucocorticoids is not uncommon in this category. Examples of anti-inflammatory and antiallergic use of glucocorticoids include symptomatic treatment of pruritic dermatoses, allergic pulmonary disease and allergic gastroenteritides. Guidelines for anti-inflammatory and antiallergic dosages vary from species to species. Prednisolone or prednisone is most commonly used in small animals at 0.55 mg/kg q12h given orally for induction, then at 0.55-2.2 mg/kg every other day for maintenance. Although all dosages should be adjusted according to effect; a general, but undocumented observation has been that cats require approximately twice the glucocorticoid dosage that dogs require to manage a similar condition. Methylprednisolone acetate may also be administered subcutaneously or intramuscularly at 1.1 mg/kg every 1-3 weeks; however, use of depot products brings the distinct disadvantage that the drug dosage cannot be stopped or reduced. Other long-acting injectable products and their duration include: prednisolone acetate, 1-2 days; dexamethasone in polyethylene glycol, 1-7 days; triamcinolone acetonide, 3-7 days; and betamethasone valerate, 7-60 days. For practical reasons of cost and potency, dexamethasone is the most commonly used glucocorticoid in large animals.

Immunosuppressive therapy

Protracted glucocorticoid use generally is required for immunosuppression. Therefore, use of a corticosteroid with well-documented side effects and efficacy is recommended. It is important to use the highest recommended dosage until clinical signs abate. After that point, the dosage may be decreased in increments. In general, in small animals, the dosage may be decreased until the equivalent prednisolone dosage of 1.1 mg/kg is being given on alternate days.

Long-term side effects of alternate-day therapy are few, and the dosage rarely must be decreased further. Therapy should not be discontinued until the autoimmune disease is in remission for 2-3 months; otherwise, signs are likely to recur. Unlike other immunosuppressants, glucocorticoids do not inhibit significantly antibody production by B-lymphocytes. If glucocorticoids provide incomplete remission of an immune-mediated disorder, other immunosuppressant agents such as the alkylating agent cyclophosphamide may be added to complement the effects of glucocorticoids. Furthermore, if side effects of the glucocorticoids are too great, other immunosuppressants may be added to the regimen. If no clinical response is obtained with glucocorticoid therapy alone, addition of other immunosuppressants is less likely to succeed. Immune-mediated thrombocytopenia and autoimmune hemolytic anemia are examples of diseases treated with immunosuppressive doses of glucocorticoids.

In small animals, immunosuppression is generally accomplished with prednisolone at 2.2-6.6 mg/kg or equipotent dosage dexamethasone at 0.33-1.1 mg/kg q12h for induction, and prednisolone at 1.0-2.2 mg/kg every other day for maintenance. Because its duration of action exceeds 24 hours, dexamethasone is acceptable for induction but not for alternate-day maintenance therapy.

The adverse effects of chronic immunosuppressive doses of glucocorticoid use can be serious. Therefore, clinicians should eventually attempt to maintain a satisfactory therapeutic result with the smallest possible dose of glucocorticoids on alternate days, if possible. Nonsteroidal drugs (e.g. aspirin for inflammation or cyclophosphamide for immunosuppression) may be used as adjunctive therapy, if necessary.

Chronic palliative therapy

Glucocorticoids are commonly used in conjunction with nonsteroidal anti-inflammatory therapy, as in treating such conditions as chronic arthritis in most species or hip dysplasia in dogs. If nonsteroidal analgesics are not satisfactory, glucocorticoids may be used on an intermittent or alternate-day basis. Conversely, when intermittent glucocorticoid therapy alone leads to signs of disease on "off" day(s), nonsteroidal analgesics can be supplemented. It is important not to administer glucocorticoids erratically, as rapid withdrawal may itself precipitate signs of lameness or stiffness.

Alternate-day therapy

Side effects of long-term glucocorticoid use can be dramatically reduced by alternate-day therapy. Allowing the hypothalamic-pituitary-adrenal axis to recover on "off" days provides greater safety if therapy should suddenly be discontinued. Successful use of alternate-day therapy depends upon the therapeutic effects lasting longer than suppressive effects. As a result, this approach is not successful for all diseases. Several common pitfalls of alternate-day therapy should be avoided. Alternate-day therapy is rarely, if ever, effective as primary therapy. It is usually first necessary to use daily therapy to achieve the desired clinical effect. Alternate-day therapy with long-acting glucocorticoids is not rational. Particularly after prolonged high-dosage therapy, rapid change to alternate-day use may result in signs of glucocorticoid withdrawal (see below). It has been shown that administration of greater than 0.5 mg/kg/day of prednisolone or an equipotent dosage of a more potent drug for longer than 2 weeks should be considered chronic therapy. However, in one study, when 0.5 mg/kg q 12h (an anti-inflammatory dosage) was administered to dogs for 35 days and stopped abruptly, it took less than 2 weeks for the HPA axis to totally recover.

Withdrawal from glucocorticoids

The identification of clinical signs of glucocorticoid deficiency may be very difficult. Signs of glucocorticoid withdrawal may include dullness, depression, decreased exercise tolerance, incoordination, unthriftiness and weight loss, loose stools, and behavioral changes. Significant adrenocortical suppression occurs in dogs within 2 weeks of initiating daily glucocorticoid therapy. Therefore, it is reasonable to assume that dogs and cats may require supplementation of glucocorticoids during episodes of stress, such as illness or surgery, particularly with signs of glucocorticoid withdrawal. It should be emphasized that short-term use of glucocorticoids in physiologic amounts has few risks despite the evidence that these "physiological" quantities significantly suppress the HPA axis resulting in adrenal atrophy.

References/suggested reading

- Boothe DM, Mealey KA: Small Animal Clinical Pharmacology and Therapeutics; Glucocorticoids and Mineralocorticoids, 2nd ed., Elsevier, 2012, pp. 1119-1149.
- Ferguson DC, Dirikolu L, Hoenig M, in Riviere JE, Papich MG (eds) Veterinary Pharmacology and Therapeutics; Adrenal Corticosteroids, Mineralocorticoids and Adrenolytic Drugs, 9th ed., Wiley-Blackwell, 2009, pp. 771-802.

Glucocorticoids +/- NSAIDs: Why, Why Not, and Washout

Duncan Ferguson, VMD, PhD, DACVIM, DACVCP
University of Illinois
Urbana, IL

In this presentation, we will review possible answers to the question: Is a “Washout” period between NSAIDs or NSAIDs and glucocorticoids medically justifiable, and documented by good evidence?

About the time that the first “COX2” inhibitor carprofen (Rimadyl™) was being marketed to veterinarians, followed by deracoxib (Derramax™), promotional material published by drug companies has advocated washout times for nonsteroidal anti-inflammatory drugs (NSAIDs). The instructions included: “Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroid use to NSAID use. Only one brand of NSAID should be administered to a dog at any given time. If at some time the owner and the veterinarian decide to try a different NSAID, a wash-out period is recommended. A wash-out period is a few days long, during which the dog does not receive any NSAID. Then the dog can be switched to another NSAID. NSAIDs should not be combined with the use of a corticosteroid, either”(1). In this presentation, we will evaluate the evidence for these statements, and seek to arrive at recommendations that will maximize efficacy for and safety of your patients.

NSAIDS approved in dogs

First generation

- Aspirin –not approved as mono-product, only in combination with a glucocorticoid
- Phenylbutazone - US approval 1974
- Meclofenamic acid - US approval 1996 (no longer marketed)

Second generation

- Carprofen (Rimadyl™) - US approval 1997; Novox (generic))
- Etodolac (Etogesic™) - US approval 1998
- Deracoxib (Deramaxx™) - US Approval 2002
- Meloxicam (Metacam™) - US approval, 2003
- Tepoxalin (Zubrin™) - 2003, removed 2012
- Firocoxib (Previcoxx™) - 2007

Debate point 1

“Washout” was a term introduced by pharmaceutical companies that developed the first veterinary-approved NSAIDs in response to inevitable side effects of this class of drugs. The concept has gained support primarily through discussions on internet sites, FDA-approved labels, and NSAID promotions by sponsors at conferences, without any convincing scientific evidence for support. Looking at the history of the post-marketing period for carprofen (Rimadyl™), As the FDA/CVM began to document side-effects, they requested Pfizer change the Rimadyl™ package insert to list adverse drug reactions. Pfizer complied in May of 1997, only five months after the drug was first introduced. Pfizer also mailed a ‘Dear Doctor’ letter to veterinarians that outlined the latest information available, and subsequently made several additional changes to the Rimadyl™ package insert. (2) Of all the adverse drug effect (ADE) reports the Center of Veterinary Medicine (CMV) received in 1998, 39% or 3626 involved Rimadyl®. The number of ADE reports received by CVM for Rimadyl® was considerably more than that received for any other animal drug. For any one ADE report, there is no absolute certainty that the suspected drug caused the effect. The adverse effects in these reports are consistent with those expected for NSAIDs. They typically involve the gastrointestinal system, renal/urinary system, hematopoietic (blood) system, neurological system, and the liver. Approximately 13% of the 1998 Rimadyl® ADE reports for dogs involved death of the dog, either on their own or by means of euthanasia (3).

Debate counterpoint 1: Adverse effects of NSAIDS can be serious

The concern from owners and veterinarians appeared to prompt another letter to veterinarians from Pfizer in 2000 about Rimadyl™. It pointed out that the incidence of reported possible adverse drug events in 1998 was approximately 0.2%. In addition, it noted, “Some of these side effects, like those of many other NSAID-class medications, may occur without warning and, in rare situations, may be serious, resulting in hospitalization or even death.” It is definitely true that gastrointestinal tract perforation can occur in dogs treated with a selective COX-2 inhibitor. A retrospective study of 29 cases between 2002-2003 in the Novartis Animal Health pharmacovigilance database, evaluated dogs treated with the approved dosage of deracoxib for chronic pain (1-2 mg/kg/day), for acute (post-operative) pain (3-4 mg/kg/day) for a maximum of 7 days. In these cases, 20 dogs died or were euthanatized and 9 survived due to GI perforations. The authors stated that there was an unclear correlation between deracoxib and the induction of GI ulceration. The manuscript discussion went on to state, “Deracoxib should be used at approved dosages and corticosteroids and other NSAIDS should not be administered at close temporal association with deracoxib and possibly with other selective COX-2 inhibitors” (4). While the

recommendation seemed prudent, the study did not specifically evaluate the issue addressed by this summary statement. Nonetheless, veterinarians received a letter from Novartis in 2003, "It should be noted that many of the side effects associated with Deramaxx™ administration occurred in cases in which dogs were also receiving corticosteroids or other NSAIDs....Observe appropriate washout periods when switching from one NSAID to another or when following corticosteroid use with NSAID therapy. The length of the washout period will vary, depending upon the patient's condition and other drugs involved." Following these notes of caution, one study did not find a difference in signs of toxicity when injectable carprofen was followed with either oral carprofen or oral deracoxib. Nonetheless, it was stated in the conclusion to the manuscript: "In general, veterinarians are advised to discontinue an NSAID for 24 hour to 7 days before initiating administration of a second NSAID." (5). While there are reasons to be concerned that the pharmacological effects of NSAIDs will impair normal mucus production, bicarbonate secretion, and maintenance of gastric mucosal blood flow, leading to ulcerogenic conditions in the g.i. tract, there was no evidence that the switchover from one NSAID to another would have additionally detrimental effects.

Point 2: There is no correlation between safety and pharmacokinetic half-lives of NSAIDs

Unapproved NSAIDs such as ibuprofen and indomethacin predictably produce toxicity in dogs even though they have short half-lives. Piroxicam has a long half-life of approximately 40 hours, but has been administered to dogs with relative safety when recommended dosing protocols are used. Among the small animal NSAIDs, half-lives do not correlate with the frequency of administration. Most NSAIDs are given once a day, but half-lives vary widely from 3 hours for deracoxib, to 8 hours for firocoxib and carprofen, and 20 hours for meloxicam. Anti-inflammatory and analgesic effects, and toxic effects, persist longer than the plasma half-lives predict (6,7,8). Indeed, NSAIDs persist longer in inflamed tissues (9). Because the pharmacologic effects may persist longer than predicted by the half-life, is a washout period between treatments warranted?

Point 3: Huge study not supporting a washout time for NSAIDs in dogs

In a study in 2007, "COX-1 sparing" firocoxib was administered to dogs after a wash-out period ranging from 1 day to 5 days. After analysis of 1,000 patients, there was no increased risk from switching from another NSAID to firocoxib within 7 days compared to a longer washout period. The washout time within a 7 day period varied from 0-7 days with most >2 days. Furthermore, there was no observed risk when switching from one NSAID to another within one week, compared to administration of an NSAID without any previous treatment (10).

Counterpoint 3: A COX1/2 inhibitor followed by a selective COX-2 Inhibitor DOES enhance GI risk: Selective inhibition of COX-1 or COX-2 does not result in significant gastric damage. Aspirin, a COX1/2 inhibitor, suppresses PG synthesis and inhibits the synthesis of gastroprotective prostaglandins via both COX-1 and COX-2, thereby impairing mucosal defense mechanisms and leading to hemorrhagic erosion formation. Aspirin triggers the cyclooxygenase-2-dependent synthesis of 15(R)-epi-lipoxin A4 also known as aspirin-triggered lipoxin (ATL), a substance that acts to diminish injury to the stomach. The generation of by COX-2, which partially counteracts the detrimental effects of PG suppression. Inhibition of COX-2 activity by a selective COX-2 inhibitor or a conventional non-steroidal antiinflammatory drug (NSAID) removes the formation of ATL by aspirin. In the absence of the protective effects of ATL, the extent of gastric damage is increased. Therefore, co-administration of aspirin and a selective cyclooxygenase 2 inhibitor results in more gastric damage than that induced following administration of either drug alone (11). There is indirect evidence that ATL develops in the dog: older studies have shown that after 1-2 weeks of aspirin, g.i. lesions resolved despite continued administration. High doses of aspirin may over-ride the process of adaptation. When dogs received aspirin at a high dose of 25 mg/kg every 8 hours, there was no evidence of adaptation as the lesions were as severe or worse on day 28 compared to earlier in the study (15).

Point 4

The evidence is insufficient and conflicting about NSAIDs other than aspirin: In one study, gastrointestinal lesions from administration of deracoxib and carprofen were worse early in the course of treatment (day 2), but improved by day 5. Furthermore, on day 1 of a crossover study, lesions were observed, despite a 16 day washout time designed to allow recovery of the previous crossover in the preceding weeks of the study. The investigators of this study suggested that sequential NSAID administration may exert long-term effects and requires further study (5). In another study, evidence for long-term adverse effects after 2 months of treatment was not observed, and there was evidence of g.i. adaptation (16).

Counterpoint 4: Glucocorticoids and/or then NSAIDs is a bad idea

It has also been recommended that a washout time is necessary between corticosteroid treatment and NSAID administration. These recommendations arise from studies of concurrent treatment with an NSAID and a corticosteroid showing exacerbation of g.i. lesions (17,18). Another study of 2 flunixin dosages (1.1 or 2.2 mg/kg q12h IM) or 1.1 mg/kg flunixin plus prednisone (0.55 mg/kg q12h po) showed gastric mucosal lesions visible via endoscopy within 4 days of initiating therapy in all treated dogs. All the treated dogs had occult blood in their feces by day 5. However, the flunixin+prednisone groups developed the earliest and most severe lesions (5). Another study evaluated healthy dogs treated for 30 days with meloxicam (0.1 mg/kg) and prednisolone (0.5 mg/kg) (MP), ketoprofen

(0.25 mg/kg) and prednisolone (0.5 mg/kg) (KP) compared to normal control (NC) animals. Severe grades of endoscopic lesions and fecal occult blood were observed in the KP group with clinical signs of anorexia, vomiting, diarrhea or melena. The MP group also developed some invasive erosions, but there was no significant difference between the dogs in MP and NC groups. (19). A similar study of simultaneous administration of meloxicam and dexamethasone in healthy dogs. The total endoscopic score of dexamethasone-meloxicam group was significantly greater than the other groups scores. Meloxicam alone seemed safe on GI tract (similar to saline group). Dexamethasone alone causes GI lesions, and the effect was significantly increased with the addition of meloxicam (17). Therefore, even in healthy dogs, concurrent administration of NSAIDs with corticosteroids may be contraindicated, even if the NSAID is a COX-2 selective.

Point 5: Inconsistent and imprudent use of NSAIDs and glucocorticoids

Interestingly, aspirin is not approved as a mono-drug product for dogs. However, a combination of 0.5 mg methylprednisolone/300 mg of aspirin (Cortaba™, Pfizer) has been approved, and used for years. In response to Counterpoint 4, the 0.5 mg/kg per day dexamethasone dosage used in the study above was much higher than a typical anti-inflammatory dose and the NSAID used, and flunixin is inherently ulcerogenic in dogs. A washout time between corticosteroid and NSAID therapy has not been established and it is not known if one is needed when low-dose anti-inflammatory doses of a corticosteroid is administered with an NSAID that has a good safety profile in dogs. A retrospective clinical report described g.i. lesions in dogs associated with administration of deracoxib. Many of the dogs had severe ulceration and had received either a high dose, concurrent treatment with a corticosteroid, or another NSAID in close temporal association with deracoxib (4). However, the NSAID therapy reported in that study was variable and consisted of different drugs and doses, making it difficult to determine whether or not these dogs were predisposed to NSAID-induced injury, or if the NSAID therapy compounded the toxicity from deracoxib.

Point 6: Wean, don't "washout" glucocorticoids

When deciding to remove an animal from glucocorticoids, the HPA suppressive action of glucocorticoids should be remembered: wean, don't "washout" an cold turkey from glucocorticoids, or there is the potential to cause gastrointestinal signs including vomiting, diarrhea and melena due to iatrogenic hypoadrenocorticism.

Recommendations based upon best evidence

If a COX2 inhibiting drug follows a gastroduodenal injury or ulcerogenic NSAID, there may be increased risk of delayed healing and further injury because of the beneficial role of COX-2 in the gastrointestinal mucosa for injury repair and mucosal protection. Most agree that washout following aspirin is a unique situation, due in part to the phenomena of Aspirin Triggered Lipoxin (ATL). The issue of "washing out" between NSAIDs is poorly researched and requires further careful evaluation. Five to seven days washout following aspirin is probably adequate. If adverse effects have occurred such as g.i. ulceration, a minimal washout time should be no less than the time required to recover from those adverse effects. Extra caution seems appropriate when switching between a COX-nonspecific inhibitor or glucocorticoid, and a COX-2 inhibitor. Finally, be sure to consider endocrine effects of glucocorticoids and wean, do not remove precipitously. When serious pain management is needed between NSAIDs, consider other agents: e.g. gabapentin, fentanyl, codeine, or tramadol.

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Future Shock of Antimicrobial Resistance: Is Antibiotic Use in Small-Animal Practice at Risk?

Duncan Ferguson, VMD, PhD, DACVIM, DACVCP
University of Illinois
Urbana, IL

In this interactive luncheon session, we will discuss the facts, the trends and the politics of antimicrobial resistance within human and veterinary medicine, with a specific focus on the likelihood of greater restriction for antimicrobial use in companion non-food animals.

As background to this discussion the participant is encouraged to read any or all of the following publications during the past 7 years. The PubMed ID is provided if the participant would like to review the abstract on PubMed or VIN, or seek the full article.

Also, the website on antimicrobial resistance developed for veterinary students (see also reference 13) may be of interest.

<http://amrls.cvm.msu.edu/>

Suggested reading

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Infectious Disease: An Interactive Clinical Pharmacology Case Discussion

Duncan Ferguson, VMD, PhD, DACVIM, DACVCP
University of Illinois
Urbana, IL

This session will focus on the interactive discussion of cases of infectious disease. The content of this manuscript may be useful to read in advance or following the session as it highlights principles to be used in the case discussions.

Introduction to principles of rational selection of antimicrobials

A veterinarian is often required to make the tentative diagnosis of a bacterial infection, and begin treatment without knowledge of culture results. For first-time infections, full courses of antimicrobial therapy may be prescribed without culture and sensitivity. Habitual use of a “broad spectrum” antimicrobial is to be discouraged. As a result, it is important to weigh all the evidence to make a rational decision for such empirical therapy. Empirical therapy is usually based upon:

1. History and P.E.
2. Clinical suspicion of microbes likely involved
3. Gram stain

Certainly, this is the time to consider whether the severity of the animal’s illness merits an immediate culture and sensitivity (C & S), as previous unsuccessful empirical antimicrobial therapy may lead to resistance, and can occasionally confound interpretation of subsequent C & S results.

Questions to ask before empirical therapy

So, more specific questions the veterinarian might ask before empirical therapy include:

1. What organ system is involved?
2. Is the problem acute or chronic?
3. What pathogen is most likely to be present in that organ system?
4. What antimicrobial is most likely to be effective against that pathogen?

General considerations

General factors to consider about the antimicrobial options include:

1. Antibacterial spectra: Gram- negative, gram -positive, anaerobic, rickettsial, and protozoal efficacy?
2. Bactericidal or bacteriostatic at achieved concentrations?
 - a. Generally -static
 - i. tetracyclines, chloramphenicol, macrolides, lincosamides (lincomycin), sulfonamides, and nitrofurans.
 - b. Generally –cidal
 - i. penicillins, cephalosporins, aminoglycosides, quinolones, polymyxins, and trimethoprim -sulfonamide combinations
3. Mechanism of action: Is there a post-antibiotic effect (PAE)? Are there synergisms or antagonisms with other drugs being used?
4. Limiting toxicities
5. Practicality of administration
6. Availability and cost

Anaerobic therapy

Successful antimicrobial culture and sensitivity is often not possible, so empirical choices are more frequently seen when anaerobes are suspected. Options for anti-anaerobe therapy include:

1. High doses of penicillin - resistance appears to be increasing
2. Chloramphenicol
3. Clindamycin
4. Metronidazole
5. Cefoxitin

Four-quadrant therapy

Serious systemic infections (bacteremia, septicemia, peritonitis) often call for immediate choice of “Four-Quadrant” therapy. The common choices are:

1. Quinolone + amoxicillin
2. Clindamycin + aminoglycoside
3. Beta-lactam + aminoglycoside
4. Penicillins + aminoglycosides
5. Cephalosporins + aminoglycosides+ metronidazole
6. Ticarcillin + carbenicillin and amikacin for resistant *Pseudomonas*

Prophylactic ("anticipatory") therapy

With increasing amounts of antimicrobial resistance developing in higher volume practices, it is worth considering that prophylactic antimicrobial therapy, that is, use of antimicrobials to prevent an infection, is not a rational or evidence-based approach except in certain high-risk patients, like diabetics and other immunosuppressed patients. The empirical use of antimicrobials (e.g. ampicillin) during intravenous or urinary catheterization has been shown to be unnecessary and has likely led to the fact that ampicillin is now only 37% effective against *Staphylococcus* species and only 55% effective against *E. coli*. Indeed, as a response to the increased incidence of multi-drug resistant (MDR) nosocomial infections, some human hospitals and tertiary care veterinary hospitals have found it necessary to resort to committees composed of infectious disease, epizootiology, and clinical pharmacology experts to approve the use of an antimicrobial within the institutional practice.

Guidelines for antimicrobial use according to organ system

The following are guidelines for "first-guess" empirical therapy of infections in selected organ systems. When available, information from culture and sensitivity tests should almost always take precedence.

Circulatory infections: Septicemia, bacteremia

1. Try to identify the original site of infection
2. Positive blood cultures in suspected bacteremia are rare. Culture several times for aerobic and anaerobic organisms timed with rise in temperature if hyperthermic
3. If intestinal trauma, assume a mixed infection with gram-positive, gram-negative, and anaerobic organisms

Common aerobic organisms causing bacteremia

1. *Staphylococcus*
2. *Streptococcus*
3. *Escherichia coli*
4. *Klebsiella*
5. *Enterobacter*
6. *Pseudomonas*

Oropharyngeal, pleuropulmonary, and intra-abdominal infections

1. 25% involve anaerobes: *Bacteroides fragilis* most common
 - a. Rational first-line empirical choice of antimicrobials: Clavulanic acid-amoxicillin or clindamycin
2. For procedures near the alimentary canal: gentamicin and cefazolin, or ceftiofur and cefotetan

Bite wounds and traumatic wounds or abscesses

- *Streptococcus*, *Pasteurella*, penicillinase-producing *Staphylococcus* are most common.
- Rational first-line empirical choice of antimicrobials: Clavulanic acid-amoxicillin
- Other drugs to consider include: oxacillin, dicloxacillin, cephalosporins, tetracyclines, quinolones, and trimethoprim-sulfadiazine/

Lower respiratory tract: Pneumonia

1. No predictable bacterial pathogen in dogs: *E. coli*, *Klebsiella* species, *Pasteurella* spp., *Pseudomonas* species, *Bordetella bronchiseptica*, or *Streptococcus zooepidemicus*
2. In cats, *Bordetella* and *Pasteurella* common
3. 2/3 are gram-negative and may be resistant to commonly used antimicrobials; C & S of transtracheal wash recommended

While waiting for the results, trimethoprim-sulfa, chloramphenicol, or quinolones are also rational choices. If a gram-positive organism is suspected or identified by Gram stain, alpha- and beta-hemolytic *Streptococci*, *Staphylococcus* spp. are common pathogens. Rational first-line empirical choice of antimicrobials include cephalexin, trimethoprim-sulfa, clavulanic acid- amoxicillin, quinolones, amoxicillin, or ampicillin.

Bronchial infections

1. More lipid-soluble drugs, such as chloramphenicol, quinolones, and larger drugs, such as macrolides, may be preferred owing to better tissue penetration
2. When bronchial secretions are severe, gentamicin may be less effective because it penetrates secretions poorly
3. Anaerobes: clindamycin and metronidazole

4. Mycoplasma: clindamycin or a tetracycline

Urinary tract

1. Entire urinary tract is at risk when one region of the tract is infected.
2. Examination of the urine and of a Gram stain is always recommended prior to choosing antimicrobial therapy.
3. Particularly in cats, it is important to distinguish inflammation from infection.
4. ~75% gram-negative: E. coli, Proteus, Klebsiella, Pseudomonas, and Enterobacter
5. ~25% due to beta-hemolytic Streptococcus or Staphylococcus.
6. Two or more organisms may be found in about 20% of cases.
7. In vitro sensitivity of microorganisms translates to >90% treatment success

Therefore, for empirical therapy of UTI's, broad-spectrum antimicrobials are recommended, but greatest consideration should be toward drugs which reach high concentrations in the urine: e.g. aminopenicillins, cephalosporins, and quinolones. For upper UTI infections (e.g. pyelonephritis), the agent should reach high concentrations in serum and, if possible, in urine.

The duration of treatment may require 4-6 weeks to achieve the goal of sterilization of the urine. Also, in some cases, after sterilization of the urine, preventive single evening doses of 50% to 70% of the daily dose of a urinary antiseptic or trimethoprim-sulfa may be required. In the case of pyelonephritis, greater than 6 weeks of therapy with an antimicrobial that has good tissue penetration (e.g., chloramphenicol, trimethoprim, or the fluoroquinolones) may be necessary.

Prostatitis

1. Penetration of most drugs during early inflammation
2. Penetration characteristics of an antimicrobial are critical – e.g. chloramphenicol
3. Chronic prostatitis – entry of basic drugs favored
 - a. Gram positive: chloramphenicol, erythromycin, clindamycin, oleandomycin, quinolones, trimethoprim
 - b. Gram negative: chloramphenicol, trimethoprim-sulfa, quinolones

Pyometra and endometritis

1. C & S should be performed on the uterine contents
2. E. coli infection is observed in most cases
3. Proteus and Streptococcus occasionally are found
4. Chloramphenicol, trimethoprim-sulfa, quinolones

If medically managed, intrauterine infusion of antiseptic or antibiotic solutions is of little value.

Central nervous system

1. High lipid solubility important: chloramphenicol, the sulfas, trimethoprim, metronidazole, and the quinolones
2. Penicillins and cephalosporins may enter an inflamed site during acute infection, but are excluded by blood-brain barrier in chronic conditions.

Pyodermas

The most useful way to consider most dermatological infections is as microabscesses.

1. Superficial: Coagulase-positive, penicillinase-producing Staph
 - a. Consider methicillin-resistant Staph aureus (MRSA)
2. Deep: gram-negative organisms, fungi, and Mycoplasma
3. Most likely to be S. pseudointermedius in small animals rather than S. aureus
4. Relatively predictable susceptibility to β -lactamase resistant antimicrobials agents with a beta-lactamase inhibitor (e.g. Clavamox ®)

Rational first-line empirical choice of antimicrobials: Dicloxacillin, oxacillin, high doses of amoxicillin and clavulanic acid, cephalosporins, erythromycin, lincomycin, trimethoprim-sulfa and the quinolones. Erythromycin and lincomycin should be used only as primary choices, because cross-resistance develops.

Orthopedics

1. Sterile orthopedic surgery, particularly long procedures, generally is considered to be high-risk surgery that merits antimicrobial prophylaxis.
2. With known infections, a culture of the wound or joint fluid is mandatory.
3. Treat for no less than 4-6 weeks.

Osteomyelitis

1. Most commonly involves Staphylococcus, Streptococcus, E. coli, Proteus, or Pseudomonas species.
2. Gram-negative: gentamicin, amikacin, or the quinolones usually are effective.
3. Gram-positive: cephalosporins, clavulanic acid-amoxicillin, and imipenem, a newer beta-lactam
4. For penicillinase-producing Staph: oxacillin and cloxacillin

Highly suggested general references

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Endocrine Disease: An Interactive Clinical Pharmacology Case Discussion

Duncan Ferguson, VMD, PhD, DACVIM, DACVCP
University of Illinois
Urbana, IL

Endocrine therapies

This session will focus on the interactive discussion of endocrine disease cases with a focus on the approach to treatment. As background reading, please review the following summaries of therapies for hyperadrenocorticism, hypothyroidism, hyperthyroidism, and diabetes mellitus.

Therapy for hyperadrenocorticism in dogs and cats: Trilostane vs. lysodren

Although neither therapy is really new, some comparisons between trilostane and o,p'-DDD are worth making. Trilostane (Vetoryl™) has been recently approved in the U.S. after several years of availability in Europe. In Europe, o,p'-DDD was legally displaced because it was not an approved drug for domestic animals. Trilostane is a reversible dose-dependent competitive 11-beta hydroxysteroid dehydrogenase inhibitor resulting in reduced concentrations of glucocorticoids, mineralocorticoids, and androgens. For dogs with PDH or adrenal tumors, a starting dosage of 2.2-6.7 mg/kg PO q 24h is recommended. Following 10-14 days of dosing, it is recommended to conduct an ACTH stimulation test 4-6 hours after the last dose. The target post-ACTH cortisol concentration should be between 20-200 nmol/L (0.7-7 ug/dl). Dosage adjustment should be made based upon clinical signs and test results. Occasionally, better results are obtained by dividing the total daily dosage and administering q12h. Aldosterone deficiency and hyperkalemia can occur, so routine measurement of Na⁺/K⁺ ratios is recommended. As trilostane reduces glucocorticoid production, endogenous ACTH concentrations rise, and further bilateral adrenal gland enlargement in PDH cases has been documented by abdominal ultrasound.

Long the most common medical treatment of adrenal hyperfunction for the dog, o,p'-DDD is a directly adrenotoxic drug which preferentially damages the zonae reticularis and fasciculata. Aldosterone deficiency is observed only when very high dosages are given chronically. In the hands of a clinician having experience with its use, o,p'-DDD may be more predictable, and some consider it to be more effective and even safer. It should be considered the drug of choice for treatment of adrenal tumors. As a cytotoxic drug, anyone administering the drug should wear gloves. Mitotane™ or Lysodren™ when used to treat pituitary-dependent hyperadrenocorticism is dosed at 50 mg/kg per day for 10-14 days (or until signs of hypoadrenocorticism are observed), and then an ACTH stimulation test is performed with the goal of post-ACTH cortisol that is not above the normal range. Once this "loading" period is complete, a maintenance dosage of 50 mg/kg/week usually given in divided doses can be used. Dividing the dosage helps to reduce side effects of hypocortisolism including weakness, inappetence and lethargy. If signs are severe, a replacement dosage of prednisolone (0.1-0.2 mg/kg q24h) or hydrocortisone (0.5-1 mg/kg q12h) can be administered (Ferguson et al, 2009).

Treatment of hypothyroidism

The strategy to manage hypothyroidism still remains to orally administer a version of L-thyroxine (Ferguson, 2009). Very recently, one trade name product (human Levoxy™) was removed from the market for most of the next year. Switching to a generic or another trade name should not be assumed to have identical efficacy in a given patient. Individual oral bioavailability can be quite variable, so when changing from one product to another, it is recommended to monitor patient clinical response and, if necessary, either serum T4 or, preferably, TSH concentrations to confirm the appropriate dosage of the new product.

Therapy for hyperthyroidism in cats

In medical therapy for hyperthyroidism in cats, the thioureyne drug methimazole, given orally and transdermally, has been shown to be effective when properly monitored for maintenance of thyroid hormone lowering effect. Starting doses are commonly 2.5-10 mg depending upon severity of the hyperthyroidism. Twice daily therapy is recommended initially, followed by maintenance q24h therapy that is possible in many cats. The primary side effect, regardless of route of administration are gastrointestinal (inappetence, nausea and vomiting), and often can be minimized by titrating the dose of downward or dividing the daily dose. In cases of drug allergy, often evidenced by facial pruritis, the adverse effect is not dose-dependent, and alternative treatments must be found. Essentially a pro-drug for methimazole, carbimazole, while approved for cats in Europe (Vidalta™, Intervet), is only available at this time as a compounded drug in the U.S. On a mg basis, due to molecular weight differences, the recommended starting dose of carbimazole are generally twice that of methimazole, and q8-q12h frequency (2.5-5 mg/dose) is more common. Pharmacokinetic studies of the controlled-release tablet of Vidalta™ (15 mg) did not produce a pronounced concentration peak and methimazole was present in the circulation for a sustained period, compared with a conventional tablet formulation. The deiodinase inhibitor iopanoic acid has been used at 50 mg/kg q12h, but lowers only T3 concentrations and has not been associated with dramatic improvement. However, it should be considered the only pharmaceutical option if drug allergy to methimazole or carbimazole occurs.

The latest development in the options for therapy of hyperthyroidism is a nutritional one. y/d™ diet by Hills has been evaluated in laboratory cases of hyperthyroidism, and has started to be used clinically. The diet is ultra-low in its iodide content, and should only be used in a cat with a definitive diagnosis of hyperthyroidism. In theory, by depletion of all nutritional sources of iodide,

thyroid hormone synthesis slows down and once the glandular storage is depleted, thyroid hormone levels fall. According to data provided by Hill's Pet Nutrition, about 75% of hyperthyroid cats exclusively eating y/d will have normal serum total T4 concentrations by 4 weeks on the diet. By 8 weeks, 90% of cats have a serum T4 level; by 12 weeks, almost all cats were reported to be within the reference range (Yu et al, 2011). To be effective and not have a rebound effect, this diet must be the only nutritional source for the hyperthyroid cat. Some medications and most treats would contain significant amounts of iodide, leading to the possibility of a relapse. Practical issues arise in multiple cat households, and it certainly cannot be considered appropriate for young, developing, and certainly pregnant cats to be fed a diet highly restricted in iodide. Beyond this general concern for use of the diet as a sole nutritional/medical treatment, the composition of y/d™ is a high-carbohydrate, low-protein diet. Compared to a cat's natural diet, y/d is 2.5 to 5 times higher in carbohydrates and contains only half of the amount of protein normally ingested. On these bases, it has been argued that feeding y/d for long periods is less than an "ideal" diet for an obligate carnivore, especially in hyperthyroid cats with severe muscle wasting or sarcopenia of aging (Peterson ME, 2012).

Diabetes therapies for dogs and cats

Insulin treatment is still the treatment of choice for people with type 1 diabetes. An explosion of New drug developments has been seen for the treatment of type 2 diabetes in humans. In cats, insulin and sulfonylureas are the drugs most frequently used. In dogs, insulin is the treatment of choice.

Insulin

Recombinant and mutated insulin preparations are used for human type 1 diabetes mellitus. In cats, recombinant human protamine zinc insulin (ProZincR, Boehringer-Ingelheim) is now the most commonly used insulin in cats. It is available as a 40 unit/ml preparation. It has recently been shown that this insulin preparation may also be useful in dogs that are poorly controlled using other preparations. Glargine, a mutated human recombinant insulin, has been used in cats and has initially been thought to be preferable to other insulin preparations in that species. However, there is no data to support such notion. Another mutated human recombinant insulin, detemir, has been shown to have similar pharmacodynamic properties to glargine. As is true for all insulin preparations, any animal reacts individually to a given preparation and dose, and there is not one preparation that is effective in all animals. The most important aspect of good glucose control is frequent glucose monitoring by the veterinarian and owner and weight control.

Sulfonylureas

Glipizide is the most frequently used sulfonylurea in cats and is administered orally. In pancreatic beta cells, sulfonylureas inhibit ATP-dependent potassium (K⁺) channels resulting in depolarization and release of insulin. For a sulfonylurea to be effective, it is necessary for beta cells to still have the capacity to release insulin. Therefore, in theory, this drug should only be administered in those cases in which insulin secretion has been documented (with glucose/glucagon stimulation tests, etc.). A recent study showed that transdermal administration of glipizide cannot be recommended because of poor drug absorption. However, it has recently been shown that glipizide accelerates amyloid deposition in cat islets, which confirmed evidence in rats that these drugs may actually be harmful. It is therefore prudent to treat all diabetic cats with insulin at this time until other oral antihypoglycemic agents have been evaluated and shown to be effective.

Thiazolidinediones

Thiazolidinediones or "glitazones" are a class of drugs that activate the transcription factor, peroxisome-proliferator-activated receptor gamma (PPARgamma). It is expressed mainly in adipose tissue where it regulates genes involved in adipocyte differentiation, fatty acid uptake and storage, glucose uptake, and cytokine expression (e.g. adiponectin). Thiazolidinediones increase insulin sensitivity and lower blood glucose because insulin-stimulated glucose uptake in tissues is increased. They also increase the number of small adipocytes. It is thought that they lead to a shift of fatty acids away from liver to subcutaneous adipose tissue. As one researcher stated: Thiazolidinediones keep fat where it belongs (Yki-Järvinen, 2004). Currently 2 PPARgamma agonists are available for use in human patients, rosiglitazone and pioglitazone. Recent pharmacokinetic and pharmacodynamics studies of pioglitazone (Actos®; Takeda) in experimental obese (but not diabetic) cats, suggests that a dosage of 3 mg/kg q24h will increase insulin sensitivity (Clark et al., 2012, 2013).

GLP-1 agonists and DPP-4 inhibitors

Glucagon-like peptide 1 (GLP-1) is an incretin that augments insulin secretion after food intake. It also inhibits glucagon release and gastric emptying. Because of its poor stability, it is not used therapeutically. However, exendin-4 (Extendin; Byetta® (Eli Lilly/Amylin), a synthetic version of a peptide isolated from the saliva of the Gila monster, binds and activates the GLP-1 receptor and is now used therapeutically for the treatment of type 2 human diabetics. In people, it is injected subcutaneously twice daily within 60 min before the morning and evening meal. There are no reports yet of the effective clinical use of this drug in animals. Because the half-life of GLP-1 is very short, a new class of drugs has been developed which inhibits the breakdown of GLP-1, the dipeptidyl peptidase 4 (DPP-4) inhibitors. Their mechanism of action is thought to result from increased incretin levels (GLP-1, and glucose-dependent insulinotropic polypeptide, GIP) leading to increased insulin concentrations. Because GLP-1 augments insulin secretion in a glucose-dependent fashion, these drugs do not lead to hypoglycemia unlike sulfonylureas. Sitagliptine (Januvia®, Merck) and

vildagliptine (Galvus®, Novartis) have been approved for use in human type 2 diabetics. There are no reports of their use in diabetic pets. GLP-1 based therapies have recently been implicated in pancreatic and thyroid cancer.

Amylin analogues

Amylin is a peptide hormone which is cosecreted with insulin from the pancreatic β -cell. It is thought that amylin secretion is low in diabetics. Amylin inhibits glucagon secretion, delays gastric emptying, and acts as a satiety agent, all effects which are beneficial in the treatment of type 2 diabetics. Because amylin exhibits physicochemical properties predisposing the peptide hormone to aggregate and form amyloid fibers, a stable analog, Pramlitide® (Amylin Pharmaceuticals), which has actions and pharmacokinetic and pharmacodynamic properties similar to amylin, has been developed. Pramlitide is given as an injection with each meal. The drug has been effective in decreasing hemoglobin A1c in people; it also has been reported to decrease food intake in human patients. There are no reports of its use in pets.

Sodium-glucose transporter 2 inhibitors

Among the new classes of oral agents currently in clinical development are those that induce renal glucosuria by targeting the renal sodium-glucose transporter 2 (SGLT2). It is well known that glucose is reabsorbed in the proximal tubule of the kidney unless the transport maximum is exceeded. Two glucose transporters (sodium glucose transporter 1 and 2) are involved. In normal circumstances, about 90% of the glucose is taken up by SGLT2, which is confined to the first, or S1, segment of the proximal tubule. SGLT1, which accounts for about 10% of reabsorbed glucose, is found in the distal S2 and S3 segments of the proximal tubule. In theory, SGLT2 inhibitors would lead to decreased reabsorption of glucose in diabetics leading to lowering of blood glucose and increased glucosuria. The increased loss of calories in the urine would also lead to weight loss, a benefit in obese type 2 diabetics. Several drugs are now in phase 3 clinical studies. Potential drawbacks might be electrolyte and fluid abnormalities. This has not been seen in short-term studies (12 weeks).

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Immune-Mediated Disease: An Interactive Clinical Pharmacology Case Discussion

**Duncan Ferguson, VMD, PhD, DACVIM, DACVCP
University of Illinois
Urbana, IL**

Immunosuppression is indicated for allergic conditions (atopic dermatitis or asthma) and for immune-mediated diseases. The optimal strategy is to apply therapy before immunogen exposure and/or during the primary immune response. Anamnestic responses are more difficult to manage. Common problems associated with immunosuppression is the potential for secondary infections

Glucocorticoids

Glucocorticoids are the most commonly used first line immunosuppressants used for managing immune-mediated disorders like autoimmune hemolytic anemia (AIHA), immune mediated thrombocytopenia (ITP), rheumatoid arthritis, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), immune-mediated skin diseases, asthma, etc. This speaker discusses these agents in another presentation and monograph. Glucocorticoids suppress primarily cellular immunity, suppressing the cells associated with the inflammatory response, reducing lymphocyte numbers and activation, and reducing macrophage function. They suppress the function of the reticuloendothelial system (lymph nodes, spleen, Kupffer cells of liver) responsible for removing damaged cells from the circulation. Glucocorticoids in high dosages (1-2 mg/kg q12h) will reduce immunoglobulin concentrations through mechanisms secondary to suppression of immune cell function and number. However such doses also have severe metabolic consequences that complicate treatment in some patients.

Calcineurin inhibitors

Cyclosporine (CsA)

In recent years, in part because of an available veterinary preparation (Atopica®, Novartis), cyclosporine has become the non-glucocorticoid immunosuppressive drug of choice. Cyclosporine acts through binding to a receptor on calcineurin and inhibits T-cell receptor-mediated function via inhibition of the activation of a nuclear transcription factor in T-cells. It suppresses interleukin-2 (IL-2) and inhibits proliferation of activated helper T-lymphocytes. The clinical applications of cyclosporine in the dog have been for managing AIHA, IBD, immune-mediated arthritides, dermatologic conditions including atopy, perianal fistulas and nodular panniculitis. Atopic disease has been treated with dosages of about 5 mg/kg q24h. This dosage has been shown to compare favorably with 0.75 mg/kg of prednisolone for atopic dermatitis. Often the dosing frequency can be reduced to q48h or even q72h, depending upon the response. Perianal fistulas are generally treated at 3 mg/kg q12h. Severe diseases generally require dosages of 10 mg/kg q24-48h. At the higher dosages, therapeutic drug monitoring (TDM) is highly recommended. The goal should be to maintain the trough CsA concentrations above 600 ng/ml. The treatment of some immune-mediated skin diseases such as pemphigus foliaceus has not shown consistent benefit. In the cat, CsA has been used for renal transplantation at a dosage of 3-4 mg/kg q12h with TDM ensuring plasma drug concentrations (see below). For inflammatory skin diseases like eosinophilic granuloma, plasmacytic stomatitis and allergic disease, including asthma, it is common to use 25 mg (~8 mg/kg) q24h because 25 mg is a common dosage form. Optimmune®, as a 0.2% ophthalmic cyclosporine ointment has been employed to effectively manage keratoconjunctivitis sicca (KCS).

CsA formulations

CsA formulations should not be considered to be bioequivalent. Recently, the microemulsion human formulation called Neoral® has shown higher bioavailability (35%) in dogs vs. 20% in Sandimmune® (20%). Bioavailability in cats ranges from 25-30%. The veterinary microemulsion formulation (Atopica®) is the same as Neoral® except there are capsule sizes of 10, 25, 50 and 100 mg. The oral CsA products may not be palatable to cats and can be diluted in olive oil. Some studies have even shown that the intraocular preparation of CsA can achieve plasma concentrations sufficient to suppress lymphocyte activity. For intransigent cats, this route might be more manageable.

Adverse effects

In dogs, vomiting, diarrhea, depression/lethargy, purities, anorexia and increase liver enzymes are most common. Hair loss, gingival hyperplasia and gingivitis can occur. Gastrointestinal signs such as anorexia, vomiting and weight loss are the most common adverse effects in cats. In contrast to humans, nephro- and hepatotoxicities of CsA are not common in dogs and cats. Nephrotoxicity is not common with current formulations. Doses used to treat atopy appear not to increase the risk of secondary infections.

Cyclosporine bioavailability, pharmacokinetics and therapeutic drug monitoring (TDM)

Cyclosporine undergoes significant hepatic metabolism leading to bioactive metabolites. However, the metabolism by cytochrome P450 enzymes and the p-glycoprotein-mediated intestinal efflux tends to reduce the bioavailability of oral preparations. Therefore,

strategies to inhibit these processes have included the co-administration of ketoconazole or grapefruit juice (flavonoids). 5-10 mg/kg q24h of ketoconazole reduces cyclosporine clearance by 85%. Generally, reduction of the maintenance dose by up to 75% has been possible, but the response is highly variable and should be confirmed by therapeutic drug monitoring (TDM).

The primary indication for TDM is to individualize treatment and recognize patient variation in bioavailability. Commonly, samples for peak (2 hours post-dose) and trough (12 hours) are drawn. Seek a laboratory familiar with accurate measurement of CsA in companion animal samples. If single sample TDM is to be used, peak concentrations appear to be more predictive of the area under the curve (drug "exposure") which should predict clinical effects. The 5 mg/kg dosages used to treat atopy generally are not considered high enough to result in significant toxicity, so TDM should be considered when clinical response is inadequate. For higher immunosuppressant dosages, it is recommended to optimize efficacy and minimize toxicity and cost. Depending upon the format of the assay, plasma values will be lower than whole-blood because CsA concentrations in RBCs and leukocytes. In cats, the TDx fluorescence polarization immunoassay overestimates the concentration determined by assays specific to CsA (HPLC or monoclonal immunoassays) by 2-fold. In dogs, the overestimate is about 1.6-fold. Half-life in dogs is from 5-8 hours. When immune-mediated disease is treated with CsA at 12 hour intervals, and a monoclonal antibody/HPLC technique is used to measure CsA, peak concentrations should be 800-1400 ng/ml, and trough levels should not be allowed to fall below 400-600 ng/ml. For renal transplantation, trough concentrations of 750 ng/ml should be achieved for the first month followed by concentrations about half of these levels thereafter. For atopy, the peak concentration should be assayed to evaluate bioavailability but trough concentrations should not fall below 250 ng/ml. For perianal fistulae, trough concentrations from 100-600 ng/ml are recommended. CsA interacts with many other drugs via pharmacokinetic and pharmacodynamics mechanisms. When monitoring CsA with co-administration of ketoconazole, both peak and trough samples should be measured because the half-life has been documented to be 12 hours to 6 days during co-administration and achievement of a new steady-state might be quite delayed (1 month) rather than several days in most dogs not on ketoconazole.

Tacrolimus

Approved only for human use as Prograf®, tacrolimus works by the same mechanism as cyclosporine. A topical version of the drug (Protopic®) has been used to treat canine dermatoses. Related drug pimecrolimus is a 1% topical cream (Elidel®). Sirolimus (Rapamycin®) has been tried in dogs but resulted in severe gastrointestinal necrosis and inflammation.

Antiproliferative-antimetabolic drugs

Cyclophosphamide

An alkylating agent, cyclophosphamide (Cytoxan®) is a potent immunosuppressive because it alters the structure of DNA of lymphocytes (and other rapidly dividing cells). It suppresses both T and B cells, but B cells are more affected because they recover more slowly from the effects of the drug. Therefore, this drug is a useful immunosuppressive agent for autoimmune conditions like AIHA with high titers of circulating immunoglobulins against red blood cells or platelets. Because of its relatively nonspecific effect, cyclophosphamide causes bone marrow suppression and associated neutropenia, thrombocytopenia and anemia. Gastrointestinal side effects, such as vomiting and diarrhea, are also common. Clinicians should monitor for secondary infections. Metabolites of cyclophosphamide, in particular, acrolein, can cause sterile cystitis, particularly when it is administered intravenously. The most common strategy to reduce this side effect is the co-administration of the loop diuretic furosemide to induce diuresis.

Dosing (dogs): 50 mg/m² q48h or 50 mg/m² q24h for 4 days/week.

Dosing (cats): 6.25-12.5 mg q24h for 4 days/week

When immunosuppressive regimens with cyclophosphamide and glucocorticoids were compared with glucocorticoids alone, the alkylating agent showed no additional benefit, and appeared to lead to greater bone marrow suppression and anemia.

Chlorambucil

This alkylating agent has been primarily used for immune-mediated disease in cats. Compared to cyclophosphamide, bone marrow suppression is not as severe.

Dosing (dogs): 2-6 mg/m² q24h then q48h during remission

Dosing (cats): 0.1 mg-0.2 mg/kg q24h po then q48h during remission

Azathioprine

Azathioprine (Imuran®) is metabolized to 6-mercaptopurine which leads to 6-thioguanine which is cytotoxic. It interferes with lymphocyte proliferation. Purines are crucial for division of activated lymphocytes. Clinical applications include treatment of autoimmune skin disease, AIHA, IBD and other immune-mediated diseases. Bone marrow suppression is significant and the CBC should be monitored. GI side effects and hepatic damage, usually within 1 month of initiating therapy.

Dosing (dogs): 2 mg/kg q24h po; chronically 0.5-1 mg/kg q48h with prednisolone on alternate days

Dosing (cats): 0.3 mg/kg q24h-48h po

Mycophenolate

This drug inhibits inosine monophosphate dehydrogenase, which is crucial for purine synthesis in lymphocytes. The result is suppression of both T and B cells. Therefore, lymphocyte proliferation is inhibited and antibody production by B cells reduced.

Clinical use has included treatment of pemphigus foliaceus at a dosage of 22-39 mg/kg/day x 3 treatments. When used chronically at 30 mg/kg q12h in dogs, diarrhea, anorexia and weight loss occurred.

Leflunomide

Leflunomide is a recently approved inhibitor of the enzyme dihydroorotate dehydrogenase, an essential for pyrimidine synthesis. Like mycophenolate, it inhibits both T and B cell proliferation. Used at a dosage of 2-4 mg/kg q24h, it has been used to treat autoimmune disorders in the dog, including polyarthritis. Side effects include leukopenia, thrombocytopenia and gastrointestinal ulceration.

Recommended reading

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CPR: Why it's Worth it

**Daniel Fletcher, PhD, DVM, DACVECC
Cornell University
Ithaca, NY**

Veterinary protocols for cardiopulmonary resuscitation (CPR) have been largely adapted from those promoted by the American Heart Association for people. The Reassessment Campaign on Veterinary Resuscitation (RECOVER) recently completed a systematic review of the literature relevant to veterinary CPR and developed the first evidence-based, consensus CPR guidelines for small animals (<http://www.acvecc-recover.org>). This web site contains thorough worksheets documenting the literature supporting the recommendations contained in this document. A complete overview of the methods used, the evidence base upon which the clinical guidelines are based, and a complete description of all of the clinical guidelines are available in the June 2012 special issue of the Journal of Veterinary Emergency and Critical Care.¹ A summary of the consensus guidelines is presented here.

Basic life support (BLS)²

Basic Life Support (BLS) should be initiated as quickly as possible following diagnosis of CPA using the Circulation, Airway, Breathing (CAB) concept. Circulation should be addressed first, as ventilation will be ineffective if there is no cardiac output, and evidence suggests that outcome worsens as delay to the initiation of chest compressions increases.

Circulation - chest compressions

Patients with CPA have no forward blood flow out of the heart and no delivery of oxygen to the tissues. An immediate consequence is the exhaustion of cellular energy stores, cell depolarization and thus loss of organ function. This quickly results in increasing severity of ischemic organ injury and sets the stage for escalating reperfusion injury upon reinstatement of tissue blood flow. The initial goals of chest compressions are to provide (1) pulmonary blood flow for oxygen uptake and CO₂ elimination, and (2) tissue perfusion for oxygen delivery to restore cellular metabolic activity. Experimental evidence suggests that even well-executed external chest compressions produce at best 30% of normal cardiac output, making proper technique critical. Chest compressions should be started as soon as possible after diagnosis or suspicion of CPA. Delay in the start of high quality chest compressions reduces the likelihood of return of spontaneous circulation (ROSC).

Chest compressions should be done with the dog or cat in lateral recumbency with a compression depth of 1/3-1/2 the width of the chest at a rate of 100-120 compressions per minute regardless of size or species. Use of aids to ensure correct compression rate, such as a metronome or a song with the correct tempo (e.g., "Staying Alive") is recommended. Leaning on the chest between compressions must be avoided to allow full elastic recoil. Chest compressions should be delivered without interruption in cycles of 2 minutes, and a new compressor should take over after each cycle to reduce the effect of rescuer fatigue. Any interruption in compressions should be as short as possible, as it takes approximately 60 seconds of continuous chest compressions before coronary perfusion pressure (CPP) reaches its maximum. CPP in turn is a critical determinant of myocardial blood flow and the likelihood of ROSC.

The physiology of blood flow generation is fundamentally different during CPR compared to spontaneous circulation. Two distinct theories exist to explain how chest compressions lead to systemic blood flow. The cardiac pump theory is based on the concept that the left and right ventricles are directly compressed, increasing the pressure in the ventricles, opening the pulmonic and aortic valves and providing blood flow to the lungs and the tissues respectively. Recoil of the chest between compressions due to the elastic properties of the rib cage creates negative pressure within the chest, improving filling of the ventricles before the next compression. The thoracic pump theory is based on the concept that external chest compressions raise overall intrathoracic pressure, forcing blood from intrathoracic vessels into the systemic circulation, with the heart acting as a passive conduit.

Given the chest wall stiffness in medium and large dogs, blood flow generated by the thoracic pump mechanism likely predominates in these patients. Therefore, it is recommended that the chest be compressed over the highest point on the lateral thoracic wall with the patient in lateral recumbency (i.e., the widest part of the chest). In contrast, in very keel chested dogs (e.g., Doberman Pinschers, sight hounds), it is reasonable to do chest compressions directly over the heart as the cardiac pump mechanism likely predominates. In markedly barrel chested dogs (e.g., English Bulldogs), compressions over the sternum with the patient in dorsal recumbency may be more effective in eliciting the thoracic pump mechanism than lateral chest compressions. In these and other large dogs with low chest compliance, considerable compression force is necessary for CPR to be effective. The compressor should maintain locked elbows with one hand on top of the other, and the shoulders should be directly above the hands. This allows compressions to be done using the core muscles rather than the biceps and triceps, reducing fatigue and maintaining optimal compression force. If the patient is on a table and the elbows cannot be locked, a stool should be used or the patient should be placed on the floor.

Most cats and small dogs tend to have higher thoracic compliance and narrower chests than larger dogs, making the cardiac pump mechanism achievable in these patients; therefore, chest compressions should be done directly over the heart. Compressions may be

performed using the same two-handed technique as described above for large dogs, or may be done using a single-handed technique where the compressing hand is wrapped around the sternum and compressions are achieved from both sides of the chest by squeezing. Circumferential compressions of the chest using both hands may also be considered.

Airway and breathing – ventilation

If an endotracheal tube and laryngoscope are available, the patient should be intubated as soon as possible. Both dogs and cats can be intubated in lateral recumbency, so chest compressions should continue during endotracheal tube placement. If an endotracheal tube is not readily available, mouth to snout ventilation will provide improved oxygenation and CO₂ removal. The patient's mouth should be held closed firmly with one hand. The neck is extended to align the snout with the spine, opening the airway as completely as possible. The rescuer makes a seal over the patient's nares with his/her mouth and blows firmly into the nares to inflate the chest. The chest should be visually inspected during the procedure and the breath continued until a normal chest excursion is accomplished. An inspiratory time of approximately 1 second should be targeted.

In non-intubated patients ventilated using the mouth to snout technique, ventilation cannot be performed simultaneously with chest compressions. Therefore, 30 chest compressions should be delivered, immediately followed by two breaths. Alternating compressions and ventilations should be continued for 2-minute cycles, and the rescuers rotated every cycle to prevent fatigue. Chest compressions and ventilations should be performed simultaneously in intubated patients because the inflated cuff of the endotracheal tube allows alveolar ventilation during a chest compression and interruptions in chest compressions are minimized. Intubated patients should be ventilated at a rate of 10 breaths per minute with an inspiratory time of approximately 1 second. If a spirometer is available, a tidal volume of approximately 10 ml/kg should be targeted. This low minute ventilation is adequate during CPR since pulmonary blood flow is reduced. Care should be taken not to hyperventilate the patient, as low arterial CO₂ tension leads to cerebral vasoconstriction, decreasing oxygen delivery to the brain.

Advanced life support (ALS)^{3,4}

Once BLS procedures have been implemented, the CPR team should initiate Advanced Life Support (ALS), which includes monitoring, drug therapy, and electrical defibrillation. Drug therapy is preferably administered by the intravenous or intraosseous route. Therefore, placement of a peripheral or central intravenous or intraosseous catheter is recommended, but should not interfere with continuation of BLS.

Monitoring

Many commonly employed monitoring devices are of limited use during CPR due to their susceptibility to motion artifact and the likelihood that decreased perfusion will compromise accurate readings. Low yield monitoring devices include pulse oximeter and indirect blood pressure monitors, including Doppler and oscillometric devices. The two most useful monitoring devices during CPR are the electrocardiogram (ECG) and end tidal CO₂ monitor (ETCO₂).

Although the ECG is highly susceptible to motion artifact and is of limited use during ongoing chest compressions, an accurate rhythm diagnosis is essential to guide drug and defibrillation therapy. The goal of ECG monitoring during CPR is to diagnose which of the three most common arrest rhythms are present: (1) asystole, (2) pulseless electrical activity (PEA), or (3) ventricular fibrillation (VF). The ECG should be quickly evaluated while compressors are being rotated between 2-minute cycles of CPR, the rhythm diagnosis should be called out to the group by the team leader, and differing opinions on the diagnosis should be solicited. Discussion about the rhythm diagnosis should not prevent rapid resumption of chest compressions.

ETCO₂ data can be used in multiple ways during CPR, and regardless of the technology used is highly resistant to motion artifact. The presence of measureable CO₂ by ETCO₂ monitoring is supportive of (but not definitive for) correct placement of the endotracheal (ET) tube. Because ETCO₂ is proportional to pulmonary blood flow, it can also be used as a measure of chest compression efficacy under conditions of constant quality of ventilation. Upon return of spontaneous circulation (ROSC), ETCO₂ dramatically increases due to the rapid increase in circulation, and therefore is a valuable early indicator of ROSC during CPR.

Drug therapy

Depending on the arrest rhythm, the use of vasopressors, parasympatholytics, and/or anti-arrhythmics may be indicated in dogs and cats with CPA. In addition, in some cases the use of reversal agents, intravenous fluids, and alkalinizing drugs may be indicated. Strict adherence to evidence-based CPR algorithms is recommended to increase the quality of CPR, the likelihood of ROSC and the chance of survival to hospital discharge.

Regardless of the arrest rhythm vasopressors are recommended to increase peripheral vasoconstriction. Because cardiac output is low even during optimal external chest compressions, shunting of blood away from the periphery and towards the core (e.g., the heart, lungs, and brain) is essential to maintain perfusion to these vital organs. Epinephrine causes peripheral vasoconstriction via stimulation of α_1 receptors. It is a nonspecific catecholamine that also acts on β_1 and β_2 receptors, but the α_1 effects have been shown to be the most beneficial during CPR. Initially low doses (0.01 mg/kg IV/IO every other cycle of CPR) are recommended, but after prolonged CPR, a higher dose (0.1 mg/kg IV/IO every other cycle of CPR) may be considered. Epinephrine may also be administered via ET tube (0.02 mg/kg low dose; 0.2 mg/kg high dose) by feeding a long catheter through the ET tube and diluting the epinephrine 1:1 with isotonic saline.

Vasopressin is an alternative vasopressor that exerts its vasoconstrictive effects via activation of peripheral V1 receptors. It may be used interchangeably with epinephrine during CPR at a dose of 0.8 U/kg IV/IO every other cycle of CPR. Potential benefits of vasopressin include continued efficacy in acidic environments in which α_1 receptors may become unresponsive to epinephrine and lack of β_1 effects (positive inotropy and positive chronotropy), which may cause increased myocardial oxygen consumption and worsened myocardial ischemia upon ROSC. Vasopressin may be administered via ET tube using the technique described above.

Atropine is an anti-cholinergic, parasympatholytic drug that has been extensively studied in CPR. Although only a few studies have shown a beneficial effect, there is limited evidence of a detrimental effect, and atropine at a dose of 0.04 mg/kg IV/IO may be considered during CPR in dogs and cats, and is reasonable in all dogs and cats with asystole or PEA associated with increased vagal tone. Atropine may also be administered via ET tube (0.08 mg/kg).

Although non-perfusing VF/ventricular tachycardia (VT) should be treated as early as possible with electrical defibrillation, patients with VF refractory to defibrillation may benefit from treatment with amiodarone at a dose of 2.5-5 mg/kg IV/IO. This drug has been associated with anaphylactic reactions and hypotension in dogs, so patients should be closely monitored for signs of peripheral vasodilation, wheals, or hives once ROSC is achieved. Treatment with diphenhydramine (2 mg/kg IM) and/or anti-inflammatory corticosteroids (0.1 mg/kg dexamethasone sodium phosphate IV) is warranted should these signs be noted.

If amiodarone is not available, patients with VF refractory to electrical defibrillation may benefit from lidocaine 2 mg/kg slow IV/IO push. Although this drug has been shown to increase the defibrillation threshold in dogs in one study, benefit was evident in others.

Although specific evidence of efficacy is not available, the use of reversal agents in dogs and cats in which reversible anesthetic/analgesic drugs were recently administered may be considered. Naloxone (0.01 mg/kg IV/IO) may be used to reverse opioids, flumazenil (0.01 mg/kg IV/IO) for benzodiazepines, and atipamezole (0.1 mg/kg IV/IO) or yohimbine (0.1 mg/kg IV/IO) for α_2 agonists.

The routine use of IV fluids in euvolemic or hypervolemic patients are not recommended during CPR, but is reasonable in patients with documented or suspected hypovolemia. In euvolemic or hypervolemic patients, fluids administered IV serve solely to increase right atrial pressure, which results in decreased perfusion of the brain and heart and should be avoided. However, in hypovolemic patients, IV fluids will help to restore adequate circulating volume, and will increase the efficacy of chest compressions and improve perfusion.

The routine use of high-dose corticosteroids during CPR in dogs and cats is not recommended. Although one retrospective study showed an association between administration of corticosteroids and increased rate of ROSC in dogs and cats, the type and dose of steroids administered were highly variable and the study design did not allow determination of a cause and effect relationship (Hofmeister et al, 2009). Other studies have shown no benefit or harm from the use of steroids during CPR. Non-CPR studies have demonstrated that single high doses of corticosteroids in dogs frequently lead to gastrointestinal ulceration and bleeding, which could also cause other ill effects such as bacterial translocation. In addition, corticosteroids suppress the immune system and reduce prostaglandin production in the kidney, a primary mechanism employed by the kidney to maintain perfusion in the face of hypotension. Because the documented risks of high-dose steroids far outweigh the potential benefit shown in one study, the use of steroids is not recommended in patients with CPA.

In patients with prolonged CPA of greater than 10-15 minutes, alkalization therapy with administration of sodium bicarbonate (1 mEq/kg, once, diluted IV) may be considered. Prolonged CPA commonly leads to severe acidemia resulting from both metabolic acidosis, due to lactate and uremic acids, and venous respiratory acidosis due to inadequate peripheral perfusion and accumulation of CO₂. This acidemia can cause severe vasodilation and inhibition of normal enzymatic and metabolic activity. Because these issues may be rapidly resolved once ROSC is achieved, bicarbonate therapy should be reserved for patients with prolonged CPA and with documented severe acidemia (pH < 7.0) that are not hypoventilating.

Electrical defibrillation

Early electrical defibrillation in patients with ventricular fibrillation (VF) has been associated with increased ROSC and survival to discharge in numerous studies, and is superior to anti-arrhythmic medical therapy. The goal of defibrillation is to stop the ventricular myocardial cells from contracting by driving them all simultaneously into a refractory period, allowing the pacemakers to take over and drive coordinated contractions of the heart. If the duration of VF is known or suspected to be of duration of 4 minutes or less, chest compressions should be continued until the defibrillator is charged and the patient should then be defibrillated immediately. If the duration of VF is known or suspected to be more than 4 minutes, one full cycle of CPR should be done before defibrillating to allow the myocardial cells to generate enough energy substrate to restore a normal membrane potential, thereby increasing the likelihood of success.

Defibrillators may be either monophasic (delivering a current in one direction across the paddles) or biphasic (delivering a current in one direction, the reversing and delivering a current in the opposite direction). The use of biphasic defibrillators is recommended over monophasic defibrillators because a lower current (and hence less myocardial injury) is required to successfully defibrillate the

patient. For monophasic defibrillators, an initial dose of 4-6 J/kg should be used, while biphasic defibrillation should start at 2-4 J/kg. The second dose may be increased by 50%, but subsequent doses should not be further increased.

After defibrillation, chest compressions should be resumed immediately and a full 2-minute cycle of CPR administered before reassessing the ECG and determining if the patient is still in VF and should be defibrillated again. Brief assessment of the ECG immediately after defibrillation to determine if a perfusing rhythm has resulted is reasonable, but should minimally delay resumption of chest compressions.

Prognosis

There is limited data in the veterinary literature regarding prognosis for patients receiving CPR after cardiopulmonary arrest. Although overall survival rates have been reported to be quite low, the underlying cause of the arrest may contribute significantly. Patients that experience CPA as a consequence of severe, untreatable or progressive chronic diseases are less likely to experience good outcomes. However, peri-anesthetic CPA carries a better prognosis for survival to discharge (as high as 47% in one recent retrospective veterinary study), and aggressive, prolonged CPR attempts in these cases are reasonable. Adherence to these evidence-based CPR guidelines may help improve survival in these cases.

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Stabilizing the Shocky Patient

Daniel Fletcher, PhD, DVM, DACVECC
Cornell University
Ithaca, NY

Pathophysiology

Shock is most broadly defined as a widespread failure of ATP production at the cellular level. Although many categorization schemes for shock have been developed, this lecture will focus on 4 broad categories of shock: (1) hypovolemic, (2) distributive, (3) cardiogenic, and (4) other. The first 3 types of shock are the most commonly encountered in veterinary practice, and result from an acute, severe decrease in oxygen delivery to tissues. The last type of shock results from cellular dysfunction leading to decreased ATP production in the face of adequate delivery of oxygen and is rarely encountered in veterinary medicine.

The severity and type of clinical signs seen in patients with shock varies with the duration of the condition. In the early stages, compensatory mechanisms are triggered, largely by catecholamine release and activation of neurohumoral responses such as the renin-angiotensin-aldosterone system (RAAS). In this stage, patients are relatively stable, but tachycardia may be noted. In the middle stages of shock, compensatory mechanisms begin to fail, leading to decreased oxygen delivery to the tissues. However, oxygen delivery to vital organs such as the heart and brain and maintained at the expense of other tissues such as the GI tract and skeletal muscle. In the final stages, full decompensation occurs and patients commonly develop refractory hypotension, peripheral vasodilation, and bradycardia. The goal of the emergency veterinarian is to identify signs of shock as early as possible, determine the type of shock present, and institute therapy targeted at the underlying cause to stabilize the patient and avoid progression to the late stages, which are associated with high mortality.

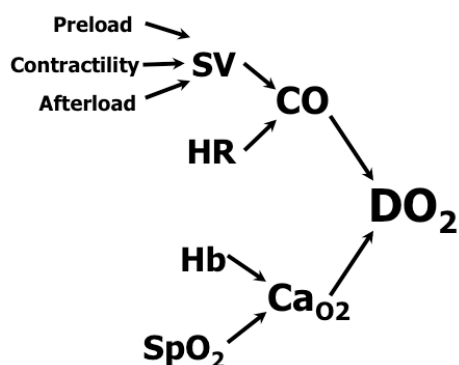


Figure 1: DO_2 = oxygen delivery, CO =cardiac output, Ca_{O_2} =arterial oxygen content, SV =stroke volume, HR =heart rate, Hb =hemoglobin concentration, S_pO_2 =arterial oxygen saturation

Because most types of shock are caused by inadequate oxygen delivery (DO_2) to the tissues, when contemplating therapeutic options for patients in shock, it is important to consider all of the determinants of DO_2 . These are depicted graphically in Figure 1.

The two main determinants of DO_2 are cardiac output (CO) and arterial oxygen content (Ca_{O_2}). CO is the product of stroke volume (SV), the volume of blood pumped out of the ventricle with each contraction, and heart rate (HR), the number of times the ventricle contracts each minute. The SV is dependent upon 3 additional factors: (1) preload, defined as the amount of blood in the left ventricle at the end of diastole (i.e., the maximal filling of the ventricle before contraction), (2) contractility, or the strength of contraction of the ventricle, and (3) afterload, which is the amount of resistance to blood flow out of the aorta, predominantly determined by the tone of the peripheral vasculature (systemic vascular resistance).

Arterial oxygen content is the amount of oxygen carried by the arterial blood, and is usually reported as the milliliters of oxygen carried in 100ml of arterial blood. Because the vast majority (generally greater than 99%) of the oxygen in

the arterial blood is carried bound to hemoglobin, the concentration of hemoglobin in the blood (Hb), is a major determinant of Ca_{O_2} . The other major contributor is the percent of the hemoglobin that is saturated with oxygen (SpO_2 or SaO_2).

Decreases in DO_2 can be caused by deficits in any of these parameters. It is the job of the emergency clinician to rapidly assess and treat these deficits. Deficits in DO_2 can be challenging to identify. When DO_2 drops below a critical point, anaerobic metabolism occurs and lactate production can overwhelm the ability of the liver to metabolize it, leading to a lactic acidosis. A more sensitive measure of adequacy of oxygen delivery is mixed venous oxygen saturation (S_vO_2), which is the saturation of the hemoglobin in blood obtained from the pulmonary artery, a mixture of all of the blood that has circulated through the entire body. When DO_2 is low, the fraction of oxygen carried in the arterial blood that is extracted for metabolic processes increases due to the relative deficit in delivery, and the S_vO_2 drops. In numerous clinical and experimental models, this parameter has proven to be a sensitive indicator of inadequate DO_2 . Due to the technical challenges associated with pulmonary artery catheterization, a surrogate measure, central venous oxygen saturation ($S_{cv}O_2$) has been used commonly in human and veterinary medicine. These samples must be obtained from a central vein (the cranial vena cava via a jugular catheter or the caudal vena cava via a hind leg PICC line). Any patient in which $S_{cv}O_2 < 70\%$ should be considered at risk of inadequate oxygen delivery, and the clinician should closely evaluate each of the parameters contributing to DO_2 in the patient to determine if any should be treated.

Diagnosis and treatment

Because optimal treatment varies among the different types of shock encountered in clinical practice, once a patient is diagnosed with shock, rapid identification of the type of shock is crucial for optimal care. The sections below review the clinical signs associated with each type of shock as well as treatment strategies.

Hypovolemic shock

Hypovolemic shock results from a large, sudden decrease in intravascular fluid volume. This can be due to hemorrhage, third spacing, or loss of fluid through the gastrointestinal or urinary tracts. When less than 20% of intravascular volume is lost, patients can generally compensate and show minimal clinical signs. Between 20-40% loss results in moderate shock, and losses of greater than 40% result in severe shock. Clinical signs include weakness, depression, and cold extremities, while on physical exam, patients commonly have pale oral mucous membranes, prolonged capillary refill times (CRT), weak peripheral pulses, and tachycardia.

Most commonly, patients with hypovolemic shock are suffering from deficits in preload (i.e., intravascular volume) and, in the case of acute hemorrhage, decreases in hemoglobin and hence oxygen carrying capacity. Treatment for this type of shock includes intravascular volume replacement (boluses of isotonic crystalloids, hypertonic crystalloids, or synthetic colloids) and/or administration of red blood cells. Options and doses for initial fluid resuscitation are listed in Table 1 below. Isotonic crystalloid solutions (e.g., Normosol-R, Plasmalyte-A, Lactated Ringer's Solution, or 0.9% Sodium Chloride) at initial doses of 20-30 ml/kg over 15 minutes are generally safe and effective. Patients with hypoproteinemia may benefit from synthetic colloid resuscitation (e.g., Hetastarch, Pentastarch) at a dose of 5-10 ml/kg over 15 minutes. In patients with concurrent head trauma, 7% hypertonic saline (4 ml/kg in dogs, 2 ml/kg in cats over 15 minutes) is a good choice as it provides volume resuscitation, reduces cerebral edema via its hyperosmolality, and has positive chronotropic effects. Dehydrated patients (as evidenced by poor skin turgor, dry mucous membranes and eyes on physical exam) should receive isotonic crystalloids initially, as the volume expansion effects of synthetic colloids and hypertonic solutions are dependent upon adequate extravascular water.

Patients with anemia due to blood loss may require blood transfusions. There is no specific "transfusion trigger" PCV in these cases, and the decision to transfuse should be made based upon clinical assessment. In patients that remain tachycardic, tachypneic, and/or hypotensive despite fluid resuscitation and that are anemic, blood transfusion should be considered. In addition, transfusion should be considered in anemic patients with central venous catheters with $S_{cv}O_2 < 70\%$ despite adequate fluid resuscitation. Transfusion of 1 ml/kg of packed red blood cells will raise the PCV by 1%; therefore, packed cells should be transfused at a dose of 10-15 ml/kg to ensure a clinically relevant increase in PCV. When transfusing whole blood, 20-30 ml/kg should be considered, as it takes 2 ml/kg of whole blood to raise the PCV by 1%.

Resuscitation should continue until the patient no longer has clinical signs consistent with shock. Pink oral mucous membranes, a CRT of < 2 sec, normal pulse quality, MAP > 80 mmHg, and $S_{cv}O_2 > 70\%$ are all good clinical resuscitation endpoints.

Distributive shock

Distributive shock results from derangements in vascular tone, with some beds inappropriately vasodilated and others inappropriately vasoconstricted. This can result in microcirculatory dysfunction including sludging of blood, platelet and coagulation activation, and ultimately microvascular thrombosis and tissue ischemia. Common diseases that may lead to distributive shock include sepsis and the systemic inflammatory response syndrome (SIRS), allergic/anaphylactic reactions, trauma, and neurologic disease. Clinical signs of early distributive shock include hyperemic mucous membranes, a fast CRT (< 1.5 sec), tachycardia and bounding pulses.

Most commonly, patients with distributive shock are primarily suffering from alterations in afterload (systemic vascular resistance) due to peripheral vasodilation. In the short term, these patients are commonly treated with intravascular volume replacement (isotonic crystalloid or colloid boluses, as described above for hypovolemic shock) because they are effectively hypovolemic due to their loss of intravascular volume. In addition, many of the causes of distributive shock lead to concurrent hypovolemia, making volume replacement even more crucial. Some patients may also require administration of vasoconstrictors to increase peripheral vascular tone and to redirect blood to the core organs (the heart and brain). Vasoconstrictors act via $\alpha 1$ stimulation (norepinephrine and dopamine) or V1 receptor agonism (vasopressin). Doses for commonly used vasoconstrictors are included in the table below.

Vasoconstrictors are only indicated in patients with evidence of persistent vasodilation in the face of adequate volume resuscitation. In patients with evidence of peripheral vasoconstriction (pale oral mucous membranes, prolonged CRT), these drugs should be avoided, as they are unlikely to be effective. In patients with adequate volume resuscitation and evidence of continued poor perfusion with peripheral vasoconstriction and poor pulses/low blood pressure, positive inotropes, such as dobutamine, should be considered, as these patients are likely suffering from poor cardiac contractility. See the table below for dosing recommendations for dobutamine.

Cardiogenic shock

Decreases in cardiac output (CO) in patients with cardiogenic shock lead to reduced perfusion to organs, including the heart. This cycle of myocardial ischemia leading to reduced CO, resulting in worsening myocardial ischemia can ultimately lead to myocardial

failure and death. In the early stages of forward failure, two major compensatory mechanisms to restore CO are initiated. Reductions in arterial blood pressure due to decreased CO result in activation of baroreceptors in the aorta and carotid arteries, leading to release of catecholamines such as epinephrine and norepinephrine from the adrenal medulla. These catecholamines cause peripheral vasoconstriction via α_1 receptor stimulation, diverting the reduced CO away from the periphery and towards the core, as well as increases in cardiac contractility and heart rate via β_1 stimulation, restoring a more normal CO. The second compensatory mechanism employed in the patient with decreased CO is activation of the renin-angiotensin-aldosterone system (RAAS). Glomerular filtration rate (GFR) is reduced in patients with decreased CO. This results in decreased delivery of sodium and chloride to the distal convoluted tubule (DCT), which is sensed by the juxtaglomerular apparatus (JGA). In response, the JGA secretes renin, which cleaves angiotensinogen (Ag) to angiotensin-I (AT-I). AT-I is then cleaved to angiotensin-II (AT-II) by angiotensin converting enzyme (ACE) in the lungs. AT-II has many effects, including stimulation of aldosterone release causing retention of water and increasing preload to the heart, peripheral vasoconstriction leading to increased perfusion of the kidneys and other core organs, and constriction of the efferent and afferent arterioles (but a greater effect on efferent) resulting in an increased pressure drop across the glomerulus and increased GFR.

These compensatory mechanisms initially act to protect the heart (and the kidney) from decreased perfusion by improving CO through increases in heart rate, cardiac contractility, and preload, and by increasing peripheral vascular tone, redirecting blood to the core. However, eventually these compensatory mechanisms contribute to the disease process, resulting in congestive heart failure.

The classic clinical signs associated with cardiogenic shock include pale oral mucous membranes and prolonged capillary refill time (due to peripheral vasoconstriction), tachycardia (due to high sympathetic tone), and poor pulses (due to poor CO). In addition, hypothermia, mental dullness and muscle weakness may be noted. Unfortunately, these signs are also found with hypovolemic shock, so it is important to look for additional signs consistent with underlying heart disease, such as a heart murmur, gallop rhythm (in cats), jugular distention, arrhythmias, respiratory distress, and pulmonary crackles. Definitive diagnosis of cardiogenic shock and/or CHF requires imaging (thoracic radiographs, echocardiogram, or both). However, patients presenting in cardiogenic shock are rarely stable enough for these diagnostics, so treatment (see below) is often initiated based on physical exam findings and continued until the patient is stable enough for definitive diagnostics.

Patients with cardiogenic shock frequently present in respiratory distress due to left sided CHF. Dogs with left sided CHF almost always present with pulmonary edema, manifested clinically as hypoxemia, inspiratory dyspnea, and pulmonary crackles or harsh lung sounds. Cats with left sided CHF may also have pleural effusion, characterized by short, shallow breaths and dull lung sounds. If there is suspicion of pleural space disease, the clinician should perform thoracocentesis as soon as possible, keeping in mind that this procedure is both diagnostic and therapeutic. A negative thoracocentesis yields useful information (i.e., the cat does not have pleural effusion!). After initial therapy as described below, the patient should be placed into an oxygen cage or receive some other type of supplemental oxygen and placed into a low stress environment.

The primary problem leading to respiratory distress in most CHF patients is pulmonary edema due to increased hydrostatic pressure in the pulmonary capillary beds as described above. Therefore, initial emergency management should be targeted at reducing hydrostatic pressure using diuretic therapy (furosemide) and/or vasodilator therapy (nitroglycerine). See the table below for dosing recommendations. If the underlying heart disease is likely to lead to decreased cardiac contractility (such as dilated cardiomyopathy or severe valvular disease), positive inotropic therapy is indicated. Ideally, this therapy is initiated only after an echocardiogram has documented a decrease in contractility, but if the patient is too unstable, echocardiography is not available, and there is a high index of suspicion that the patient has poor contractility, positive inotropic therapy may be initiated presumptively. The most common type of heart disease leading to cardiogenic shock and left sided CHF in cats is hypertrophic cardiomyopathy (HCM). In this disease, the ventricles become thickened and stiff and cannot fill during diastole (i.e., they have diastolic dysfunction). Administration of positive inotropes in these patients is contraindicated because it exacerbates the underlying disease by causing the ventricles to be stiffer, reducing filling, however, negative chronotropic therapy can help increase the time for filling of the heart and thus improve CO. Note that in patients with systolic dysfunction (such as animals with DCM or severe valvular disease), negative chronotropic therapy is contraindicated because the tachycardia in these cases are appropriate compensatory responses to decreased stroke volume in order to maintain adequate CO.

Summary

When treating patients with shock, rapid identification of the underlying type of shock is crucial. Identification and treatment of deficits in any of the determinants of oxygen delivery in these patients can mean the difference between life and death in these critically ill patients. Thorough physical evaluation and targeted therapy directed at the deficits in O₂ delivery are crucial to successful resuscitation of these patients.

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Blood Gases: The Anion Gap is Actually USEFUL

Daniel Fletcher, PhD, DVM, DACVECC
Cornell University
Ithaca, NY

Acid-base disturbances are common in critically ill and emergency patients, but the clinical signs associated with these disturbances are often vague. A systematic approach to blood gas analysis can yield a large amount of information in a short period of time. This lecture will cover a basic, 7 step approach to traditional blood gas analysis that can be used clinically to rapidly identify acid-base disturbances and guide treatment for emergent and critically ill patients. The following are the 7 steps:

1. Determine sample type
2. Interpret the pH
3. Evaluate the respiratory component
4. Evaluate the metabolic component
5. Determine the primary disorder(s)
6. Look for evidence of compensation
7. Evaluate oxygenation

Step 1: Determine the sample type

There are 2 basic types of blood gas samples: peripheral venous and arterial. For the purpose of acid-base analysis, any sample type can be used. When evaluating oxygenation of the sample (step 7), it is important that the type of sample is considered, as this will have a major impact on interpretation.

Step 2: Interpret the pH

The pH of the blood is the negative log of the hydrogen ion concentration and is normally between 7.35 and 7.45. If the blood pH is less than 7.35, the patient is *acidemic*, and if the pH is greater than 7.45, the patient is *alkalemic*. These terms reflect disturbances in the pH, not the underlying physiologic processes leading to the pH change, which are termed acidosis and alkalosis. It is important to remember that a patient may have a normal pH despite serious underlying acid-base disturbances, so all 7 steps must be completed even if the pH is found to be normal.

Step 3: Evaluate the respiratory component

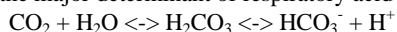
CO₂ acts as an acid in the blood and lowers the pH. The partial pressure of CO₂ in the blood (PCO₂) is inversely proportional to minute ventilation, the product of respiratory rate and tidal volume. The higher the minute ventilation, the lower the PCO₂ in arterial and venous blood. The gradient between arterial and venous PCO₂ is usually less than 5 mmHg, so PCO₂ can be evaluated in arterial, peripheral venous, or central/mixed venous samples. Normal PCO₂ is 35-45 mmHg.

Respiratory Acidosis: Patients with decreased minute ventilation, due to a decrease in respiratory rate, tidal volume, or both are by definition hypoventilating, leading to a respiratory acidosis from a PCO₂ of greater than 45 mmHg. Differential diagnoses for respiratory acidosis include any disease processes that compromise minute ventilation, such as upper airway obstruction, lower airway obstruction (asthma, bronchitis), pleural space disease, chest wall disease, abdominal distention, central nervous system disease, and peripheral neuropathies.

Respiratory Alkalosis: An increased minute ventilation leads to a decrease in PCO₂ and a respiratory alkalosis. Stress, pain, fear, hyperthermia, and anxiety can all cause respiratory alkaloses. However, anemia and hypoxemia will both also lead to hyperventilation and respiratory alkalosis, and are potentially life-threatening. Therefore, it is imperative that a packed cell volume and pulse oximetry reading or arterial blood gas analysis be done in all patients with respiratory alkaloses to rule out these 2 differential diagnoses.

Step 4: Evaluate the metabolic component

Metabolic disturbances may be identified in patients by deviations in blood bicarbonate (HCO₃) concentrations. Bicarbonate is the major extracellular buffer, and changes in bicarbonate reflect metabolic disturbances that can affect the blood pH. Intracellularly, other buffer systems are more important for maintaining acid-base balance, including phosphate and proteins like hemoglobin. Normal blood bicarbonate concentrations are approximately 20-25 mmol/L, and patients with low bicarbonate have metabolic acidoses, while those with high bicarbonates have metabolic alkaloses. Although bicarbonate is the major determinant of metabolic acid-base balance and CO₂ is the major determinant of respiratory acid-base balance, the 2 exist in an equilibrium:



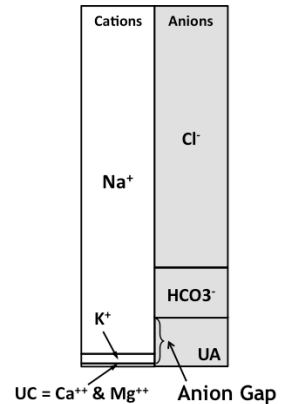
If a patient hypoventilates (has a respiratory acidosis), the CO₂ will increase and the equilibrium above will be shifted to the right, increasing the bicarbonate concentration. This has nothing to do with metabolic acid-base status, but is simply a reflection of this

equilibrium. Conversely, if the patient hyperventilates (has a respiratory acidosis), the CO₂ will decrease and the equilibrium will be shifted the left, decreasing the bicarbonate concentration.

Because the bicarbonate concentration is affected by changes in CO₂, when evaluating the metabolic component of acid-base balance, the use of the base excess (BE) may be preferable. The concept behind the BE is that if the patient's blood sample were equilibrated to a PCO₂ of 40 mmHg (the middle of the reference range), and acid was titrated into the sample until the pH reached exactly 7.40, the amount of acid added would be the BE. Therefore, the BE represents the extra base present in the sample when the CO₂ is normalized, and is a more reliable measure of the metabolic acid-base balance of the patient. The BE normally ranges between 0 and -4 mmol/L.

Metabolic acidosis

Patients with a bicarbonate of less than 20 mmol/L or a BE of less than -4 mmol/L have metabolic acidoses. A metabolic acidosis can be due to two causes: (1) excess acid, or (2) loss of buffer (base). When a patient is diagnosed with a metabolic acidosis, the anion gap can help differentiate between these 2 causes. The principle behind the anion gap is that electroneutrality is always maintained in the blood, meaning that the sum of the positive charges (the cations, in the left column of the figure to the right) must be equal to the sum of all of the negative charges (the anions, in the right column). The cations consist of sodium and potassium, with a small net positive charge being contributed by the "unmeasured cations" (UC) calcium and magnesium. The anions consist mostly of chloride and bicarbonate, with a larger (compared to the UC) net negative charge contributed by the unmeasured anions (UA). In a healthy patient with no underlying acid base disturbance, the majority of the UA is comprised of albumin, which has many negatively charged groups. The anion gap (AG) is the difference between the UA and the UC ($AG = UA - UC$). Due to electroneutrality, this can be calculated using parameters commonly available on a blood gas using the equation:



$$AG = (Na + K) - (Cl + HCO_3)$$

Because acidic compounds consist of an anion with an associated hydrogen ion, patients with metabolic acidosis due to an increase in acidic compounds will have an increase in the unmeasured anions, a decrease in bicarbonate, and an **increase** in the anion gap. There are 4 differential diagnoses for patients with metabolic acidosis associated with an elevated anion gap, all of which are due to an increase in acidic compounds:

1. Lactic acidosis (acid = lactic acid)
2. Diabetic ketoacidosis (acid = ketoacids)
3. Uremic acidosis (acid = sulfates and phosphates)
4. Exogenous acid ingestion (examples = ethylene glycol and salicylates)

In contrast, patients may develop a metabolic acidosis due to a primary loss of buffer (bicarbonate). Bicarbonate can be lost in 2 places:

1. Small bowel diarrhea
2. Renal tubular acidosis (RTA)

Note that patients with RTA do not have elevations in BUN and creatinine, but suffer from primary renal tubular dysfunction resulting in inappropriate handling of bicarbonate and hydrogen ion. Because the primary disturbance in these diseases is loss of bicarbonate rather than increased acid, these diseases are associated with a **normal** anion gap. Therefore, the anion gap can be useful to prioritize these 2 groups of differential diagnoses in patients with metabolic acidoses.

Metabolic alkalosis

The most common cause of metabolic alkalosis in dogs and cats is vomiting, especially when it is due to an upper GI obstruction. Large amounts of chloride and hydrogen ion are lost in the vomitus. The ensuing hypovolemia stimulates reabsorption of sodium in the kidney to maintain intravascular volume and release of aldosterone. In the absence of chloride (which is lost in the vomitus), proximal tubular reabsorption of sodium is limited and the patient must reabsorb as much sodium as possible in the distal tubule under the influence of aldosterone, resulting in potassium depletion. This also leads to excretion of hydrogen ions in the distal tubule and reabsorption of bicarbonate, leading to progressive metabolic alkalosis and excretion of acidic urine. The constellation of a hypochloremic metabolic alkalosis, hypokalemia, and paradoxical aciduria (called "paradoxical" because the urine would be expected to be acidic in the face of a metabolic alkalosis) is suggestive of an upper GI obstruction. Other causes of metabolic alkalosis are primarily iatrogenic, and include sodium bicarbonate administration and the use of furosemide, which blocks the sodium, potassium, 2 chloride co-transporter in the loop of Henle, leading to excessive loss of chloride and retention of bicarbonate.

Step 5: Determine the primary disorder

If only a single acid-base disturbance is noted in steps 3 and 4, it is the primary disorder and differential diagnoses should be considered as discussed above. If both a respiratory and metabolic disturbance is noted, and both are of the same type (i.e., both metabolic and respiratory acidosis or both metabolic and respiratory alkalosis), then both disorders are independently contributing to the abnormal pH and differential diagnoses for both disorders must be investigated. If both a respiratory and metabolic disorder are identified and they are affecting the pH in opposite ways (e.g., metabolic acidosis and respiratory alkalosis), the primary disturbance will always be consistent with the pH change. For example, if the patient is acidemic, has a metabolic acidosis and a respiratory alkalosis, the metabolic acidosis is likely the primary disturbance.

Step 6: Look for evidence of compensation

When an acid-base disturbance develops, in an attempt to normalize the pH, a compensatory disturbance may develop. The primary disturbance will always be consistent with the pH change. For example, if the patient is acidemic, has a metabolic acidosis and a respiratory alkalosis, the metabolic acidosis is likely the primary disturbance, and it is possible that the respiratory alkalosis is compensatory. It is possible to determine whether the degree of compensation noted on a blood gas is appropriate for the severity of the primary disorder using the following compensation equations.

Acid-Base Disorder	Expected Compensation
Metabolic acidosis	Each 1 mEq/L decrease in HCO_3^- will decrease PCO_2 by 0.7 mmHg.
Metabolic alkalosis	Each 1 mEq/L increase in HCO_3^- will increase PCO_2 by 0.7 mmHg.
Respiratory acidosis Acute Chronic	Each 1 mmHg increase in PCO_2 will increase HCO_3^- by 0.15 mEq/L. Each 1 mmHg increase in PCO_2 will increase HCO_3^- by 0.35 mEq/L.
Respiratory alkalosis Acute Chronic	Each 1 mmHg decrease in PCO_2 will decrease HCO_3^- by 0.25 mEq/L. Each 1 mmHg decrease in PCO_2 will decrease HCO_3^- by 0.55 mEq/L.

It is important to note that respiratory compensation for a primary metabolic disorder will happen rapidly, within seconds to minutes of the disturbance occurring. However, metabolic compensation for a respiratory acid-base disturbance is accomplished by excretion or retention of bicarbonate in the kidney, which can take hours to start and more than a day to reach maximal efficiency. Therefore, absence of metabolic compensation for a respiratory disturbance is suggestive of an acute process, whereas evidence of compensation suggests the problem is more chronic.

Step 7: Evaluate oxygenation

Oxygen saturation (SO_2) or the partial pressure of oxygen dissolved in the plasma (PO_2) can provide useful information for some type of blood gases. When interpreting these values, it is important to first confirm the sample type.

Peripheral Venous Sample: Assessment of oxygenation for peripheral venous blood samples is rarely helpful. Because the value will be affected by local factors and the degree to which the vessel was held off to collect the sample, it yields very little information about global patient status.

Arterial Sample: Because blood sampled from a peripheral artery has not yet perfused a tissue bed, the oxygen content of the arterial blood can yield important information about pulmonary gas exchange. In patients breathing room air, arterial PO_2 (P_aO_2) should be between 80-100 mmHg and arterial hemoglobin saturation (S_aO_2) should be 95-100%. Patients with values less than these are *hypoxemic* and are at risk of tissue hypoxia and organ damage. Supplemental oxygen should be provided as soon as possible in these patients until the type of respiratory disease is definitely identified and treated.

Conclusions

With practice, a full evaluation of a blood gas using this 7 step approach can be accomplished in 1-2 minutes, yielding important information about emergent or critically ill patients.

Panting, Wheezing, and Crackles: How to Quickly Get to the Bottom of Respiratory Distress, and Fix it

Daniel Fletcher, PhD, DVM, DACVECC
Cornell University
Ithaca, NY

Timely assessment and intervention are crucial in the management of animals with acute respiratory distress. An approach based upon the eight basic causes of respiratory distress can afford the clinician the ability to rapidly identify a small number of possible disorders and provide appropriate, directed, life-saving care. An abbreviated, targeted physical examination based upon observation of the character of respiration, thoracic auscultation, and palpation can quickly narrow down the causes to a small subset of differentials, which can then be treated.

Respiratory function can be viewed in terms of two separate but related components: ventilation and oxygenation. When approaching animals with respiratory distress, it is important to rapidly assess whether the source of the distress is a problem with ventilation, or a problem with oxygenation.

Ventilation involves the efficient movement of adequate fresh gas into and out of the alveoli, and is reflected in a patient's blood CO₂ concentration (PCO₂). The major determinant of PCO₂ is minute ventilation, which is the product of tidal volume (the volume of air in each individual breath) and the respiratory rate. Therefore, the primary clinicopathologic feature of impaired ventilation is an elevation of PCO₂, and decreases in PCO₂ are indicative of hyperventilation. It is important to remember that animals that are tachypneic may hypoventilate if they have very small tidal volumes, while animals breathing slowly may actually be hyperventilating if they have very large tidal volumes. Because there can be significant changes in blood CO₂ content with relatively small changes in the PCO₂, a small gradient typically exists between venous and arterial PCO₂, and venous blood gas samples usually accurately reflect ventilation.

Oxygenation is primarily related to the ability of the lungs to efficiently move oxygen into the blood. It is reflected in the arterial PO₂. In contrast to PCO₂, venous PO₂ cannot be used to assess global oxygenation because of significant oxygen uptake from the tissues, which will decrease the PO₂ in venous blood. Arteries contain blood that has not yet reached a tissue bed, and therefore arterial blood samples yield critical information about the oxygenating efficiency of the lungs. Similar information may be obtained non-invasively using pulse oximetry, which measures hemoglobin saturation. Low PaO₂ (below 80 mmHg in animals breathing room air) or low SpO₂ (below 95% in animals breathing room air) is consistent with a diagnosis of hypoxemia. There are five categories of differential diagnoses for hypoxemia: (1) Decreased inspired O₂ concentration (FiO₂), such as seen under anesthesia with inappropriate gas mixtures or at altitude; (2) Hypoventilation, such as neurologic disease, sedation, or airway obstruction; (3) V/Q Mismatch, such as alveolar disease or pulmonary hypertension; (4) Shunt, such as severe alveolar disease or atelectasis; and (5) Diffusion Impairment, such as pulmonary fibrosis and other, rare interstitial diseases.

The eight causes of respiratory distress

There are many underlying disease processes that can lead to respiratory distress in small animals. However, these differentials can be grouped into eight categories based upon the source of the distress, each of which is treated in a similar fashion. The eight causes are: (1) upper airway disease, (2) lower airway disease, (3) pulmonary parenchymal disease, (4) pleural space disease, (5) chest wall disease, (6) pulmonary thromboembolism, (7) abdominal distention, and (8) look-alikes.

(1) Upper airway disease

Clinical signs

The classic signs associated with upper airway disease are stridor and stertor. Some animals may also cough, and depending upon the location of the disease, distress may be inspiratory (with extrathoracic disease) or expiratory (with intrathoracic disease).

Primary respiratory dysfunction

Hypoventilation due to decreased alveolar filling. Hypoxemia may also develop with severe upper airway obstructions.

Differentials

There are many, and a systematic approach (such as the DAMNIT-V scheme) is useful.

- Degenerative: Laryngeal paralysis, collapsing trachea, left atrial enlargement (MVD)
- Anomalous: Brachycephalic airway syndrome
- Metabolic: Hypothyroidism
- Neoplasia: Primary vs. metastatic disease
- Infectious/Inflammatory: Abscess, granuloma, foreign body, sterile laryngitis
- Trauma: Hematoma, swelling, fracture
- Vascular: Coagulopathy

Treatment

Relieve the obstruction! In some cases, sedation is adequate. If unsuccessful, patients should be intubated, or a tracheostomy tube should be placed.

(2) Lower airway disease

Clinical signs

Wheezes on auscultation are the hallmark finding in patients with lower airway disease. Patients may also cough, and distress is expiratory.

Primary respiratory dysfunction

Hypoventilation due to fluid, inflammation, or constriction of small airways, leading to air trapping in alveoli.

Differentials

Cats with lower airway respiratory distress most likely have feline asthma. Dogs rarely present acutely with lower airway disease, which is usually due to chronic bronchitis.

Treatment

Bronchodilators (β_2 agonists – terbutaline 0.01 mg/kg IM, PDE-I – aminophylline 5-10 mg/kg IM) and corticosteroids (dexamethasone SP 0.1 mg/kg IM) are the mainstay of therapy. Minimize handling, provide supplemental oxygen and a quiet environment.

(3) Pulmonary parenchymal disease

Clinical signs

Fluid and inflammatory debris in the alveoli, leading to alveolar collapse during expiration and alveolar re-expansion during inspiration, cause the characteristic crackles heard on auscultation in animals with pulmonary parenchymal disease. Areas of parenchyma that are completely consolidated may sound dull. Distress is most commonly inspiratory.

Primary respiratory dysfunction

Hypoxemia due to V/Q mismatch, shunt, or diffusion impairment is the primary dysfunction associated with parenchymal disease. In severe cases or in animals that develop fatigue, elevated CO₂ levels may also be seen.

Differentials

Alveoli may contain water (cardiogenic or non-cardiogenic edema), inflammatory exudates (pneumonia, ARDS), blood (contusion), or non-inflammatory exudates (neoplasia). Interstitial disease (e.g., pulmonary fibrosis) should also be considered, but is rare in small animals.

Treatment

Supplemental oxygen should be administered to all hypoxemic patients. Treatment varies, and should be guided by the underlying cause

(4) Pleural space disease

Clinical signs

Dull lung sounds or the absence of lung sounds should raise the clinician's index of suspicion for pleural space disease. In addition, rapid, shallow, and frantic respirations are common.

Primary respiratory dysfunction

An inability to fully expand the lungs leads to decreased minute ventilation, and therefore hypoventilation. In severe cases, hypoxemia may also develop.

Differentials

Pneumothorax (air secondary to trauma or ruptured bullae), hydrothorax (serous fluids secondary to congestive heart failure or hypoproteinemia), pyothorax (from lung abscess rupture or penetrating wounds), hemothorax (trauma, coagulopathy), chylothorax (heart disease, neoplasia, heartworm, idiopathic), and other exudative processes (FIP, neoplasia) should be considered.

Treatment

Thoracocentesis is indicated in all cases in which respiratory distress is present. In cases of pyothorax, tension pneumothorax, or rapidly recurring effusions, thoracostomy tube placement should be considered.

(5) Chest wall disease

Clinical signs

Palpation of chest wall defect, pain on palpation, or visualization of a flail segment are the common findings.

Primary respiratory dysfunction

Only flail segment, which leads to hypoventilation, leads to true respiratory distress.

Differentials

Penetrating wounds cause pleural space disease, and rib fractures are look-alikes, leaving flail segment as the only true chest wall cause of respiratory distress.

Treatment

Placing the animal with the affected side down will sometimes partially stabilize a flail segment and allow maximal inflation of the opposite lung. Patients that cannot be stabilized should be anesthetized, intubated, and the flail segment stabilized with external or internal coaptation.

(6) Pulmonary thromboembolism (PTE)

Clinical signs

Clinical significant PTE usually results in severe hypoxemia that is often minimally responsive to oxygen supplementation due to severe V/Q mismatch and shunt.

Primary respiratory dysfunction

Decreased blood flow to areas of the lung served by pulmonary arteries that are occluded with thromboemboli leads to a number of processes, including: (1) decreased surfactant production, causing alveolar collapse and shunt, (2) production of inflammatory mediators, leading to lung injury and V/Q mismatch, and (3) increased pulmonary artery pressure, increasing the fraction of blood flowing through normal shunts in the lung. The result is severe hypoxemia.

Differentials

Identification of underlying, predisposing diseases such as Cushing's disease, protein-losing enteropathy/nephropathy, immune mediated diseases, cardiac disease, and other causes of endothelial damage such as sepsis and SIRS is crucial. Diagnosis is typically by exclusion, with V/Q scanning and CT angiography as well as other advanced imaging modalities required for definitive diagnosis.

Treatment

Oxygen supplementation is essential. Some patients may require mechanical ventilation if the PaO₂ is persistently < 60 mmHg in the face of oxygen supplementation. Thrombolytic therapies (tPA, streptokinase) and anticoagulant therapies (heparin), and anti-platelet therapies (aspirin, clopidogrel) can also be considered.

(7) Abdominal distention

Clinical signs

Diagnosed via abdominal palpation on physical exam.

Primary respiratory dysfunction

Compromise of diaphragmatic function leads to decreased tidal volumes and hypoventilation.

Differentials

Ascites (transudates, exudates, hemorrhage), organomegaly, neoplasia, and fat are common causes of abdominal distention. Acute respiratory distress due to abdominal distension is typically due to acute onset of ascites.

Treatment

Abdominocentesis is indicated to allow restoration of appropriate tidal volumes. Until the underlying disease process leading to the effusion is identified and treated, only the amount of fluid needed to improve tidal volume should be tapped, as fluid shifts leading to hypovolemia and electrolyte disturbances can occur if large volumes of fluid are removed.

(8) Look-alikes

Clinical signs

Vary depending on the underlying disease.

Primary respiratory dysfunction

Neither hypoxemia nor hypoventilation are present. Look-alikes are disease processes that make patients appear to be in distress, but no underlying respiratory dysfunction is present.

Differentials

There are 3 categories of look-alikes: (1) Behavioral causes, such as stress, fear, pain, or anxiety, (2) Metabolic causes, such as metabolic acidosis or anemia, and (3) Environmental causes, such as hyperthermia.

Treatment

Treatment is aimed at the underlying causes. Behavioral causes may be treated with anxiolytics or analgesics. Metabolic acidosis, if severe, may be treated with sodium bicarbonate administration. Anemic patients should be treated with packed red blood cells, or other oxygen carrying solutions such as oxyglobin.

Conclusions

Few emergencies are as stressful for the emergency clinician as respiratory distress. However, with a brief physical examination, the 8 potential causes of respiratory distress can be quickly reduced to 2 or 3, and appropriate, life-saving therapy can be administered.

Fibrinolysis: Why Clot Breakdown May be Just as Important as Making the Clot

Daniel Fletcher, PhD, DVM, DACVECC
Cornell University
Ithaca, NY

Diagnosis and treatment of coagulation disorders associated with many veterinary diseases have been well studied, but the degree to which disorders of fibrinolysis may contribute to bleeding in veterinary patients is unknown. Recent data in the human and experimental literature suggests that the fibrinolytic pathway may be a useful target in patients with bleeding disorders and thrombotic disease.

A Review of hemostasis

Coagulation

The coagulation cascade consists of sequential activation of a series of coagulation factors. Most of these are serine proteases, but some of the factors involved in coagulation are glycoproteins (factors VIII and V) or transglutaminases (factor XIII). Most are synthesized in the liver.

The traditional model of the coagulation system is presented in abbreviated form in Figure 1. It is described as 2 arms representing the intrinsic (or contact pathway) and extrinsic (or tissue factor pathway) cascades, which then enter the common cascade, concluding in the production of thrombin, which catalyzes the conversion of fibrinogen (Fg, factor I) into fibrin (Fb, factor Ia). This model represents the processes leading to measureable coagulation resulting from *in vitro* testing, but in recent years, a more physiologic model of the coagulation system has been proposed.

The cell-based model of coagulation more likely represents the actual processes occurring *in vivo*. It begins with activation of platelets (primary hemostasis), which provide a stimulus and a surface upon which the coagulation cascade can be initiated and amplified (secondary hemostasis).

Coagulation begins with primary hemostasis, consisting of activation of platelets by exposure of subendothelial collagen. In addition, von Willebrand factor (vWF) is released from the endothelium and from activated platelets, and increases adhesion of the platelets to the damaged endothelium. Activated platelets release substances stored in cytoplasmic granules that contribute to activation of more platelets. The result is a shape change in the platelets to a stellate conformation, and the platelets then become crosslinked via fibrinogen bound to surface receptors, forming an initial platelet plug. Secondary hemostasis, also referred to as the coagulation cascade, is triggered after platelet activation. The initiation phase of coagulation is accomplished via the tissue factor pathway (extrinsic cascade). Damaged endothelial cells, activated platelets, and sub-endothelial fibroblasts express tissue factor (TF), which activates factor VII, producing VIIa, ultimately resulting in the production of thrombin (IIa) via the common cascade. This process produces only a small amount of IIa, which serves mainly to activate factors V and VIII. The amplification phase of coagulation (Figure 3) is largely the result of activation of the contact pathway (intrinsic cascade). The trace IIa produced during initiation serves to activate more platelets, which express receptors for Va and VIIIa, ultimately leading to a “thrombin burst,” a massive increase in the amount IIa produced by the common cascade. This large production of IIa catalyzes both the conversion of Fg (I) to Fb (Ia) and activation of factor XIII, which initiates crosslinking of Fb and formation of a stable clot. Figure 2 shows a summary of the cell-based model of coagulation.

Anticoagulation

Several negative feedback mechanisms antagonize hemostasis and maintain localization of the coagulation process. Protein C is a vitamin K dependent anticoagulant synthesized in the liver that is activated by thrombin (IIa) bound to thrombomodulin on the endothelial cell surface. Activated protein C (APC) has its anticoagulant effect by deactivating Va and VIIIa in the presence of its cofactor Protein S. Antithrombin (AT) is produced by the liver and deactivates thrombin as well as IXa, Xa, XIa and XIIa. Its activity against Xa is markedly enhanced by heparan sulfates on the endothelial cell surface and by exogenous heparin. Endogenous heparan sulfate and

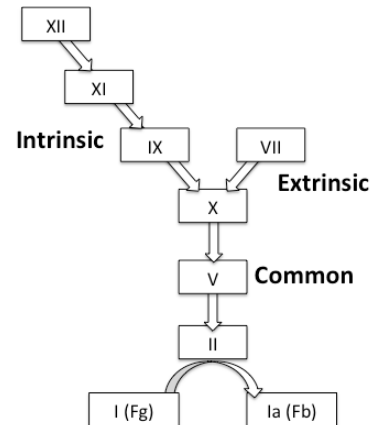


Figure 2: The traditional coagulation cascade model.

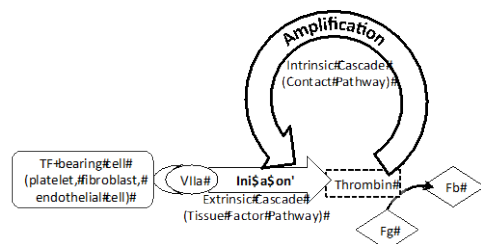


Figure 2: The cell-based model of coagulation

some exogenous heparins (larger molecular weight) also enable AT to directly deactivate IIa (thrombin). Tissue factor pathway inhibitor (TFPI) inhibits the action of TF on activation of VII as well as TF mediated activation of IX and X. Finally, prostacyclin is released by endothelial cells, activating G_s-linked receptors on platelets, increasing intracellular cAMP levels and decreasing intracellular calcium concentrations, inhibiting platelet degranulation and activation.

The fibrinolytic system

Activation of fibrinolysis

Clot breakdown (fibrinolysis) is initiated by release of plasminogen activators, predominantly tissue plasminogen activator (tPA) from endothelial cells and urokinase-like plasminogen activator (uPA), which circulates in plasma and is produced by various tissues. tPA binds to fibrin and predominantly activates plasminogen bound to fibrin in the area of a clot. Fibrinolysis is enhanced locally by protein C via a dis-inhibition mechanism in response to clot formation. Protein C is activated by the thrombin-thrombomodulin complex as described above. Activated protein C (APC) enhances fibrinolysis by inhibiting both activated TAFI and PAI-1, the major inhibitors of fibrinolysis. Kallikrein activates circulating pro-uPA into active uPA, which also leads to plasmin generation from plasminogen. This process is initiated by factor XIIa from the coagulation cascade, which catalyzes production of kallikrein from prekallikrein. These processes all occur locally in the area of clot formation, stimulating clot breakdown.

Inhibition of fibrinolysis

Several endogenous mechanisms antagonize fibrinolysis. A major antagonist of fibrinolysis is thrombin-activatable fibrinolysis inhibitor (TAFI), which is produced by the liver and circulates in the plasma in an inactive form. It is activated by the thrombin-thrombomodulin complex on the surface of endothelial cells in the area of a clot and directly inhibits the activity of plasmin. The other major fibrinolysis inhibitor is plasminogen activator inhibitor-1 (PAI-1), which is present free in the circulation and inhibits the activity of both tPA and uPA. There is evidence that PAI-1 is produced by endothelial cells, liver, and/or platelets. In addition, there is recent evidence that significant production may also occur in adipocytes. Less important inhibitors of fibrinolysis include α -2 antiplasmin and α -2 macroglobulin. They are synthesized in the liver and by platelets and directly inhibit the actions of plasmin. Factor XIIIa also catalyzes the binding of α -2 antiplasmin to fibrin, making the fibrin more resistant to breakdown by plasmin. There are also 2 main classes of pharmacologic agents that inhibit fibrinolysis. Aprotinin is a serine protease inhibitor that directly inhibits the activity of plasmin. At higher concentrations, it also inhibits kallikrein, which reduces the production of plasmin directly. The other class of fibrinolysis inhibitor drugs is the lysine analogs (epsilon-aminocaproic acid, EACA, and tranexamic acid, TEA). These drugs block lysine binding sites on plasminogen that are essential for its activation to plasmin, decreasing plasmin production.

Species differences in fibrinolysis

There is strong evidence that compared to humans, dogs demonstrate enhanced fibrinolysis. This was first noted when investigators attempted to develop a canine model of pulmonary thromboembolism (PTE), but found that the emboli lysed within hours both *in vitro* and post mortem in dogs compared to emboli that frequently last months to years in people. There is also evidence in the literature that horses may have reduced fibrinolytic activity compared to people, demonstrated by lower basal plasminogen activity and increased α -2 antiplasmin and PAI-1 activity in adult horses and foals. In addition, horses require 10-fold higher concentrations of tissue plasminogen activator (tPA) to induce fibrinolysis in an *in vitro* assay compared to humans. The fibrinolytic system in cats has been poorly studied.

Laboratory evaluation of fibrinolysis

Common laboratory tests of coagulation, such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT), are insensitive to the status of the fibrinolytic system, and tests to evaluate the fibrinolytic potential in an individual patient are limited. Options to investigate the fibrinolytic system clinically include individual fibrinolysis factor assays, *in vitro* clot lysis tests, and viscoelastic testing methods.

Viscoelastic coagulation tests, such as Thrombelastography (TEG) and Rotational Thromboelastometry (ROTEM), were designed to provide a more global view of hemostasis and fibrinolysis than traditional testing. They are *in vitro* tests in which whole blood or plasma are allowed to clot in a cuvette and the strength of the clot over time is measured using the torsion detected on a pin submerged in the sample. Clot formation can be accelerated by the addition of various activators, and clot lysis can be measured if the assay is allowed to run for sufficient time.

ROTEM and TEG measures of fibrinolysis include the % of clot strength remaining 30 or 60 minutes after maximum clot strength (TEG CL30, CL60) and the % reduction of the maximum clot area at 30 or 60 minutes after maximum clot strength (TEG LY30, LY60). However, because *in vitro* clot lysis proceeds slowly due to plasma anti-fibrinolytic agents (such as α -2 antiplasmin) and the lack of locally produced pro-fibrinolytic agents that would enhance fibrinolysis in areas of clot formation (tPA and APC-induced inhibition of TAFI and PAI-1), *in vitro* fibrinolysis proceeds slowly and may not be detectable before the samples dehydrate. More recent modifications of these assays using added recombinant tPA to accelerate fibrinolysis, allowing measureable lysis to occur quickly, have been validated in human patients, shown to be reliable and reproducible, and were reflective of plasma concentrations of

PAI-1. A similar assay has been applied in dogs and cats by the author, and may offer a more global, point of care test for diagnosis of fibrinolytic disorders.

Hyperfibrinolysis

There has been very little investigation of disorders of fibrinolysis in veterinary patients, but there are several well-described syndromes of hyperfibrinolysis in people. It is likely that similar disease processes occur in other species, but further investigation is needed. The following is a review of these disorders in humans and the small amount of veterinary data available.

Hyperfibrinolytic disorders may be congenital or acquired, and commonly lead to spontaneous bleeding or worsened hemorrhage in patients with other underlying bleeding disorders. Congenital hyperfibrinolytic disorders are exceedingly rare in people and, to the author's knowledge, have not been reported in veterinary species. Acquired hyperfibrinolysis is more common in humans. Hepatic cirrhosis is the most common disorder leading to hyperfibrinolysis in people, and is due to increased plasma tPA from decreased hepatic clearance as well as decreased hepatic production of α -2 antiplasmin. Combined with the coagulopathy and thrombocytopenia commonly seen in this disease, severe bleeding can result. Recent data in humans showed objective evidence of hyperfibrinolysis in patients with cirrhosis. In some cases refractory to other therapies, dramatic responses to EACA have been reported, suggesting that hyperfibrinolysis may be important in this clinical bleeding disorder. Neoplasias, such as acute promyelocytic leukemia (APL) and some solid tumors, most commonly metastatic carcinomas, can demonstrate hyperfibrinolysis in conjunction with DIC. Neoplastic promyelocytes produce leukocyte elastase, which can inactivate α -2 antiplasmin, and myeloid leukemic blasts have been shown to produce tPA and uPA *in vitro*. Clinically, there are case reports of bleeding patients with APL responding to treatment with EACA. Snake venoms, especially eastern and western diamondback snakes, may contain a tPA-like substance or may stimulate endothelial cells to produce tPA. Marked consumption of α -2 antiplasmin and PAI-1 are measurable in these patients. However, due to the high risk of DIC in envenomated patients, the use of anti-fibrinolytic agents in these patients is not recommended.

Recently, the effect of hyperfibrinolysis on the bleeding disorder associated with trauma has been intensively investigated. Although the coagulopathy associated with trauma has been well documented, the mechanism associated with it is still poorly understood. Trauma patients with coagulopathy have a higher mortality rate (46%) than those without coagulopathy (10.9%), suggesting that this disorder is at a minimum an important marker of severity of injury and may be causally related to mortality in trauma patients. Previously, it was believed that a combination of dilution from fluid resuscitation, inactivation of the coagulation cascade from acidemia, and consumption of coagulation factors from endothelial damage were the primary causes. However, 10-34% of human trauma patients have documented coagulopathies prior to fluid administration, suggesting that dilution is unlikely the sole explanation for this phenomenon.

Recently, it has been determined that regardless of injury severity, less than 3% of patients without evidence of significant shock after trauma (patients with a base deficit \leq 6mEq/L) developed clinically significant coagulopathy, while 19.6% of patients with base deficit $>$ 6mEq/L had coagulopathy. These data suggest that the combination of trauma and shock increases the risk of development of coagulopathy. That same study showed that in patients with BD $>$ 6mEq/L, the risk of coagulopathy increased as injury severity increased, documenting a combined effect of severity of injury and shock on development of coagulopathy. Although patients with worsening severity of injury generated more thrombin, worsening base deficit did not affect thrombin generation or levels of factor VII, suggesting that consumption of coagulation factors is unlikely a significant contributor to the coagulopathies documented in this study.

The degree of fibrinolysis (as determined by d-dimer and prothrombin fragment concentrations) in the trauma patients also increased with increasing injury severity in the presence of shock, but only increased in the most severely injured patients without evidence of shock. Further supporting the concept that hyperfibrinolysis is present in poorly perfused trauma patients, tPA and thrombomodulin concentrations were increased, and protein C concentrations were decreased (suggesting that more circulating protein C was converted to the active form, which is not measured by this assay) in these patients. Additional evidence supporting the concept that hyperfibrinolysis plays an important role in the poor outcomes associated with trauma patients in shock comes from the CRASH-2 trial and subsequent post-hoc and meta-analyses, which showed an approximately 10% reduction in risk of death in trauma patients treated with a fibrinolysis inhibitor (tranexamic acid). In summary, there is evidence that patients with trauma in combination with hypoperfusion commonly develop coagulopathies, which are associated with a worse outcome. These coagulopathies are most commonly due to a combination of systemic anticoagulation and hyperfibrinolysis due increased activation of protein C and release of tPA.

Treatment of fibrinolytic disorders

Fibrinolytic disorders in dogs and cats are poorly understood and likely under-diagnosed due to limited diagnostic options. In addition, therapeutic options for these disorders are limited due to a lack of pharmacokinetic studies and clinical trials documenting a benefit. In patients with or at risk of hyperfibrinolysis due to trauma, the lysine analog anti-fibrinolytic agents have been shown to improve outcomes in humans with no increased risk of thrombosis. Unfortunately, veterinary dosing regimens for these drugs are currently

extrapolated from human data, and recent studies suggest that these schemes may result in overdosing in horses and underdosing in dogs. However, some benefit of EACA has been reported in post-operative greyhounds, a breed that has been noted to be at risk of bleeding due to potential hyperfibrinolysis. In addition, a recent study documented hyperfibrinolysis in dogs with spontaneous hemoperitoneum. It is likely that anti-fibrinolytic drugs, which are inexpensive and safe, may prove useful in bleeding veterinary, and may represent an alternative to expensive therapies like plasma.

Essential Steps for Patients with Traumatic Brain Injury

Daniel Fletcher, PhD, DVM, DACVECC
Cornell University
Ithaca, NY

Pathophysiology

The pathophysiology of head trauma can be separated into two categories: primary injury and secondary injury. Primary injury is the immediate result of the traumatic event, while secondary injury is comprised of a cascade of physiologic and biochemical events that occur in the subsequent hours to days.

Primary injury

The least severe primary brain injury is concussion, characterized by a brief loss of consciousness. After regaining consciousness, some patients will exhibit mild disorientation for a short time. Concussion is not associated with any underlying histopathologic lesions and consists of parenchymal hemorrhage and edema. Contusions occur due to displacement of the brain within the skull causing impact. Although mild contusion can be difficult to differentiate from concussion, unconsciousness for more than several minutes should raise the clinician's index of suspicion for cerebral contusion. Laceration is the most severe of primary brain injuries, and is characterized by physical disruption of the brain parenchyma. The resulting intracranial hemorrhage can be severe, and can accumulate in various spaces within the calvarium, including axial hematomas within the brain parenchyma as well as extra-axial hematomas in the subarachnoid, subdural, and epidural spaces.

Secondary injury

Traumatic brain injury triggers a series of biochemical events that ultimately results in neuronal cell death. These events, termed "secondary injury," include excitotoxicity, ischemia, inflammation, and ATP depletion, and are caused by a combination of intracranial and systemic insults. Systemic insults that contribute to secondary brain injury include hypotension, hypoxia, systemic inflammation, hyperglycemia, hypoglycemia, hypercapnea, hypocapnea, hyperthermia, electrolyte imbalances and acid-base disturbances. Intracranial insults include increased intracranial pressure, compromise of the blood-brain barrier, mass lesions, and cerebral edema.

Primary and secondary injuries ultimately result in worsening of cerebral injury due to compromise of Cerebral Perfusion Pressure (CPP), defined as the difference between Mean Arterial Pressure (MAP) and Intracranial Pressure (ICP), as shown in equation 1 below.

$$CPP = MAP - ICP \quad (1)$$

Blood flow to the brain (Cerebral Blood Flow or CBF), is a function of CPP and Cerebrovascular Resistance (CVR). The normal brain is capable of maintaining a constant CBF over a wide range of CPP (approximately 50 mmHg – 150 mmHg). However, the traumatized brain often loses much of this autoregulatory capacity, making it susceptible to ischemic injury with decreases in MAP. Because the calvarium is a closed, rigid compartment filled with incompressible fluids (brain tissue, blood, and cerebrospinal fluid), the volume of the intracranial contents can be considered fixed (the "Monro-Kellie Doctrine").

$$V_{\text{intracranial}} = V_{\text{brain}} + V_{\text{CSF}} + V_{\text{blood}} + V_{\text{mass lesion}} \quad (2)$$

Sudden increases in any of these volumes can lead to dramatic increases in ICP. Both the primary and secondary brain injuries ultimately lead to increased ICP due to development of cerebral edema, loss of cerebrovascular tone leading to pooling of blood within the brain, and expansion of mass lesions due to intracranial hemorrhage.

Severe, acute increases in ICP will trigger the "Cushing's Reflex," a characteristic rise in MAP and reflex decrease in heart rate. Briefly, this occurs due to an initial drop in CPP caused by the increase in ICP at a given MAP (see equation 1). The resulting decrease in CPP triggers massive catecholamine release, which increases MAP, restoring CPP. The increase in MAP triggers baroreceptors in the carotid body and aortic arch, which causes reflex vagal stimulation, slowing the heart rate. The presence of the Cushing's Reflex in a patient with head trauma is a sign of a potentially life threatening increase in ICP and should be treated promptly.

Assessment, diagnostics, and monitoring

Neurologic assessment

The Modified Glasgow Coma Scale score (MGCS) is a quantitative measure that has been shown to be associated with survival to 48 hours in dogs with TBI, and provides a score that can be used to assess initial neurologic status as well as progression of signs. This scale incorporates three domains: level of consciousness, posture, and pupillary size/response to light, with a score of 1-6 assigned to each domain. The final score ranges from 3-18, with lower scores indicating more severe neurologic deficits. The initial neurological examination should be interpreted in light of systemic status, as shock can cause significant neurologic dysfunction.

Initial diagnostics

Initial diagnostics should focus upon a global assessment of stability. An emergency database should consist of a packed cell volume and total solids to assess for hemorrhage, blood glucose to assess severity of injury, and a blood gas (venous or arterial) to assess

perfusion, ventilation, oxygenation, and acid-base status. Occlusion of the jugular vein is contraindicated in patients with TBI, as this can lead to increased ICP; therefore, samples should be obtained peripherally, or via peripherally inserted central catheters (PICC lines).

Imaging of the head is indicated in patients with localizing signs of brain dysfunction, those with moderate to severe neurologic deficits that do not respond to stabilization, and those with progressive signs. These studies can guide surgical intervention in the case of hemorrhage or skull fractures. Skull radiographs have low sensitivity in patients with TBI and rarely yield useful diagnostic information. Computed tomography (CT) is a sensitive imaging modality that yields excellent detail for assessment of skull fracture, acute hemorrhage, and brain edema.

Monitoring

The duration and frequency of episodes of hypoperfusion have been associated with poorer outcomes in people with TBI. Serial monitoring of perfusion is essential for successful management. Frequent qualitative assessment of tissue perfusion via mucous membrane color, capillary refill time, heart rate and pulse quality, as well as quantitative assessment of blood pressure, oxygenation, and ventilation are crucial. A minimal MAP of 80 mmHg should be targeted to decrease the risk of inadequate CPP. If the Doppler technique is used for monitoring, a minimum of 100 mmHg should be target, as it most closely reflects systolic pressure in small animals. Continuous ECG monitoring should also be employed if possible; if episodes of sinus bradycardia are noted, blood pressure should be assessed for evidence of the Cushing's Reflex, which warrants aggressive therapy directed at lowering ICP.

Treatment priorities

Treatment priorities for patients with TBI can be divided into two broad categories; extracranial priorities and intracranial priorities. Successful management of patients with TBI is dependent upon addressing both categories.

Extracranial priorities

Assessment of potential extracranial injuries is an essential part of the initial diagnostic workup. The basics of Airway, Breathing, and Circulation should be evaluated and addressed as necessary. Endotracheal intubation or tracheostomy should be considered if complete or partial obstruction is present. Even mild hypercapnea can have a significant effect on intracranial pressure and should not be tolerated. Conversely, hyperventilation leading to hypocapnea can cause cerebral vasoconstriction, decreasing cerebral blood flow. Manual or mechanical ventilation should be employed to maintain CO₂ at the low end of the normal range in patients with head trauma (e.g., venous PCO₂ 40-45 mmHg, arterial PCO₂ 35-40 mmHg). The pharynx and larynx should be visually inspected and suctioned as needed to maintain airway patency. Supplemental oxygen is indicated in the initial management of all patients with significant head injury. Patients with pulmonary contusions may require mechanical ventilation with positive end expiratory pressure (PEEP) to maintain adequate oxygenation.

Patients with TBI commonly present in hypovolemic shock, and volume resuscitation goals should be aggressive (MAP of 80-100 mmHg). For patients without electrolyte disturbances, normal saline (0.9%) is the best choice of the isotonic crystalloids, as it is least likely to contribute to cerebral edema. Synthetic colloids can have a more rapid and long lasting effect, but are not effective in dehydrated patients. Patients with hypotension due to hypovolemia and concurrent increased ICP will benefit from a combination of a synthetic colloid (Hetastarch or Dextran 70) and hyperosmotic (hypertonic saline) solution. See table 1 for recommended doses. Patients who do not respond to volume resuscitation require vasopressor support. Systemic hypotension must not be tolerated.

Intracranial priorities

The main goals of intracranial stabilization are maintaining adequate cerebral perfusion by controlling ICP, reducing cerebral metabolism, and maintaining adequate systemic blood pressure. A number of medical and surgical therapies are available to achieve these goals, and successful management of cases of TBI is dependent upon choosing the most appropriate of the available interventions.

Hyperosmotic agents

Mannitol is an effective therapy for patients with increased ICP, and has been shown to reduce cerebral edema, increase CPP and CBF, and improve neurologic outcome in TBI. It has a rapid onset of action, with clinical improvement occurring within minutes of administration, and these effects can last as long as 1.5-6 hours. Mannitol boluses of 0.5-1 g/kg have been recommended for treatment of increased ICP in dogs and cats. Mannitol may increase the permeability of the blood-brain barrier (BBB), an effect that is most pronounced when the BBB is exposed to the drug for prolonged periods of time, allowing mannitol to leak into the brain parenchyma, worsening edema. To reduce the risk of this effect, the drug should be administered in repeated boluses rather than as a constant rate infusion. The diuretic effect of mannitol can be profound and can cause severe volume depletion; therefore, treatment must be followed with isotonic crystalloid solutions and/or colloids to maintain intravascular volume. Hypertonic saline (HTS) may be used as an alternative to mannitol in patients with TBI. HTS has similar osmotic effects to mannitol, and can also improve hemodynamic status via volume expansion and positive inotropic effects, as well as beneficial vasoregulatory and immunomodulatory effects. Rebound hypotension is uncommon with HTS administration because unlike mannitol, sodium is actively reabsorbed in the kidneys, especially in hypovolemic patients. This makes it preferable to mannitol for treating patients with increased ICP and systemic hypotension due to hypovolemia. HTS is contraindicated in patients with hyponatremia, as it can cause rapid rises in serum sodium

concentrations, leading to central pontine myelinolysis and delayed neurologic signs. In euvolemic patients with evidence of intracranial hypertension, both mannitol and HTS can have beneficial effects. If an individual patient is not responding to one drug, the other may yield a beneficial response.

Corticosteroids

Corticosteroids are potent anti-inflammatory medications, and have been recommended in human and veterinary medicine to treat a wide variety of disorders, including TBI. A recent clinical trial evaluating over 10,000 human adults with head injury showed that treatment with corticosteroids was associated with worse outcome at 2 weeks and 6 months post-injury. Due to the lack of evidence of any beneficial effect of corticosteroids after TBI, and strong evidence from the human literature showing a detrimental effect on neurologic outcome, corticosteroids should not be administered to dogs and cats with TBI.

Furosemide

Furosemide has been proposed for treatment of cerebral edema secondary to TBI either as a sole agent or in combination with mannitol. However, this has been called into question due to the potential for intravascular volume depletion and systemic hypotension, ultimately leading to decreased CPP. Furosemide should be used for those patients in whom it is indicated for other reasons, such as those with pulmonary edema or oligo-anuric renal failure.

Decreasing cerebral blood volume

Cerebral vasodilation and blood pooling can contribute to increased ICP. Hypercapnea due to hypoventilation can cause cerebral vasodilation and increased CBV. Ventilatory support should be targeted at maintenance of normocapnea (arterial CO₂ of 35-40 mmHg). In severe, acute intracranial hypertension, short term hyperventilation to an arterial CO₂ of 25-35 mmHg may be used to reduce CBV and ICP. Chronic hyperventilation is not recommended due to evidence that the decrease in CBF leads to cerebral ischemia and worsens outcome. Head elevation by 15-30 degrees reduces CBV by increasing venous drainage, decreasing ICP and increasing CPP without deleterious changes in cerebral oxygenation. It is imperative that occlusion of the jugular veins be avoided by using a slant board to prevent bending the neck. Angles greater than 30 degrees may cause a detrimental decrease in CPP.

Anticonvulsant therapy

Seizures are common after TBI in people, with reported incidence rates of up to 54%, and patients who have at one seizure after TBI have an 86% risk of additional seizures within the next 2 years. Post-traumatic seizures are divided into three groups: immediate, occurring within 24 hours of the trauma; early, occurring 24 hours – 7 days post trauma; and late, occurring greater than 7 days after trauma. Several controlled clinical trials have been undertaken in human medicine to investigate the efficacy of prophylactic anticonvulsant therapy after TBI, and a meta-analysis showed an overall reduction in the risk of immediate and early seizures with prophylactic anticonvulsant therapy, but no effect on risk of late seizures. Given this data, short term prophylactic therapy for 7 days after trauma may be indicated in patients with TBI, and anticonvulsant therapy should always be instituted for patients who have seizures, but there is little evidence to support the utility of long term anticonvulsant therapy to prevent late seizures in these patients. Suggested anticonvulsant drugs and doses are listed in Table 1.

Polyethylene glycol (PEG)

PEG is an inorganic hydrophilic polymer that has a white matter sparing effect after induced traumatic CNS injury when injected intravenously. It also been shown to have antioxidant effects and to decrease free radical production. In experimental studies of TBI, it reduced cellular damage and compromise of the BBB, and improved behavioral recovery in rats when administered within 2-4 hours after brain injury. A small clinical trial of the use of PEG in dogs with intervertebral disk disease also showed improved outcomes compared to untreated controls. Clinical trials utilizing this drug in TBI are needed, but this drug shows promise in the treatment of TBI.

Decompressive craniectomy

Although infrequently employed in veterinary medicine, several surgical procedures to address increased ICP have been described in human medicine, including CSF drainage and decompressive craniectomy. The goal of these therapies is to overcome the constraints of the Monroe-Kellie doctrine (see Equation 2) and to allow expansion of the various intracranial compartments without a subsequent increase in intracranial pressure. The use of decompressive craniectomy in human patients with TBI is controversial, and a large scale, randomized human clinical trial is currently underway (the RESCUEicp Trial), which will compare aggressive medical management with decompressive craniectomy in 500 patients with TBI. Until the results of this trial are available, it seems wise to adopt the current recommendations in the human literature, which are to consider decompressive craniectomy within 12 hours in patients with sustained, increasing ICP that is refractory to medical therapy.

Prognosis

Prognosis is difficult to predict following TBI, and only the MGCS has been shown to be correlated with outcome in small animal patients. However, the author's clinical experience would suggest that even patients with severe neurologic deficits at presentation can show marked improvement over the subsequent 24-48 hours. Therefore, serial neurologic exams are recommended. Client education is also of paramount importance, as persistent or permanent neurologic deficits in patients with TBI are common.

Table 1: Drugs and doses for patients with traumatic brain injury

Indication	Drug	Dose	Comments
Intracranial Hypertension			
Euvolemic, normotensive or hypertensive patients.	Mannitol 25%	0.5 – 1 g/kg IV over 15 minutes. May repeat.	<input type="checkbox"/> Potent osmotic diuretic. <input type="checkbox"/> Follow with crystalloids and/or colloids to maintain intravascular volume. <input type="checkbox"/> Monitor osmolality with repeat dosing
Hypovolemic patients.	Hypertonic saline (7%) [†] + Dextran-70 or Hetastarch	3-5 ml/kg over 15 minutes. May repeat	<input type="checkbox"/> Contraindicated in hyponatremic patients. <input type="checkbox"/> Monitor serum sodium concentrations with repeat dosing.
Hypovolemic or euvolemic patients.	Hypertonic Saline (7-7.8%)*	3-5 ml/kg over 15 minutes. May repeat.	<input type="checkbox"/> Contraindicated in hyponatremic patients. <input type="checkbox"/> Monitor serum sodium concentrations with repeat dosing. <input type="checkbox"/> If using 23.4% solution, dilute 1 part HTS with 2 parts 0.9% saline or sterile water.
Anticonvulsant Therapy			
Actively seizing patients.	Diazepam or Midazolam	0.5 mg/kg IV or rectal bolus. .2 -.5 mg/kg/hr CRI.	<input type="checkbox"/> Do not administer diazepam CRI into peripheral catheters due to the risk of phlebitis.
	Levetiracetam (Keppra™)	20 mg/kg IV bolus	<ul style="list-style-type: none"> • Not metabolized by the liver, so potentially safer in animals with hepatic disease • Minimal sedative effects
Prophylaxis for immediate or early seizures. Status epilepticus or cluster seizures.	Phenobarbital	16 mg/kg loading (divide into 4 doses). 2 mg/kg q 12hr maintenance dose.	<input type="checkbox"/> Evaluate chemistry for evidence of hepatic dysfunction. <input type="checkbox"/> Monitor ventilation and blood pressure during loading.
	Potassium Bromide	120 mg/kg/day PO for 5 days, then 30 mg/kg/day PO	<input type="checkbox"/> Sodium bromide can be substituted at the same dose and given IV.

[†] 23.4% HTS: dilute 1 part HTS with 2 parts Dextran-70 or Hetastarch.

* 7-7.5% HTS: administer separate doses of HTS and Dextran-70 or Hetastarch (3-5 ml/kg each).

Never Let a Patient Die Without the Benefit of Steroids: What's the Evidence?

Daniel Fletcher, PhD, DVM, DACVECC
Cornell University
Ithaca, NY

Corticosteroids have been used for a wide variety of disorders in human and veterinary medicine for years. Few drugs have been used as extensively, as evidenced by the familiar adage “never let a patient die without the benefit of steroids.” This lecture will focus on the use of steroids for 2 common conditions in veterinary emergency medicine, neurotrauma and hypovolemic shock.

There are many glucocorticoid medications, which vary greatly in their potency, durations of biologic action, mineralocorticoid effects and other systemic effects. There are glucocorticoid receptors in the cytosol of almost every cell in the body, affording these drugs a wide range of cellular effects. Therefore, before using a glucocorticoid, the risk/benefit ratio and the potential for unrelated physiologic effects must be considered. The table below summarizes the relative potencies and durations of action of some of the more commonly prescribed glucocorticoids in veterinary medicine.

Drug	Relative Glucocorticoid Potency	Relative Mineralocorticoid Potency	Duration of Action
Hydrocortisone	1	1	< 12 hours
Prednisone/Prednisolone	4	0.8	12 – 24 hours
Dexamethasone	30	0	24 – 48 hours
Methylprednisolone	5	0.5	12 – 24 hours
Trimacinalone	5	0	12 – 24 hours

Corticosteroid dosing is typically done in prednisone equivalents and three dosing ranges are commonly employed.

Immunosuppressive dosing of 2-4 mg/kg/day of prednisone is typically use for immune mediated disease. Anti-inflammatory effects are typically achieved with dosing of 1-2 mg/kg/day. For Addisonian patients, 0.25-0.5 mg/kg/day is generally sufficient to replace baseline glucocorticoid requirements.

Glucocorticoids have permissive effects on many vital physiological processes, and in the absence of normal physiologic levels of these hormones, serious systemic sequelae occur. For example, in the gastrointestinal tract, mucus production and enterocyte turnover are dependent upon basal cortisol concentrations. Vascular tone, glucose homeostasis, calcium homeostasis, and immune function are also dependent upon normal glucocorticoid metabolism. However, high concentrations of glucocorticoids can also be detrimental. For example, high doses of glucocorticoids reduce mucus production in the GI tract leading to ulceration, and prostaglandin production in the kidney, essential for maintaining renal perfusion in the face of hypotension, is inhibited by high concentrations of these compounds. Therefore, clinical use of these drugs can have significant consequences on homeostasis, especially at higher doses.

Traumatic brain injury

Despite their traditional role in the treatment of CNS trauma, there is little evidence to support the use of glucocorticoids in victims of severe head trauma. Early experimental studies showed a neuroprotective effect of high dose methylprednisolone in head injured animals, but only when the drugs were administered before the traumatic injury. This protocol involves the intravenous administration of a 30-mg/kg bolus of methylprednisolone sodium succinate (Solu-Medrol) at time 0, and 15 mg/kg boluses at 2 hr and 6 hr. The “high-dose” protocol was suspected to provide therapeutic benefit via free-radical scavenging action, rather than by activation of steroid receptors. No studies have shown any efficacy of prednisone/prednisolone or dexamethasone for treatment of head injury. Despite this, “standard” dosing protocols of prednisone and dexamethasone can be found in many veterinary formularies, and are commonly at doses far exceeding immunosuppression. Recent evidence from a large, prospective, randomized, placebo-controlled clinical trial (the CRASH-2 Trial) showed significantly increased mortality in people with traumatic brain injury treated with this high-dose protocol compared to a placebo group. Given this evidence of a detrimental effect in head injured people and the potential side effects of these drugs, including gastrointestinal ulceration, immunosuppression, and hyperglycemia, corticosteroids are no longer recommended in human patients with head trauma, and in fact are considered a contraindicated therapy. It is likely that the same approach should be followed in veterinary medicine.

Spinal cord injury

Corticosteroids have been proposed to ameliorate secondary injury after spinal cord trauma in both human and veterinary medicine. However, this is a highly controversial topic and has been the subject of intense debate in the human literature for over a decade. Experimental and clinical studies have documented both benefit and harm from the use of these drugs in patients with spinal cord injury. A thorough understanding of the evidence for both benefit and harm is essential for the clinician considering administration of these drugs. Methylprednisolone sodium succinate (MPSS) has been extensively studied in both experimental studies and clinical trials as a therapy for secondary spinal cord injury. Proposed neuroprotective mechanisms include improvement of spinal cord blood

flow, free-radical scavenging effects, and anti-inflammatory activity. Free radical scavenging has been shown experimentally to be the most important protective effect in patients with spinal cord injury. Other common corticosteroids (e.g., dexamethasone, prednisone) have minimal anti-oxidant effects, and are unlikely to have any significant neuroprotective effect, although they may reduce the discomfort associated with the injury. A series of three human clinical trials (the National Acute Spinal Cord Injury Study or NASCIS) provide the primary evidence of a beneficial effect of MPSS in human patients with spinal cord injury. The only placebo-controlled trial (NASCIS 2) showed a mild improvement in motor scores at 6 weeks for patients treated with MPSS (30 mg/kg bolus, followed by a constant rate infusion of 5.4 mg/kg/hr for 48 hours) compared to the placebo group, but this effect was not present at 6 months or 1 year post-injury. Only in a post-hoc, sub-group analysis were the authors able to show an improvement in motor scores at 6 weeks, 6 months and 1 year in the group of patients treated with MPSS for 48 hours beginning 3-8 hours post injury. No difference in outcome between the treatment groups was noted at any of the time points for patients treated less than 3 hours or greater than 8 hours after injury. There were no differences in mortality between the groups, but there was an increased incidence of severe pneumonia and a trend for an increased risk of sepsis in the groups treated with MPSS for 48 hours at the 6 week time point.

There has been much debate in the human literature over the results of the NASCIS 2 trial. Although the use of high dose MPSS for patients with spinal cord injury continues to be considered standard of care, several surveys have shown a lack of confidence in this therapy among human neurosurgeons. No placebo-controlled trials evaluating the efficacy of MPSS in veterinary patients with spinal cord injury have been done. Studies have shown significant side effects of corticosteroid treatment in spinal cord injured dogs, including gastrointestinal ulceration as well as prolonged hospital stays. Given the prevalence of complications, the lack of clinical trials demonstrating efficacy in veterinary species, and the likelihood that the mild functional improvements noted in the NASCIS 2 trial would not correlate to significant improvements in quality of life in veterinary species, it is the author's opinion that the risks of high dose steroid therapy outweigh the potential benefits.

Hypovolemic shock

Hypovolemic shock results from loss of intravascular volume, leading to decreased tissue perfusion. The ensuing tissue hypoxia promotes the arachidonic acid cascade and leads to production of inflammatory cytokines. Systemic inflammation, vasodilation, and increased vascular permeability results. Ultimately platelet activation and neutrophil chemotaxis and adhesion occurs. Upon reperfusion, reactive oxygen species exacerbate tissue damage. Physical obstruction of capillaries by thrombi, activated platelets, and edematous endothelial cells exacerbate maldistribution of flow even after volume resuscitation.

Because of their anti-inflammatory effects, corticosteroids have potential benefits in limiting the inflammatory cascade triggered by hypovolemic shock. In addition, they antagonize vasoactive substances such as histamine and kinins that may cause vasodilation, and stabilize lysosomal and endothelial cell membranes. Some corticosteroids, most notably methylprednisolone, also limit the generation of free-radicals.

In experimental studies, short-term survival is improved when high dose glucocorticoids are administered with fluids within an hour of initiation of shock. Lysosomal enzyme release is decreased in canine hemorrhagic shock models, but only when animals are treated before the initiation of shock. No clinical study has ever shown a survival benefit of using corticosteroids in patients with hypovolemic shock.

The massive doses of corticosteroids recommended for shock have substantial negative effects, including gastric ulceration and bleeding via inhibition of cyclooxygenase-1 formation. Immunosuppression is also likely with these treatment protocols, increasing the risk of infection. Finally, by decreasing prostaglandin production in the kidney, acute kidney injury may be induced by blunting the normally protective auto-regulatory functions.

The use of corticosteroids in hemorrhagic shock has been discouraged in human medicine for decades. Two extensive meta-analyses published in 1967 and 1973 concluded that there was no indication for the use of glucocorticoids in hypovolemic shock, and these drugs are no longer considered standard of care in these cases. Finally, a veterinary review of the available literature published in 1998 concluded, "Although it has long been stated that no animal should die without the benefit of corticosteroids, it may be time that we allow some of our patients to live without them." When considering the potential risks and benefits of steroids for hypovolemic shock, it is difficult to continue to recommend their use.

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Veterinary ER Team Training: How it Can Transform Your Practice Culture

Daniel Fletcher, PhD, DVM, DACVECC
Cornell University
Ithaca, NY

Teamwork is defined by a set of interrelated knowledge, skills, and attitudes (KSAs) that facilitate coordinated, adaptive performance, improving a group's ability to meet its objectives. Both teamwork and taskwork (i.e., operational skills) are required for teams to be effective in complex environments like veterinary medical settings. However, knowledge and skill at the task level are not sufficient for success in the clinic. Teamwork depends upon the ability of each member of the team to:

- Anticipate needs of others
- Adjust to each other's actions and the changing environment
- Have a shared understanding of how a plan of care should happen

In human health care, there has been significant progress in defining team requirements since the Institute of Medicine (IOM) published "To err is human" in 1999.¹ This report documented as many as 98,000 preventable deaths in hospitals in the US each year due to medical errors. It is estimated that 80% of serious medical errors in human health care occur due to miscommunication among the team of caregivers. The publication of this report and the research upon which it was based led to the development of TeamSTEPPS® by the Department of Defense (DoD) and the Agency for Healthcare Research and Quality (AHRQ), which was released in 2006. In 2014, the TeamSTEPPS® program was updated to version 2.0 to streamline some of the tools and update the evidence base. The TeamSTEPPS approach leads to increased desirable teamwork and safety attitudes, as well as increased communication, teamwork behaviors, clinical process compliance, efficiency, and overall performance in a variety of medical settings.²⁻⁴ This lecture will focus on the 4 basic concepts of the TeamSTEPPS® program, leadership, communication, situation monitoring, and mutual support, as well as the knowledge, skills and attitudes necessary to achieve optimal team performance and maximize patient outcomes. We will introduce several tools that you can use in your practice to improve team dynamics and communication, reduce medical errors, and improve staff morale.

Highly functioning team members can anticipate the needs of other team members, dynamically adjust to a changing environment, and have a shared understanding of what should happen. In addition, clients should be considered part of the health care team and empowered to take an active role in patient care.

Effective leaders manage resources and facilitate team actions to ensure that all members of the team are seeking information, plan and continually refine team duties, coordinate team actions, resolve conflict among team members, and provide coaching and feedback. Leaders must balance the role of handing down solutions to problems with that of facilitating problem solving the team. By developing a shared vision with the team, facilitating coordination and collaboration, and motivating team members, effective leaders maximize the performance of each team member and improve patient care. Three communication tools can be used by team leaders to establish a supportive, collaborative environment in which each member of the team can maximally contribute to patient care: briefs, huddles, and debriefs.

A **brief** is a team strategy used by team leaders to share a patient care plan and encourage input from team members. During a brief, the leader forms the team, designates the role and responsibilities of each team member, establishes the climate and sets goals, and engages all members of the team in planning. During the brief, it is important that all of the following questions are answered: Who is on the core team? All members understand and agree upon the goals? Roles and responsibilities understood? Does everyone understand the plan of care? Can all team members manage additional workload? Are all necessary resources available? This simple communication tool allows the entire team to establish a shared mental model of the needs of the patient and reduces miscommunication among team members, one of the major contributors to serious medical errors.⁵

A **huddle** is used when patient status has changed or a modification to the treatment plan is needed for any reason. It's an ad hoc meeting to re-establish a shared mental model among team members, discuss critical issues, reassign resources, express concerns, and to anticipate outcomes and contingency plans. In addition to improving patient safety, the use of huddles has been shown to improve the working relationships between members of inter-professional teams.⁶

A **debrief** is a tool for team development and process improvement. It is a brief information exchange and feedback session done after a shift or a specific critical event. It is focused on identifying teamwork challenges with the goal of improved team performance and patient outcomes. The debrief is focused on answering the following questions: Was communication clear? Were roles of each team member understood? Was workload distributed effectively? Was assistance asked for and offered? Were errors made or avoided? What went well, and what could be improved?

The debrief should be informal, and all team members should be encouraged to participate. Consistent use of debriefing has been shown to increase individual and team performance and to improve patient outcomes.^{7,8}

Leadership is an essential component of the TeamSTEPPS® approach, and is crucial for sustaining the trained behaviors and desired outcomes of the program. Ultimately, effective teams are defined by excellent communication, a shared mental model of patient status, and leadership that maximizes the performance of each team member, with the ultimate goal of improved patient care.

Situation awareness

Situation monitoring is an individual skill that involves active assessment of the clinical setting and continual scanning of the environment that allows each member of a health care team to maintain an accurate awareness and understanding of the current “situation.” It is essential that all members of the health care team maintain these monitoring activities, which contribute to team cognition. By practicing situation monitoring, the team can develop a shared mental model of any clinical situation and work as a highly effective unit in which each member is contributing maximally to patient care, unfettered by misunderstandings or conflicting assessments. Ultimately, good situation monitoring skills and a shared mental model lead to shared situation awareness, in which each member of the team is on the same page at all times.^{9,10}

The important individual components of situation monitoring can be summarized by the acronym **STEP**. The table below lists each aspect of situation monitoring and examples of individual items of which all team members should remain aware. This approach can help inform the initial brief called by the team leader, and as the status of the patient changes, any member of the team may call a huddle to discuss the change and suggest alterations to the plan.

S	Status of the Patient	Hx, Vitals, Medications, PE, Plan of Care
T	Team Members	Fatigue, Workload, Skill Level, Stress Level
E	Environment	Facilities, Triage Acuity, Equipment
P	Progress to Goal	Goal of Team, Tasks/Actions to be Completed, Is the Plan Still Appropriate?

There are many ways team members can improve situation awareness and improve the ability of the team to develop a shared mental model, including sharing new information with all team members, requesting information from other members of the team, directing information explicitly to specific team members, including the client in communication about the case, maintaining a thorough and complete medical record, knowing and understanding the plan, and informing all team members when the plan has changed, ideally with a huddle.

The TeamSTEPPS® approach includes several tools to facilitate situation awareness. In general, all communication between team members should adhere to the following 4 principles of effective communication: (1) Complete: communicate all relevant information, (2) Clear: convey information that is plainly understood, (3) Brief: communicate all information concisely, (4) Timely: make information available when needed, verify its accuracy, and acknowledge the information.

Call-outs are used to communicate important or critical information to all team members simultaneously in an emergency. As a team member acquires information that is important to patient care, he or she clearly and succinctly calls out that information so that all team members can hear. This allows all team members to maintain an accurate shared mental model, and helps team members to anticipate next steps. There is strong evidence in multiple practice settings that simple tools like the call-out improve patient outcomes and team performance in varied practice settings.^{11,12}

The **check-back** is a tool that uses closed-loop communication to ensure that vital information is received and understood by a specific team member. A check-back is initiated by someone with information or a request directed at a specific team member. The receiver acknowledges that the message was received and repeats back the pertinent information to ensure that the information was received accurately. The sender then verifies that the information received was correct. Proper use of the check-back is an efficient way to minimize errors, and has been shown to improve patient outcomes and team performance in a number of studies.^{13,14}

When important information must be conveyed from one member of the team to another, such as a change in patient status, the **SBAR** provides a framework for efficient, effective communication of that information. By using this standardized approach, essential information can be communicated quickly and concerns can be addressed efficiently. The components of an SBAR are:

- **Situation** – What is going on with the patient?
- **Background** – What is the relevant clinical background or context?
- **Assessment** – What do you think the root problem is?
- **Recommendation** – What would you suggest the team member do?

Using the SBAR approach can streamline communication of important information between members of the team and minimize misconceptions.

Transferring care of a patient from one team to another (such as from the day shift to the night shift or from one service to another) is called a **handoff**. Many studies have identified handoffs as major risks for medical errors, and a structured approach to handoffs is now widely advocated.¹⁵⁻¹⁷ The **I-PASS** approach has recently been developed and is associated with a 40% reduction in medical errors and significant reductions in verbal and written miscommunication rates in an initial pilot study.¹⁸ The components of an I-PASS handoff include

- Illness Severity – categorized as (1) stable, (2) “watcher”, (3) unstable
- Patient Summary – events leading up to admission, hospital course, ongoing assessment, plan
- Action List – To do list, Time line and ownership
- Situation Awareness / Contingencies – Know what’s going on, plan for what might happen
- Synthesis by Receiver – Receiver summarizes what was heard, Asks questions, Restates key action items

Mutual support

Mutual support can be thought of as the employment of “back-up behaviors” among members of a team. It involves reallocating resources to a member of a team to help that team member achieve the desired goal when it is apparent that the team member is failing. At its core, mutual support is simply the concept of helping others on the team perform their tasks to optimize patient care and address team member limitations and other demands. Backup behaviors often include filling in for a team member who cannot perform a task (e.g., inexperienced, incapable, overburdened, about to make an error), helping others correct mistakes, or redistributing work to a team member who is underused.

Ultimately, mutual support in a healthcare environment is an acknowledgement that the clinical setting is frequently characterized by a high workload in combination with the requirement to efficiently complete acute, time-sensitive tasks. Demands and priorities change frequently in this setting, and mutual support provides a safety net to reduce errors, increase effectiveness, and minimize stress due to workload. Incorporation of mutual support training into health care curricula have been shown to reduce length of hospital stay by 50%, reduce hospital costs by 19%, and reduce both medical errors and mortality.¹⁹⁻²¹

Mutual Support involves three actions: (1) assisting other team members, (2) providing and receiving feedback, and (3) assertive and advocacy behaviors when patient safety is threatened. It is essential that team members foster an environment in which these actions are not only encouraged, but are expected behaviors that become part of the culture.

Assisting Team Members: Acknowledgement that the veterinary healthcare environment is one of rapidly shifting workloads and demands, it is essential that all team members understand that a workplace in which assistance with tasks is actively sought *and* offered is a highly effective method of reducing medical errors and improving patient care. Encouraging all members of the team to check in with colleagues and to offer and ask for help will help create a culture of mutual support.

Feedback: Feedback is an essential component of improving team performance and addressing limitations of individual team members and of the overall team dynamic. Both formal, evaluative feedback, such as performance reviews and case conferences, and informal, real-time feedback, such as huddles and debriefs are needed for professional development and honing team skills.

Advocacy and Assertion: All members of the team must be comfortable advocating for the patient when their viewpoints are at odds with those of a decision maker. It is the responsibility of each team member to assert a corrective action in these cases in a *firm* but *respectful* manner. An assertive statement should be respectful and supportive of authority, but clearly assert the concern of the team member as well as the suggested alternative approach. It should be non-threatening, and include all critical information that led to the alternative conclusion reached by the team member. **CUS** is an acronym used to frame an assertion by a team member.

- I am **C**oncerned – explain the patient data that lead to your concern
- I am **U**ncomfortable – explain why the data could lead to a patient safety issue
- This is a **S**afety Issue – explain what consequences you feel could occur and your suggested plan of action

Resources

TeamSTEPPS® Homepage: <http://www.ahrq.gov/professionals/education/curriculum-tools/teamsteps/>

I-PASS Handoff Materials: <http://www.ipasshandoffstudy.com/>

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Shake, Rattle, and Roll: How to Manage Patients with Acute Seizures

Daniel Fletcher, PhD, DVM, DACVECC
Cornell University
Ithaca, NY

Seizures are initiated by a high frequency burst of action potentials within a hypersynchronized population of neurons. Hypersynchronization of a large enough population of neurons leads to the characteristic “spike” seen in the electroencephalogram (EEG), measured via electrodes placed on the scalp surface. Causes of seizures can be divided into two main categories: extracranial diseases and intracranial diseases. Determining the definitive cause an individual patient’s seizures can require an extensive diagnostic workup.

Extracranial diseases

Metabolic disturbances and systemic disease can lead to alterations in the electrophysiology of the brain, causing paroxysmal neuronal discharges and seizures. In general, these types of diseases are likely to cause widespread disturbances affecting both hemispheres. Therefore, generalized seizures are more common than focal seizures. Endogenous toxins accumulating due to hepatic or renal disease can lead to seizures. Metabolic disturbances such as hypoglycemia, hyperlipidemia, and hypocalcaemia, as well as endocrine diseases such as hypothyroidism and diabetes mellitus (hyperosmolar non-ketotic) can also lead to seizures. Many toxicoses, including bromethalin, theobromine, caffeine, lead or organophosphate poisoning may also result in seizures.

Intracranial diseases

There are many, primary intracranial causes of seizures. A classification scheme, such as DAMNIT-V, can be helpful for organizing this large list.

- Degenerative: Storage diseases
- Anomalous: Hydrocephalus, lissencephaly
- Metabolic: See extracranial diseases above
- Neoplastic: Primary brain tumors as well as metastatic disease
- Infectious: Viral (rabies, distemper, FIP), Bacterial, Fungal (Cryptococcus), Protozoal (Toxoplasma, Neospora), Rickettsial (Rocky Mountain Spotted Fever)
- Inflammatory: Granulomatous meningoencephalomyelitis (GME), sterile meningitis, necrotizing encephalitis
- Trauma: Head trauma
- Toxin: See extracranial diseases above
- Vascular: Thromboembolic disease, intracranial hemorrhage

Extracranial stabilization

Rapid identification and treatment of life-threatening extracranial sequelae of seizures is key to successful case management and good patient outcome.

Hyperthermia

Sustained seizure activity can result in dramatically elevated body temperature. Body temperature should be measured as soon after presentation as possible. The temperature at which animals experience clinical sequelae of hyperthermia varies depending on previous conditioning, but any patient presenting with a core body temperature greater than 105°F (40.6°C) should be actively cooled. Room temperature intravenous fluids, wetting the fur, and cooling with fans are recommended. Core body temperature should be rechecked frequently, or a continuous rectal temperature probe placed. Active cooling should be discontinued when the temperature drops to 103°F (39.4°C). The use of ice packs or ice baths is not recommended, as these can lead to peripheral vasoconstriction, decreasing heat loss through the skin. Hyperthermia can lead to many systemic sequelae, including DIC, hypoglycemia, acid-base disturbances, hypotension, and pulmonary edema. Close monitoring and appropriate therapy for these sequelae, should they arise, should be initiated.

Perfusion

Perfusion deficits can develop in patients with severe, acute seizures due to vasodilation secondary to hyperthermia or neurogenic shock. Blood pressure should be closely monitored and hypotension aggressively treated. Cerebral blood flow is determined, in part, by Cerebral Perfusion Pressure (CPP), which is the difference between Mean Arterial Pressure (MAP) and Intracranial Pressure (ICP). Decreases in MAP can lead to profound decreases in CPP, leading to compromised cerebral blood flow and reduced delivery of oxygen and glucose to the brain. This can compound the neuronal injury inflicted by the seizures themselves. Aggressive fluid therapy with isotonic crystalloids, hypertonic crystalloids, and/or synthetic colloids should be initiated early in the course of treatment to

normalize blood pressure. In patients with persistent, inappropriate vasodilation that remain hypotensive in the face of adequate volume resuscitation, pressor therapy (e.g., dopamine or norepinephrine infusions) should be considered.

Ventilation

The partial pressure of carbon dioxide in the arterial blood (PaCO_2) is a potent regulator of cerebrovascular tone. The contents of the calvarium include the cerebrospinal fluid (CSF), brain parenchyma, and blood. These contents are confined within a rigid skull, and significant increases in any of these volumes without a compensatory drop in another can lead to severe increases in ICP.

Hypoventilation causes an increase in the PaCO_2 , which leads to cerebral vasodilation and an increased volume of blood within the calvarium. This can then cause increased ICP, which compromises cerebral perfusion. Conversely, hyperventilation, leading to a decreased PaCO_2 causes cerebral vasoconstriction, decreasing cerebral blood flow and the delivery of oxygen and glucose to the brain. Therefore, normocapnea is essential to maintaining cerebral perfusion. Some anticonvulsants can lead to sedation and hypoventilation (barbiturates, propofol), requiring intubation/tracheostomy and mechanical ventilation. Acid-base disturbances and hyperthermia can lead to hyperventilation, and should be treated aggressively to minimize effects on cerebral blood flow.

Oxygenation

The brain has a high basal metabolic rate and is intolerant of decreases in oxygen delivery. Patients with severe, acute seizures can develop hypoxemia secondary to non-cardiogenic pulmonary edema, aspiration pneumonia, or hypoventilation. Oxygen supplementation should be provided via mask, oxygen cage, nasal catheters, or intubation. In cases of severe edema or pneumonia, mechanical ventilation with Positive End Expiratory Pressure (PEEP) may be required to address hypoxemia. Finally, oxygen carrying capacity of the blood is determined primarily by the amount of hemoglobin present. Anemic patients should receive transfusions of blood or Hemoglobin Based Oxygen Carriers (e.g., Oxyglobin) to address decreased oxygen carrying capacity.

Intracranial stabilization

Once major, life-threatening extracranial issues have been addressed, attention should be turned to the treatment of intracranial sequelae of the seizures. Aggressive treatment of cerebral edema and increased ICP, and facilitation of cerebral venous outflow are the major therapeutic interventions available.

Hyperosmotic therapy

Development of cerebral edema is common during and after severe, acute seizures. Intracellular accumulation of sodium and calcium, oxidative damage, inflammation and ischemia all contribute to edema formation. As described above, small increases in intracranial volume can lead to large increases in ICP due to the presence of the rigid skull. Mannitol is an effective therapy for patients with increased ICP, and has been shown to reduce cerebral edema, increase CPP and CBF, and improve neurologic outcome in patients with cerebral edema. It has a rapid onset of action, with clinical improvement occurring within minutes of administration, and these effects can last as long as 1.5-6 hours. Mannitol boluses of 0.5-1.5 g/kg have been recommended for treatment of increased ICP in dogs and cats. Mannitol may increase the permeability of the blood-brain barrier (BBB), an effect that is most pronounced when the BBB is exposed to the drug for prolonged periods of time. The increased permeability can allow mannitol to leak into the brain parenchyma, where it can exacerbate edema. To reduce the risk of this effect, the drug should be administered in repeated boluses rather than as a constant rate infusion. The diuretic effect of mannitol can be profound and can cause severe volume depletion. Therefore, treatment must be followed with isotonic crystalloid solutions and/or colloids to maintain intravascular volume. In people, mannitol may induce acute renal failure if serum osmolality exceeds 320 mOsm/L; therefore, serum osmolality should be measured if possible when repeated doses are administered.

Hypertonic saline (HTS) is a hyperosmotic solution that may be used as an alternative to mannitol in patients with cerebral edema. Because sodium does not freely cross the intact BBB, HTS has similar osmotic effects to mannitol. Other beneficial effects of HTS include improved hemodynamic status via volume expansion and positive inotropic effects, as well as beneficial vasoregulatory and immunomodulatory effects. Rebound hypotension is uncommon with HTS administration because unlike mannitol, sodium is actively reabsorbed in the kidneys, especially in hypovolemic patients. This makes it preferable to mannitol for treating patients with increased ICP and systemic hypotension due to hypovolemia. In euvolemic patients with evidence of intracranial hypertension, both mannitol and HTS can have beneficial effects. If an individual patient is not responding to one drug, the other may yield a beneficial response.

Decreasing cerebral blood volume

Cerebral vasodilation and blood pooling can cause increases in the total volume of blood within the calvarium, or cerebral blood volume (CBV), and can contribute to increased ICP. In cases of severe, acute intracranial hypertension, short term hyperventilation to an arterial CO_2 of 25-35 mmHg may be utilized to reduce CBV and ICP. However, chronic hyperventilation is not recommended due to evidence that the decrease in CBF leads to cerebral ischemia and worsens outcome. of the head by 15-30 degrees reduces CBV by increasing venous drainage, decreasing ICP and increasing CPP without deleterious changes in cerebral perfusion. It is imperative that occlusion of the jugular veins be avoided by using a slant board to prevent bending the neck. Angles greater than 30 degrees may cause a detrimental decrease in CPP.

Acute anticonvulsant therapy

It is vital that seizure activity be stopped as soon as possible to prevent continued injury to the brain and to reduce the potential for systemic sequelae. Anticonvulsant therapy should be initiated immediately to stop the seizure and to allow further evaluation and stabilization of the patient

Benzodiazepines

Intravenous diazepam (0.5 – 1.0 mg/kg) or midazolam (0.066 – 0.22 mg/kg) should be considered first line therapy for patients with severe, acute seizures. These drugs are GABA agonists, leading to hyperpolarization of neurons and cessation of seizure activity. They are generally effective and safe in dogs and cats, and have a low likelihood of significant side effects. For patients in whom intravenous access is not readily available, diazepam at a dose of 1 – 2 mg/kg is rapidly absorbed intrarectally. Other benzodiazepines, such as midazolam and lorazepam, may be poorly absorbed after intrarectal administration and are not recommended. Intranasal administration of diazepam (0.5 mg/kg), lorazepam (0.2 mg/kg) and midazolam are also effective, but place the administrator at increased risk of being bitten by a seizing animal. If the patient responds to benzodiazepine therapy but rapidly recrudesces, an intravenous constant rate infusion (CRI) is a good option. Diazepam at 0.5 – 2.0 mg/kg/hr is often effective. Diazepam administered undiluted via a peripheral vessel can cause vasculitis; use of a central line or dilution in intravenous fluids is recommended. In addition, injectible benzodiazepines are light sensitive, so infusion lines should be wrapped.

Barbiturates

For patients refractory to benzodiazepine therapy, barbiturates (pentobarbital, Phenobarbital) can sometimes be effective. Pentobarbital (2 - 15 mg/kg IV) can effectively terminate the physical manifestations of seizure activity within several minutes, but it is not generally considered to be an effective anticonvulsant and is unlikely to stop seizure activity in the brain. Phenobarbital is an effective anticonvulsant (2 – 6 mg/kg IV), but can take 15-20 minutes to have an effect. If an effect is not noted within 15-30 minutes, the dose may be repeated to raise blood levels to the therapeutic range more rapidly (to a maximum loading dose of 16 mg/kg within the first 24 hours), but care must be taken to avoid overdose.

Propofol

Propofol is a rapidly acting injectible anesthetic that is a centrally acting GABA agonist. It may be administered via slow IV injection at a dose of 1 – 6 mg/kg and has been shown to be effective for stopping seizure activity (cluster seizures and status epilepticus) in human and veterinary medicine. If the initial bolus dose is effective but seizures recur, a CRI at 0.1 – 0.6 mg/kg/min may be instituted. Apnea and cardiovascular depression are important side effects to consider, and it is the author's opinion that any animal receiving a propofol infusion should be intubated to protect the airway, and ventilation should be closely monitored to avoid the sequelae of hypoventilation. In addition, propofol has been associated with transient seizure activity on induction and discontinuation of infusion in people.

Levetiracetam (Keppra)

Levetiracetam is a piracetam anticonvulsant that has shown efficacy for treatment of seizures in people and experimental animals. The mechanism of action of this drug is not fully understood but it seems to stabilize pre-synaptic vesicles, inhibiting the release of excitatory neurotransmitters. It has a high bioavailability in dogs and is excreted unchanged in the urine without any significant hepatic metabolism, suggesting that it may be safer than benzodiazepines or barbiturates for treatment of seizures in patients with hepatic disease. It has no sedative side effects, making it easier to evaluate neurologic status in treated patients. Intravenous administration of levetiracetam appears to be well tolerated in dogs, even at very high doses of 400 mg/kg (published oral dose = 20 mg/kg PO q 8hr). Although the use of this drug for severe, acute seizures has not yet been described in the veterinary literature, it may prove to be a useful addition to the anticonvulsant armamentarium, and is available in an intravenous formulation (also administered at 20mg/kg as a bolus).

Derailing the Pain Train: Analgesia in the ER

Garret Pachtinger, DVM, DACVECC
Veterinary Specialty and Emergency Center
Levittown, PA

Veterinarians are faced with clinical challenges every day with the goal of solving diagnostic dilemmas, reducing morbidity and mortality, and ultimately restoring patient health. One of the most challenging issues we face is determining the best sedation and/or anesthesia protocol for the sick, small animal patient. The objective of this lecture is to provide a clinical tool for understanding common sedation and/or anesthesia options for veterinary patients.

Regardless of the presenting complaint, an important concept to remember when approaching any emergency patient is a rapid primary survey, keeping in mind the ABCDs of evaluation and resuscitation. Briefly, "A" refers to Airway or Arterial Bleeding. "B", Breathing is equally important assessing the character of the patient's respirations. "C" refers to Circulation and the overall perfusion status of the patient. Finally, "D" refers to Disability notably the patients mental status.

What can we control?

The importance of oxygenation and perfusion can not be over emphasized. Supplemental oxygen either on presentation or pre-oxygenation prior to anesthesia are important concepts to remember in the sick, small animal patient.

Oxygen supplementation techniques

Supplementation technique	Required flow rate	Maximum inspired oxygen concentration achieved
Flow-by	3-15 l/min	40%
Oxygen cage	15 l/min	45-60%
Oxygen hood (unsealed bag)	5-15 l/min	85-95%
Oxygen collar	1 l/10 kg bodyweight/min	<80%
Nasal cannula	50-100 ml/kg/min	40%
Nasal catheters	50-100 ml/kg/min	40-50%
Nasopharyngeal catheter	50-100 ml/kg/min	60-70%
Nasotracheal catheter	25-50 ml/kg/min	80-90%

Aside from oxygenation, perfusion is an essential part of health to assess and address. Perfusion is defined as the flow of blood through arteries and capillaries delivering nutrients and oxygen to cells (hence the importance of oxygen supplementation as listed above) and removing cellular waste products.

Aside from oxygen, what else can we control?

Blood products

Oxygen delivery to the tissues is more than just administration of oxygen. Oxygen is carried in the blood in two forms: (1) dissolved in plasma and RBC water (about 2% of the total) and (2) reversibly bound to hemoglobin (about 98% of the total). It is therefore easy to see how oxygen molecules need a carrier to transport to the vital organs, hemoglobin. Patients that are anemic (PCV <20%) may require supplementation of red blood cells to improve their oxygen carrying capacity prior to sedation or anesthesia. This can be achieved with red blood cell products such as packed red blood cells or hemoglobin based oxygen carrying solutions (i.e. Oxyglobin®).

Volume

Aside from oxygen and a carrier molecule (hemoglobin within red blood cells), hypovolemic patients require volume replacement to improve perfusion and therefore oxygenation. Volume replacement is commonly achieved with crystalloid and/or colloid solutions.

Once the patient is deemed to be stable for sedation / analgesia / anesthesia, the clinician must critically evaluate which medication or medications would be most suitable.

Anesthesia / analgesia drug review

Alpha-2 agonists (medetomidine, dexmedetomidine, xylazine)

Alpha-2 agonist dexmedetomidine (Dexdomitor®) is a very specific drug affecting the alpha-2 receptor. More specifically, alpha-2 agonists work in the CNS via pre-synaptic receptors to decrease norepinephrine release, resulting in enhanced parasympathetic tone. Following administration, sedation lasts approximately 2 to 4 hours with analgesia lasting for a shorter period of time.

Dexmedetomidine is reversible with atipamezole (Antisedan®).

Side effects of alpha -2 agonists include stimulation of peripheral alpha-1 and alpha-2 receptors in the vasculature causing peripheral vasoconstriction (increased systemic vascular resistance). Clinicians commonly note hypertension with a reflex bradycardia, often with heart rates of 50 beats per minute or less! Additional clinical findings include an appearance of pale mucous membranes and peripheral vasoconstriction with cold extremities.

The combination of the dissociative tiletamine and benzodiazepine, zolazepam (Telazol®), is also commonly in small animal medicine, notably as a feline premedication. Telazol® provides mild analgesia and should not be used alone for procedures in which moderate to severe pain is expected, including castration, ovariohysterectomy, and dental extraction.

Xylazine, another alpha-2 agonist is less potent as compared to dexmedetomidine but induces a longer duration of hypertension through vasoconstriction. Xylazine is reported to induce a bi-phasic blood pressure with initial hypertension followed by prolonged hypotension. Anticholinergic agents such as atropine or glycopyrrrolate are often used in combination with xylazine. Conversely, the use of anticholinergic agents with dexmedetomidine is discouraged due to the risk of hypertension and arrhythmias. The sedation and analgesia induced by xylazine can be reversed with yohimbine.

Benzodiazepines (diazepam, midazolam)

The benzodiazepines, diazepam (Valium®) and midazolam (Versed®), are tranquilizers, specifically enhancing the activity of the central nervous system inhibitory neurotransmitter, gamma-aminobutyric acid, as well as, combining with benzodiazepine receptors in the central nervous system. These medications induce mild sedation, muscle-relaxation, and acts as an anticonvulsant.

Importantly, the benzodiazepine class of drugs does not have analgesic activity. They are reversible with flumazenil (Romazicon®).

Diazepam is supplied in a propylene glycol base, not a water based preparation, and therefore it is recommended to administer this intravenously as uptake from IM or SQ injection may be slow, unpredictable, and painful. Moreover, IV administration of propylene glycol based solutions have the risk of hemolysis, thrombophlebitis and cardiotoxicity. Conversely, midazolam is water-soluble and can be administered IV, SQ or IM with predictable uptake.

Dissociatives (ketamine)

Ketamine, a NMDA Receptor Agonist, provides both analgesic and sedative effects and cause dose-dependent depression of the central nervous system. Although the patient is dissociated from the environment, pharyngeal, laryngeal, corneal, and pedal reflexes persist and the eyes remain open. Tiletamine, which is chemically similar to ketamine, is more potent and has a longer duration of effect than ketamine.

These dissociative medications have minimal cardiovascular or respiratory depression. Ketamine should be used with caution in patients with cardiac disease such as hypertrophic cardiomyopathy, ischemic heart disease and renal insufficiency as it increases sympathetic tone and thus can increase blood pressure, heart rate and cardiac output. Ketamine also increases intra-cranial and intraocular pressure so should be used with caution with head trauma or seizure history.

Etomidate

Etomidate is a non-barbiturate anesthetic. Unlike other medications used for sedation or anesthesia, it does not affect cardiovascular function, notably having no effect on blood pressure, heart rate, or cardiac output. Concerns with this medication include its high osmolality (>4000 mOsm) which has the potential for hemolysis. It also interferes with cortisol production following induction.

Opioids (hydromorphone, methadone, morphine, oxymorphone, buprenorphine, butorphanol)

Opioids are considered to have three notable receptors, but clinically the mu and the kappa receptors are the ones most often considered when planning for sedation and analgesia.

Opioids commonly used in practice include hydromorphone, methadone, oxymorphone, morphine, butorphanol, and buprenorphine. Hydromorphone, methadone, oxymorphone and morphine are μ receptor agonists and are good choices for patients expected to experience moderate-to-severe pain. These opioids provide excellent analgesia as well as good sedative properties. Common clinical side effects include hypersalivation, vomiting, nausea, and panting. Morphine is also known to cause histamine release following IV administration.

Butorphanol is a not a pure agonist, rather considered an μ agonist/ K antagonist, meaning that it will reverse some μ opioid effects. These provide less potent analgesia as compared to the primary μ agonists and should be used only for mild pain or short-term pain.

Buprenorphine is considered a partial μ agonist with four-to-six-hour duration of effect. Clinically, the author uses this more in cats than dogs.

Phenothiazines (acepromazine)

Acepromazine is the most common drug used in the class of drugs known as the phenothiazines. Acepromazine provides sedation via anti-dopaminergic (D2) effects and suppression of the sympathetic nervous system. It causes an alpha-adrenergic blockade which results in vasodilation and often hypotension. It has a relatively long duration of action, considered to be 6-12 hours and is not recommended for patients with liver disease as decreased hepatic metabolism may result in a prolonged recovery. Acepromazine does not result in analgesia and therefore should not be used as a pain medication. It should also be avoided in patients with hypotension, hypovolemia, shock, significant heart disease, or coagulopathy/ platelet disease.

While previously it was believed that acepromazine may result in seizures in dogs with a history of seizures, A recent retrospective study has shown that acepromazine does not cause seizures in dogs with a history of seizures of various origins.

Propofol

Propofol is a non-barbiturate anesthetic and a popular medication in veterinarian medicine. Propofol undergoes hepatic metabolism as well as extra-hepatic metabolism. This drug has significant cardiovascular effects, decreasing cardiac output and causing vasodilation without a reflex tachycardia. Propofol should be used with caution in animals with hypotension, hypovolemia or cardiovascular dysfunction.

Alfaxalone

Alfaxalone is another drug that is becoming more popular in veterinary medicine and reported to have less cardiopulmonary depression than other intravenous induction agents such as thiopental or propofol. Alfaxalone, a progesterone analogue, is a neurosteroid which interacts with the gamma aminobutyric acid (GABA)_A receptor and produces anesthesia and muscle relaxation.

Opioid drug potency chart

Drug	Other names	Potency*
Morphine	Generic	1
Codeine	Generic	1/10
Hydrocodone	Vicodin, generic with acetaminophen	6x
Oxycodone	Percocet, OxyContin	3–6x
Oxymorphone	Numorphan	10x
Hydromorphone	Dilaudid, generic	8x
Meperidine	Demerol	1/6
Propoxyphene	Darvon	1/3–1/6
Buprenorphine	Buprenex	25x
Fentanyl	Sublimaze	100x
Butorphanol	Torbagesic, Stadol	5x

Common drug doses

	Dogs	Cats
Acepromazine mg/kg	0.01–0.02 S/C 0.005–0.01 IV	Acp is not an effective sedative
Alfaxalone mg/kg	Premedicated: 2mg/kg IV Not premedicated 3mg/kg IV	Premedicated: 2mg/kg IV Not premedicated 3mg/kg IV
Buprenorphine mg/kg	0.01–0.02 mg/ kg SQ, IM, IV	0.01–0.02 mg/ kg SQ, IM, IV
Butorphanol mg/kg	0.2–0.4mg/kg SQ, IM, IV	0.2–0.4mg/kg SQ, IM, IV

Dexmedetomidine micrograms/m ²	375 IV; 500 IM micrograms/m ²	40 micrograms/kg IM micrograms/m ²
Etomidate mg/kg	1–2 mg/kg	1–2 mg/kg
Fentanyl µg/kg	CRI: 0.1–0.7 µg/kg/min	CRI: 0.1–0.7 µg/kg/min
Hydromorphone mg/kg	0.05–0.2mg/kg SQ, IM, IV	0.05–0.2mg/kg SQ, IM, IV
Methadone mg/kg	0.1–1.0 mg/kg SQ, IM, IV	0.05–0.5 mg/kg SQ, IM, IV
Midazolam mg/kg	0.1–0.5 SQ, IM, IV	0.1–0.5 S/C, IV
Morphine mg/kg	0.1–1.0 mg/kg SQ, IM, IV	0.1–1.0 mg/kg SQ, IM, IV
Propofol mg/kg	1-6mg/kg IV	1-6mg/kg IV

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Respiratory Complications of Trauma

Garret Pachtinger, DVM, DACVECC
Veterinary Specialty and Emergency Center
Levittown, PA

Trauma is one of the most common emergencies seen in the busy emergency room. Examples of common veterinary trauma presentations include motor vehicle accidents (i.e. hit by car) interaction with other animals, interaction with humans, fall from heights, and penetrating trauma such as gunshot wounds, knife wounds, and impalement by sticks.

Trauma may affect only one body system or it may affect multiple organ systems. For this reason, the initial approach to the trauma patient must be rapid, thorough, and detailed to decrease further morbidity and mortality.

The initial triage evaluation should be rapid, developing a problem list outlining life-threatening conditions. The goals of the initial triage examination are to:

1. Assess / evaluate the ABCD's of triage medicine:

- Airway:** Does the patient have a patent airway? Upper airway or lower airway abnormalities?
- Breathing:** Does the patient have an abnormal breathing pattern? Is the patient dyspneic? Is there a rapid, shallow breathing pattern? Is there a slow, labored breathing pattern? Is there increased stertor or stridor?
- Circulation:** Is there an abnormal heart rate? Are the mucous membranes an abnormal color with evidence of internal or external hemorrhage? Are the pulses weak? Are the extremities cold?
- Disability:** Is there evidence of head trauma or other neurological injury?

2. Specifically regarding thoracic trauma, the goal is to rapidly determine if there are respiratory abnormalities. If present, the goal is to localize the cause for respiratory distress to best provide treatment:

- Inspiratory wheezes: associated with narrowing of the upper airways by inflammation, hemorrhage, mucosal edema, or mucus.
- Expiratory wheezes: associated with narrowing of the lower airways by inflammation, hemorrhage, mucosal edema, or mucus.
- Crackles: fluid present within the lower airways / alveoli (e.g. edema, hemorrhage)
- Stridor or stertor: indicates an upper airway respiratory abnormality
- Short / shallow pattern: may indicate pleural space disease such as pneumothorax, pleural effusion, or diaphragmatic hernia
- Paradoxical breathing: recognized by a lack of synchronous movement of the chest and abdominal walls.

Initial therapy chosen will be based on the degree and location of injury. Common therapies include oxygen supplementation, intravenous fluid therapy, and analgesia. Procedures such as a thoracocentesis may also be required, which can be both diagnostic and therapeutic.

Oxygen supplementation is one of the mainstays of therapy for a patient with respiratory difficulty. Initially, oxygen is often provided by facemask or flow-by to permit the clinician to perform the initial assessment. While oxygen cages may allow a higher percentage of oxygen to be delivered, it is difficult to assess the patient once in the closed oxygen cage, and therefore placement into the oxygen cage is often delayed until after initial assessment has been performed.

Oxygen supplementation techniques.

Supplementation technique	Required flow rate	Maximum inspired oxygen concentration achieved
Flow-by	3-15 l/min	40%
Oxygen cage	15 l/min	45-60%
Oxygen hood (unsealed bag)	5-15 l/min	85-95%
Oxygen collar	1 l/10 kg bodyweight/min	<80%
Nasal cannula	50-100 ml/kg/min	40%
Nasal catheters	50-100 ml/kg/min	40-50%

Nasopharyngeal catheter	50-100 ml/kg/min	60-70%
Nasotracheal catheter	25-50 ml/kg/min	80-90%

Intravenous access for fluid therapy and drug administration is also important. Initially, intravenous access is preferred via the use of peripheral veins, notably the cephalic or saphenous veins. Other sites such as the jugular vein, while available, are not preferred as placement is not only more technically challenging but requires increased restraint which can be distressing to the dyspneic patient. Moreover, the use of the jugular vein should be avoided if there is a concern for head trauma and increased intracranial pressure. If patient stability allows, when placing the catheter it is advised to pull blood for anticipated testing including a minimum database (packed cell volume (PCV), total protein (TP), Azostick / dipstick BUN, and blood glucose concentration). A complete blood count, chemistry panel, and coagulation panel can also be drawn at that time if patient stability allows.

Once intravenous access is obtained, fluid therapy for resuscitation can be initiated. The goal of fluid resuscitation is to restore tissue perfusion and oxygenation. The type, volume, and rate of fluid administration are determined based on the patient assessment and underlying injuries. The two most common fluid choices for the resuscitation phase are isotonic crystalloids and synthetic colloids. Examples of isotonic crystalloid replacement fluids are 0.9% saline, lactated Ringer's solution, Normosol-R or Plasmalyte-A. Typically smaller doses of fluids are administered (10-30ml/kg in the dog, 5-10ml/kg in the cat) with frequent re-assessment rather than large volumes at once with the risk of worsening respiratory distress. Colloids are larger molecular weight fluids considered intravascular volume expanders. Examples of synthetic colloids include Hetastarch and Vetstarch. Typically smaller doses of fluids are administered (2-5ml/kg in the dog, 1-3ml/kg in the cat) with frequent re-assessment rather than large volumes at once with the risk of worsening respiratory distress. Once initial evaluation, treatment, and stabilization have started, the clinician can further evaluate the patient with a more thorough general examination to assess other complications of thoracic trauma.

Airway trauma

Trauma to the major airways may be seen with penetrating wounds or blunt trauma to the neck and chest. Clinical signs of upper airway trauma include abnormal upper airway noise on inspiration and expiration. Respiratory changes may result from traumatic inflammation, edema, hemorrhage, or even tracheal rupture or avulsion.

Subcutaneous emphysema may also be noted on examination, prompting a thorough airway integrity assessment. Pneumomediastinum and pneumothorax are more severe complications of airway trauma. While subcutaneous emphysema and pneumothorax may be easily found on examination alone, the diagnosis of pneumomediastinum is made radiographically by increased contrast with the mediastinal structures resulting in a clear visualization of the thoracic vena cava, aorta and esophagus.

Pneumothorax

Pneumothorax is defined as the abnormal accumulation of air in the pleural space. Air accumulation is most commonly bilateral but unilateral pneumothorax can occur. It is the most common complication of blunt trauma to the chest. Studies have shown that animals hit by car with fractures had evidence of pneumothorax 47.1% of the time. Furthermore, 36% of dogs and 63% of cats that fell from high rises had evidence of pneumothorax on examination. Pneumothorax can be further classified as closed, open, and tension pneumothorax.

- Closed pneumothorax is seen following trauma due increased intra-thoracic pressure against a closed glottis causing rupture of alveoli or small airways, laceration of lung by fractured rib, iatrogenic, and airway or esophageal rupture causing pneumomediastinum which has progressed to pneumothorax.
- Open pneumothorax may result from gunshots, dog bites, knife wounds, and stick impalement.
- Tension pneumothorax is the third type, resulting when an air leak acts as one-way valve increasing intrathoracic pressure, compressing the lungs and decreasing venous return to the heart.

The astute clinician often makes the diagnosis of a pneumothorax based on history and examination alone. Common examination abnormalities include an increased respiratory rate and effort characterized by a short and shallow breathing pattern, dull lung sounds dorsally, and muffled heart sounds. Less specific examination abnormalities may include pale or cyanotic mucous membranes, poor pulses, and an abnormal posture with the head and neck extended and elbows abducted. While useful in the diagnosis of a pneumothorax, thoracic radiographs risk increased stress on the compromised patient. Radiographic signs of pneumothorax include elevation of the cardiac silhouette from the sternum, collapse of the lung lobes, and absence of vascular markings out to the periphery of the thorax.

Recently, the use of ultrasound has been documented for rapid detection of pleural space disease, specifically the "TFAST" (thoracic focused assessment with sonography for trauma) procedure. It does, however require practice to be competent in its use.

When radiographs are not suitable, the unstable patient may benefit from thoracocentesis, which can be both diagnostic and therapeutic. The equipment needed for this procedure includes clippers, scrub, sterile gloves, a 10-60ml syringe, 3-way stop-cock, butterfly catheter or needle and extension tubing. The site preparation and eventual needle placement for a patient suspected of a pneumothorax is on the dorsal 1/3 of the thorax between the 7th-10th intercostal spaces. The needle is inserted cranial to the rib to avoid the intercostal artery, vein, and nerve located caudal to each rib. Air is aspirated until negative pressure is obtained.

A chest tube is indicated when thoracocentesis needs to be repeated multiple times over a short period of time or when the clinician cannot achieve negative pressure on simple thoracocentesis. Large bore chest tubes require sedation or general anesthesia. Smaller bore chest tubes are also available, placed via the modified seldinger technique with the patient awake or receiving local analgesia. Equipment required for chest tube placement includes clippers, surgical scrub, surgical blade, local analgesia, suture material, the thoracostomy tube, 3-way stop-cock and syringes for initial aspiration. The chest tube can be used intermittently or attached to a suction device for continuous suction. The technique for chest tube placement will depend on the type of tube used, including surgical and trocar methods for the larger bore tubes or the modified seldinger technique for the smaller bore tubes. Similar to the thoracocentesis, surgical preparation of the site between the 7th-10th intercostal spaces is recommended.

Pulmonary contusions

Pulmonary contusions result from blunt or crushing trauma and are one of the most common problems associated with thoracic trauma, seen in approximately 50% of all thoracic injuries. Thoracic trauma leads to blood within the alveoli, ventilation/perfusion mismatch, increased pulmonary shunt fraction, and loss of lung compliance. Hypoxemia, increased work of breathing, and hypercarbia, are the physiologic results.

Physical examination findings may include tachypnea, hemoptysis, increased respiratory effort, and harsh lung sounds or crackles on auscultation. Radiographically, there may not be evidence of pulmonary contusions on presentation, delayed anywhere from 12 to 48 hours following trauma. When present, contusions appear radiographically as dense patchy, interstitial to alveolar disease.

As discussed above, initial fluid resuscitation must be started with caution as large volumes of rapidly administered fluid can exacerbate the fluid within the alveolar space with increased vascular permeability, worsening the hypoxemia. If radiographs have evidence of pulmonary contusions, the astute clinician should carefully look for concurrent abnormalities including pneumothorax and/or rib fractures. Additional diagnostic findings may include hypoxemia on pulse oximetry or arterial blood and an increased A-a gradient.

There is no specific medication or reversal therapy for pulmonary contusions. Common supportive care measures include oxygen supplementation, judicious IV fluid therapy, and analgesics. Although evidence is lacking, low dose diuretic therapy has been described anecdotally (furosemide, 0.5 to 1 mg/kg IV intermittently or CRI) in the treatment of pulmonary contusions.

Fractured ribs

Rib fractures result in discomfort and reduced diaphragmatic and chest wall motion. More specifically, the reduced chest wall motion and pulmonary expansion results in decreased oxygenation, ventilation, and atelectasis of the lungs. Rib fractures should be a clue to the astute clinician that severe thoracic trauma occurred prompting careful evaluation for additional injuries such as pulmonary contusions or a pneumothorax. Physical examination findings may include an increased respiratory rate with shallow respirations, subcutaneous emphysema, palpation of crepitus over the fracture site, and/or conformational changes of the chest wall.

Treatment of rib fractures consists of treating concurrent injuries such as pulmonary contusions, oxygen therapy if hypoxemia exists, and pain management with local or systemic analgesia.

Flail chest

A flail chest is a more severe manifestation of the simple rib fracture. A flail segment occurs when 2 or more ribs are fractured at the junction of ribs and the sternum producing a paradoxical movement of the flail segment. On inspiration, the chest wall normally expands. With a flail segment, the negative intrapleural pressure causes the flail segment to collapse inward during inspiration. On expiration, the chest wall normally collapses. With a flail segment, the intrapleural pressure becomes less negative and the flail segment moves outward on expiration. Abnormal chest movement and the accompanying pain from the fractures themselves result in decreased oxygenation, ventilation, and pulmonary atelectasis.

Treatment consists of placing the patient in lateral recumbency with the flail side down, minimizing movement of the flail segment and reducing the associated fracture discomfort. Pain management includes local nerve blocks and systemic opioid analgesia. Surgical stabilization of the flail segment may also be indicated.

Hemothorax

A hemothorax is defined as an accumulation of blood in the pleural space. This is uncommon following trauma. If present, the amount of blood loss into the pleural space is usually minimal and does not contribute significantly to respiratory compromise. If a large amount of hemorrhage into the pleural space is documented, there should be an increased suspicion for rupture of a large vessel.

More common causes for a hemodynamically insignificant hemothorax include laceration of pulmonary or intercostal vessels and/or lung laceration by a fractured rib.

The diagnosis of hemothorax is often made on physical examination with signs including dyspnea, tachypnea, dull lung sounds ventrally, muffled heart sounds, and signs of hypovolemic or hemorrhagic shock. Thoracocentesis confirms the diagnosis when hemorrhagic fluid is obtained during aspiration with a PCV and TP of the effusion similar to that of the PCV and TP of the peripheral blood.

Treatment of a traumatic hemothorax may include diagnostic and therapeutic thoracocentesis, intravenous crystalloid or synthetic colloid therapy and blood products, notably whole blood or packed red blood cell transfusions. Autotransfusion can be considered if blood products are not available.

Diaphragmatic hernia

Diaphragmatic hernia is defined as disruption of the diaphragm, allowing displacement of abdominal organs into the thoracic cavity. Diaphragmatic hernia occurs most often as a result of blunt trauma where intra-abdominal pressure is suddenly increased causing rupture of the diaphragm. The resulting herniation of abdominal contents can range from a single organ or component of an organ (such as a single liver lobe) to almost all the abdominal contents moving cranially through the diaphragmatic rent into the chest cavity. The result is restriction of lung expansion and respiratory distress.

The diagnosis of diaphragmatic hernia can be made with physical examination findings and radiographic abnormalities. Clinical signs of diaphragmatic hernia depend upon the type and number of organs within the chest cavity as well as associated abnormalities such as fluid in the pleural space or pulmonary contusions. Examination findings may be mild and include a slight tachypnea or may result in severe dyspnea, dull lung sounds, muffled heart sounds, borborygmi from the stomach or intestines ausculted in the thorax, abnormal percussion, and a tucked/empty abdomen on palpation. Thoracic radiographs are often diagnostic with the presence of abdominal organs in the thorax.

Treatment for diaphragmatic herniation will depend on the clinical signs of the patient with surgical repair being the definitive therapy. Although there are no recent studies which outline the recommended time from stabilization to surgical correction, worsening respiratory distress or compromised blood supply to the displaced organs and ischemia would warrant a more rapid surgical correction.

Summary

Thoracic trauma is common in small animal medicine. Most patients respond well to rapid and aggressive support therapy. Concurrent injuries are common and the clinician should carefully evaluate their patients to address each specific medical condition to reduce patient morbidity and mortality.

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Emergency Management of Cardiac Disease

Garret Pachtinger, DVM, DACVECC
Veterinary Specialty and Emergency Center
Levittown, PA

Cardiac diseases commonly seen in the small animal emergency room include congestive heart failure (mitral or tricuspid regurgitation, hypertrophic cardiomyopathy, dilated cardiomyopathy), myocardial failure (dilated cardiomyopathy, end-stage heart disease), pericardial effusion, arrhythmias, and aortic thromboembolism in cats secondary to HCM.

Regardless of the presenting complaint, an important concept to remember when approaching any emergency patient is a rapid primary survey, keeping in mind the ABCDs of evaluation and resuscitation. Briefly, "A" refers to Airway or Arterial Bleeding. "B", Breathing is equally important assessing the character of the patient's respirations. "C" refers to Circulation and the overall perfusion status of the patient. Finally, "D" refers to Disability notably the patients mental status.

Emergency therapy

Emergency management of the patient presenting with respiratory distress includes systemic oxygen delivery and minimizing patient stress. While flow-by and oxygen mask oxygen delivery will allow concurrent patient assessment, there are times when other methods of oxygen delivery are needed.

Oxygen supplementation techniques

Supplementation technique	Required flow rate	Maximum inspired oxygen concentration achieved
Flow-by	3-15 l/min	40%
Oxygen cage	15 l/min	45-60%
Oxygen hood (unsealed bag)	5-15 l/min	85-95%
Oxygen collar	1 l/10 kg bodyweight/min	<80%
Nasal cannula	50-100 ml/kg/min	40%
Nasal catheters	50-100 ml/kg/min	40-50%
Nasopharyngeal catheter	50-100 ml/kg/min	60-70%
Nasotracheal catheter	25-50 ml/kg/min	80-90%

Once initial patient assessment is made, a more thorough physical examination is essential in the diagnosis and management of emergency cardiac patient.

Congestive heart failure

Patients with congestive heart failure often present in respiratory distress. Common examination findings include an increased respiratory rate and effort. If pulmonary edema is present, auscultation commonly is reported to have pulmonary crackles. More common in feline patients, dull lung sounds may be present ventrally with pleural effusion. Ascites may also be present with right sided heart failure as a result of tricuspid regurgitation, DCM, or heartworm disease. Other common physical examination findings include auscultation of a heart murmur, hypothermia in cats, pale mucous membranes, and other signs of respiratory distress (i.e. extension of the head/neck abduction of the elbows, and reluctance to lay down). Although uncommon in dogs, absent femoral pulses, cold rear extremities, and hindlimb paresis are seen with aortic thromboembolism (ATE), seen most commonly as a consequence of hypertrophic cardiomyopathy (HCM) in cats.

Along with the history and physical examination, diagnostics to consider include blood pressure, pulse oximetry, thoracic radiographs, or thoracic ultrasound. Before performing diagnostics, it is important to make sure the patient is stable and can tolerate the diagnostics without a risk of decompensation.

Thoracic radiographs are often considered the mainstay diagnostics in evaluating the heart and lungs. In fulminant congestive heart failure, radiographs commonly show congestion / distension of the pulmonary vessels and interstitial to alveolar pulmonary infiltrates.

In dogs, the pulmonary interstitial to alveolar disease is often seen in the perihilar area while cats may have a more generalized pulmonary patent of edema. Specific cardiac disease may also become more apparent with the use of radiographs, notably a large, globoid heart with dilated cardiomyopathy (DCM) or pericardial effusion. When performing thoracic radiographs, at least two views should always be taken with many cardiologists preferring a lateral view and dorsoventral (DV) view.

While thoracic radiographs often confirm the diagnosis of CHF, thoracic ultrasound is an upcoming diagnostic in the ER. Along with the TFAST and AFAST, a new term, "Vet Blue" has recently been discussed. Using these ultrasound techniques, lung pathology is assessed based on the distinction between wet (ultrasound lung rockets (ULRs) vs. dry lung (A-lines with a glide sign). The goal of using this technique is to provide rapid, point-of-care global evaluation of the emergent patient with minimal restraint and risk of decompensation. For the TFAST (Vet Blue) procedure, the patient is placed in either right lateral recumbency and/or sternal recumbency. Dorsal recumbency is not recommended as it has not been validated for VetBlue and it also may increase patient stress. The Vet Blue "L"ung Scan (VBLS, and "blue" for cyanosis, "L" for the scan pattern) is a rapid respiratory evaluation primarily based on the concept of wet vs. dry lung. In human patients lung ultrasound has been shown to be superior to chest auscultation for the detection pulmonary pathology. The goal of the VBLS scan is to identify pulmonary patterns that improve the speed of diagnosis for the respiratory distressed patient preempting the stress of thoracic radiography.

The initial treatment of congestive heart failure will vary slightly depending on the specific patient as well as specific diagnosis but involves oxygen, furosemide (1-4 mg/kg IV as often as every 1-2 hours initially for fulminant edema), and monitoring including blood pressure, pulse oximetry, hydration status, electrolyte status, and renal status. In severe case, sodium nitroprusside may be considered. Sodium nitroprusside is a balanced vasodilator effective in reducing pulmonary edema by increasing venous capacitance and reducing ventricular afterload. The dose is 0.5-10µg/kg/min IV as a CRI. The author starts at a dose of 1-2µg/kg/min and increases based on the response to therapy by 1µg/kg every 20-30 minutes until there is an improvement in respiratory rate, effort and thoracic auscultation. When using sodium nitroprusside, blood pressure must be monitored as it may cause moderate to severe hypotension.

In cases of low output failure (weak pulses, pale membranes, slow CRT, weakness, hypothermia, azotemia), dobutamine is a synthetic beta-adrenergic agonist is considered. This is commonly used in patients with DCM. Dobutamine has a dose range of 2–20 mcg/kg/minute. At lower doses, dobutamine improves cardiac contractility with minimal effects on chronotropy or heart rate. At higher doses, however, dobutamine can be pro-arrhythmogenic.

Pimobendan (0.25 mg/kg PO BID) has been used with success in dogs with CHF secondary to DCM and mitral valve insufficiency. Pimobendan is a phosphodiesterase-III inhibitor that sensitizes the myocardium to calcium, and improves inotropic activity in addition to causing arteriolar and venous dilation. In addition to its use as a long-term inodilator in the treatment of dogs with CHF, Pimobendan is also recommended for use in emergency therapy of CHF, as it can have an onset of effects within one hour.

Cardiac tamponade

Cardiac tamponade results from the pressure of pericardial effusion on the heart leading to decreased filling, decreased cardiac output, and ultimately left and right heart failure. The degree of pressure exerted by the pericardial effusion depends on several factors. These include the volume of pericardial effusion, the rate of pericardial fluid accumulation, and the distensibility of the fibrous pericardium. In the author's opinion, there are two common presentations of pericardial effusion. Patients presenting with acute cardiac tamponade often have a small volume of pericardial effusion (50–100 ml) which causes marked intrapericardial pressure and cardiac tamponade. However, we do also see patients with a more chronic, slower accumulation where there is increased compliance, allowing the pericardial sac to accommodate a significantly larger amount of fluid before intrapericardial pressure increases enough to result in cardiac tamponade.

Clinical signs of patients suffering from pericardial effusion may include tachycardia, tachypnea, poor or absent femoral pulses, pulsus paradoxus, jugular venous distension, dull heart sounds, exercise intolerance, weakness, and syncope. If more chronic in nature, patients may display signs of right-sided congestive heart failure including hepatomegaly, ascites, and jugular venous distension.

Aside from the traditional diagnostics listed above, echocardiography is recommended for the diagnosis of pericardial effusion. Pericardial effusion is diagnosed by the presence of hypochoic fluid between the epicardium and the pericardium.

Diagnostic and therapeutic pericardiocentesis is indicated in patients with pericardial effusion.

Equipment needed for pericardiocentesis include clippers, antimicrobial scrub, 70% ethyl alcohol, sterile drapes, sterile gloves, electrocardiogram (ECG), ultrasound (if available), large intravenous catheter or pericardiocentesis catheter, extension set, three-way stopcock, syringe, sampling tubes (red top and EDTA) and 2% lidocaine (both for local analgesia and preparedness if ventricular tachycardia develops.)

To perform a pericardiocentesis, the patient is placed in sternal recumbency or lateral recumbency. Anesthesia is not necessary although sedation with an opioid/diazepam combination can be helpful for mild chemical restraint. A local block with 2% lidocaine can be used to reduce discomfort as well. Cardiovascularly compromising medications such as propofol, acepromazine, and inhalant anesthesia should be avoided. Unless ultrasound guidance dictates a more appropriate location, the patient is prepared by clipping and

scrubbing between the 4th and 6th intercostal space. While there is controversy as to the best side to use, the author prefers to enter the right side of the thorax. Similar to the thoracocentesis discussed above, the needle should enter cranial to the rib as the intercostal vessels and nerve runs caudal to the rib.

At the preference of the clinician, to prevent drag of the catheter through the skin a small skin stab incision can be made with a No. 11 scalpel blade. Also at the preference of the clinician, side holes can be placed in the distal portion of the pericardiocentesis catheter. If side holes are made, avoid a hole greater than 40% of the circumference of the catheter and holes directly opposite each other on the catheter, both which increase the risk of catheter weakness.

With appropriate patient monitoring including ECG, the catheter is inserted through the skin and into the pleural space. Once within the pleural space, the catheter is advanced slowly (1-2mm at a time) towards the heart while continuously monitoring the patient for discomfort and the ECG for arrhythmias. As the catheter is advanced, the clinician is watching carefully for fluid accumulation into the hub of the catheter. Typical fluid from the pericardial space will range from red to a port wine color. Once the fluid is seen within the hub of the catheter, the catheter is advanced another 1-2mm to make certain it is best seated within the pericardial space. The stylet is then removed and the catheter is connected to the extension tubing along with a three-way stopcock. Using a 10-20ml syringe, the fluid is aspirated. A sample of the aspirated fluid is placed into a red top tube and a lavender top tube for further analysis. Specifically, the red top tube is monitored for clotting. A clot within the red top tube is a concern for trauma to the heart via the catheter and the catheter should be removed from the pericardial space. The amount of fluid obtained will vary but may be as much as 1/2 to 1 liter in a large breed dog. As they are often tachycardic on presentation, the clinician should notice a fairly dramatic decrease in heart rate within a few minutes of successful pericardiocentesis.

Life-threatening arrhythmias

The most common arrhythmia the small animal veterinarian will see is a tachyarrhythmia. These are also considered to be the most concerning as tachyarrhythmias require increased oxygen consumption and lead to reduced diastolic filling and coronary artery perfusion. Underlying causes of tachyarrhythmias include shock, anemia, hypoxia, hyperthyroidism, infection, inflammation, and pain. Supraventricular tachycardias should improve with treatment and resolution of the underlying cause (i.e. fluid therapy for hypovolemic shock or oxygen therapy for hypoxemia). If the heart rate does not decrease with appropriate therapy, a vagal maneuver can be attempted by applying pressure to the eyes or carotid sinus pressure. If there is no improvement despite appropriate therapy and despite a vagal maneuver, drug therapy is considered, notably digoxin. Other antiarrhythmics which may be effective include propranolol (20-60 mcg/kg IV slowly over 5-10 min.) or verapamil (.05 mg/kg IV q 10-30 min, up to 3 times). Both of these are negative inotropes and should be used with caution if there is concurrent evidence of congestive heart failure. Intravenous diltiazem (0.25 mg/kg administered slowly over 3 minutes) can be used instead of verapamil to control supraventricular tachycardias.

Ventricular tachycardia is another common arrhythmia seen, associated with primary cardiac disease or secondary to systemic disease. The arrhythmia is treated pharmacologically if signs of hemodynamic instability are present, notably with EKG findings including tachycardia (>160bpm), multiform QRS configurations, R on T phenomenon, and or hypotension. Lidocaine is the drug of choice for ventricular arrhythmias, dosed initially with a bolus of 2-4mg/kg IV given slowly to effect while monitoring the electrocardiogram. This bolus is followed by a CRI (25-80 µg/kg/min). Refractory ventricular arrhythmias can be treated with procainamide (2-15 mg/kg IV over 20-30 minutes).

Bradyarrhythmias are not as commonly seen in clinical practice, although bradycardia as a result of hyperkalemia seen with (feline) urethral obstruction is often seen. Aside from hyperkalemia as a result of urethral obstruction in male cats, other common causes include hypoadrenocorticism and renal failure. Treatment will depend on the underlying cause, but for hyperkalemia may include fluid therapy, Calcium gluconate (0.2-0.5 ml/kg IV), regular insulin (0.25 U/kg IV), dextrose (0.5g/kg), or sodium bicarbonate (1-2 mEq/kg IV slowly).

Summary

Patients presenting with evidence of emergent cardiac disease should be triaged quickly and treated immediately to reduce morbidity and mortality. Oxygen is a mainstay therapy for cardiac patients and should be administered on presentation and during the initial assessment phase. Prognosis will vary on the underlying cause of disease although patients may live for several years with careful monitoring.

Common medications, dosages and indications

<i>Key Drug</i>	<i>Drug Class</i>	<i>Dose Range</i>	<i>Frequency</i>	<i>Route</i>	<i>Indications</i>
Furosemide	Diuretic	2-4 mg/kg	Every 2-4 hours as needed, then every 8 hours	IV best in patients with CHF; IM	Pulmonary edema due to CHF
Nitroglycerin	Vasodilator	1/8" strip on ear pinnae	Every 6 hours	Topical	Vasodilation to decrease afterload on the heart
Dobutamine	β -1 agonist	2-10 μ g/kg/min	CRI	IV	Positive inotrope to increase cardiac output in patients with primary myocardial failure
Lidocaine	Class I antiarrhythmic	40-80 mcg/kg/min	CRI	IV	Ventricular tachycardia
Procainamide	Class I antiarrhythmic	25-40 mcg/kg/min	CRI	IV	Ventricular tachycardia
Diltiazem	Calcium channel blocker	0.25 mg/kg slow bolus	Q 20 min	IV	SVT +/- atrial fibrillation
Esmolol	Beta-blocker	0.01 mg/kg slow bolus	Q 5 min	IV	SVT
Nitroprusside	Nitrate	2 to 10 mcg/kg/min	CRI	IV	Refractory CHF

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Emergency Approach to the Hemoabdomen

Garret Pachtinger, DVM, DACVECC
Veterinary Specialty and Emergency Center
Levittown, PA

Hemoabdomen is defined as free blood in the peritoneal or retroperitoneal space. It is most commonly categorized into nontraumatic and traumatic causes with non-traumatic causes being further categorized into coagulopathic and non coagulopathic (spontaneous). Patients can present with internal hemorrhage that is mild and self-limiting. Patients can also present with rapid and severe hemorrhage, which is ultimately fatal without rapid intervention. It is up to the clinician to perform a rapid assessment and provide emergency treatment to reduce further morbidity and mortality.

Signalment & history

Breed, age, and history can be extremely helpful when evaluating a patient with hemoabdomen. Trauma is often a presenting complaint, offered as information by the owner and part of the immediate triage history directing further patient assessment and treatment. If the history is unknown, clinical examination findings (see below) can provide some important clues regarding the possibility of trauma. If there is no history or evidence of trauma, signalment can help form a differential diagnosis and treatment plan. For example a spontaneous hemoabdomen in a 2 year old dog is more likely from rodenticide exposure whereas a 14 year old large breed dog with a spontaneous hemoabdomen is more likely to have a neoplastic cause.

Physical examination

Most animals presenting with a hemoabdomen will have historical clues lethargy, collapse, exercise intolerance, and weakness. Physical examination abnormalities include pale mucous membranes, prolonged capillary refill time, snappy (short and narrow) femoral pulses, tachycardia, and tachypnea. Evidence of traumatic causes of hemoabdomen may include bruising, abrasions, lacerations, fractures, and/or road rash. Whether the bleeding is traumatic or non traumatic, the abdominal cavity is the most common place for clinically significant internal hemorrhage. Dependent on the amount and the speed of blood loss signs may range from mild anemia to hemorrhagic shock. Surface bleeding of the skin and mucosa such as petechia, ecchymoses, epistaxis, gingival bleeding, melena, hematochezia, and/or hematuria are more likely to be seen with a primary hemostatic disorder (thrombocytopenia or thrombocytopathia) and are less common with coagulation defects that cause cavity bleeding.

Diagnostic testing

A minimum database of a bleeding patient includes a packed cell volume (PCV), total protein (TP), blood urea nitrogen (BUN) and blood glucose (BG). Further emergency database information includes blood gas analysis, lactate, and electrolytes. Blood pressure and ECG should also be obtained. Common Findings consistent with hemoabdomen include decreased PCV, decreased TP, and increased lactate. Additionally, hypotension (low blood pressure) and a sinus tachycardia (on ECG) are common. A blood smear is useful to provide a platelet estimate, to evaluate RBC morphology, and to perform a differential blood count. Each platelet per high power oil emersion field represents approximately 15–20,000 platelets/ μ l blood. The feathered edge of the slide should be carefully evaluated as white blood cells and platelet clumping may be found there, notably platelet clumping which can explain a lower than expected platelet count in the monolayer when attempting to calculate an estimated platelet count.

Imaging studies can also be a valuable diagnostic tool for patients presented with hemoabdomen. Radiographs may show decreased serosal detail, organ enlargement, abdominal masses, diaphragmatic and/or body wall hernia. Decreased serosal detail may indicate free peritoneal fluid. Alternatively, many are now using ultrasound as a more detailed diagnostic tool. Specifically, ultrasound is used in combination with the FAST (focused assessment sonography trauma) protocol. The FAST protocol is the quickest and most sensitive way to detect a hemoabdomen. If ultrasound is not readily available, a four quadrant abdominocentesis can be performed to obtain free abdominal fluid. Obtaining non-clotting hemorrhagic fluid via this technique supports a diagnosis of free abdominal fluid unless a coagulopathy is present. If grossly hemorrhagic, then PCV and TP of the fluid should be evaluated. Acute hemorrhage tends to have PCV and TP that is similar to peripheral blood. A cytological evaluation should be performed on the fluid to assess for inflammation, bacteria or neoplastic cells.

Finding hemorrhagic fluid in the abdominal cavity confirms the diagnosis of hemoabdomen. Other diagnostics on the effusion that can be considered depending on the clinical presentation includes:

- Measurement of potassium and creatinine if urinary bladder rupture is suspected.
- Measurement of bilirubin if gall bladder rupture is suspected.
- Let's discuss more the general categories of hemoabdomen:

Coagulopathic hemoabdomen

Hemorrhage as a result of coagulopathy is most commonly caused by disorders of the secondary hemostatic system. Disorders of the primary hemostatic system (platelets) less commonly cause cavity bleeding.

One of the most common coagulopathic causes of hemoabdomen is toxicity, specifically vitamin K deficiency due to anticoagulant rodenticide poisoning. While this can happen at any age, it is the most common cause for spontaneous (non traumatic) hemoabdomen in young patients. If anticoagulant rodenticide toxicosis is suspected, the goals are to prevent further hemorrhage and reverse coagulopathy by administration of vitamin K1. Treatment for the coagulopathic patient may also include transfusion medicine including whole blood, packed red blood cells, and/or fresh (frozen) plasma.

Traumatic hemoabdomen

Treatment of the patient that presents with a hemoabdomen as a result of trauma will depend on the severity of bleeding, resulting anemia, and concurrent injuries. Regarding traumatic causes of hemoabdomen, ultimately, there is a lack of evidence to support immediate surgery versus medical therapy. In the author's opinion, most traumatic hemoabdomen cases can be managed with non-surgical measures. If stabilization fails, the clinician should be prepared to perform surgery. While surgical intervention can often be avoided, these patients may require immediate and intensive care including intravenous fluid therapy and blood transfusions.

If hypovolemia is present, intravenous fluid resuscitation is warranted. Choices for fluid therapy include isotonic crystalloid therapy, hypertonic crystalloid therapy, or synthetic colloid therapy.

- Isotonic crystalloid 10-30 ml/kg IV bolus
- Synthetic colloid 2-5 ml/kg IV bolus
- Hypertonic saline (7.5%) 2-4 ml/kg IV

Regardless of the fluid choice, careful monitoring is warranted due to the risk of abrupt increases in systemic blood pressure and the concern for increased hemorrhage. With severe acute blood loss, blood transfusions or blood substitutes are indicated. The blood product used (packed RBCs, whole blood) depends on the availability and on the type of the hemostatic disorder.

Specific variables to monitor to help direct further therapy and case management include:

- Blood pressure
- Heart rate
- PCV and TP
- Lactate

A specific resuscitation therapy reported for traumatic conditions such as this is hypotensive resuscitation. This technique employs small volumes of fluid rather than large rapid volumes with the goal of increasing perfusion but tolerating slight hypotension with a Doppler blood pressure of 80-100mmHg. This method has been shown to reduce mortality in human patients with abdominal bleeds after trauma. The theory is that there is less likelihood of disrupting blood clots that are forming, and that bleeding will stop. Additional supportive measures include external abdominal counterpressure, strict cage rest, analgesia, and careful handling.

Measuring intra-abdominal pressure can be done if you have a urinary catheter in place. It is just like measuring central venous pressure and can be done easily with a stopcock and water manometer. Pressures above 25cm H₂O are associated with decreased organ perfusion.

Spontaneous hemoabdomen

This category is distinct from other common causes of a hemoabdomen. Obtaining a thorough history and point-of-care diagnostics can quickly decrease the suspicion of a traumatic hemoabdomen or coagulopathy. Often with a traumatic hemoabdomen, the patient presents with a recent history of trauma, such as vehicular trauma. Physical examination findings can also increase the suspicion for an unwitnessed trauma, such as bruising, fractured ribs, or skin abrasions or lacerations. Point of care diagnostics such as a PT clotting test (prothrombin time), can also be very helpful. A PT test that is normal or slightly elevated in the presence of a hemoabdomen would decrease the suspicion of the primary cause being a coagulopathy, as clinical experience would require a PT test to be out of range (or close to out of range) to increase the suspicion of the primary cause being a coagulopathy to result in a hemoabdomen. A slight elevation often can be considered a consumptive coagulopathy.

Once trauma and coagulopathic causes have been ruled out, especially in an older, and often large breed dog (although there are no studies to say smaller breed dogs are any different), the term spontaneous (or non-traumatic, non-coagulopathic) hemoabdomen can be used.

There are several studies that have evaluated the spontaneous (non-traumatic, non-coagulopathic) hemoabdomen. These studies indicate an overwhelming likelihood neoplasia as an underlying cause, most commonly a ruptured splenic hemangiosarcoma (65-85%). Other causes do exist, both benign (ruptured hematoma) and malignant (e.g. mesothelioma, carcinoma, pheochromocytoma, lymphoma), but unfortunately the overwhelming likelihood is that a spontaneous hemoabdomen in an older dog will result from a splenic hemangiosarcoma.

Often these patients present in shock, specifically hypovolemic shock. Physical examination findings may include tachycardia, poor pulses, pale mucous membranes, increased respiratory rate and effort, and a distended abdomen with a palpable fluid wave. As in other causes of hemoabdomen, the first priority should be stabilization (e.g. intravenous catheter placement, fluid therapy, oxygen therapy, etc). Based on the patient's state of illness, fluid therapy options to debate would include isotonic crystalloids, hypertonic saline, colloids, and even blood products.

Following diagnosis and stabilization, as these are often older dogs with a primary concern for a neoplastic process, diagnostics that to considered should include:

- Bloodwork (CBC and Chemistry Screen) – to check for cell counts, organ values, electrolytes, and overall assess for metabolic or electrolyte derangements which would need correction
- Coagulation testing (specifically a prothrombin time – PT) – this should have been performed in the initial diagnostics on presentation to place the patient in this specific category (non-traumatic, non coagulopathic) – but if not, should be performed pre-operatively.
- Thoracic X-Rays – While helpful to assess cardiac size and shape, often the primary reason to recommend thoracic x-rays is to identify pulmonary metastasis. The presence of pulmonary metastasis would worsen the prognosis substantially and likely make this patient a poor candidate for surgery and anesthesia.
- Abdominal Ultrasound - My personal experience with an abdominal ultrasound and interpretation for clients falls in 1 of 3 scenarios:
 1. There is a solitary mass (spleen, liver, etc) that can be identified. Often radiologists are reluctant (and refuse) to note their impression of malignancy and while not helpful in differentiating between a benign or malignant tumor for the owners in their decision, a solitary mass present would hopefully lead one to assume this patient is a better surgical candidate in the absence of diffuse disease. The owner must also understand that there is a possibility that microscopic disease exists (not able to be seen on ultrasound) which may be identified during the exploratory procedure.
 2. There are multiple masses present (not just on one organ). While malignancy cannot be confirmed, the presence of multiple masses throughout the abdomen would give the impression that malignancy is more likely and this patient is likely a worse surgical candidate than the previous patient with one solitary mass.
 3. No masses/lesions have been identified. At that time further investigation is warranted (unwitnessed trauma?) and further stabilization may be needed to note progression.

Does every patient need an ultrasound? I have clients that would like to save their pet regardless of the ultrasound findings. Are the ultrasound findings then academic in nature? If the client understands the risk that diffuse disease may be present and identified during surgery, resulting in a phone call to discuss humane euthanasia on the table, wouldn't it then be reasonable to save the \$400-\$600 on the ultrasound and proceed directly to surgery following stabilization and additional diagnostics? Ultimately, once stabilized to the best of the clinician's ability, an exploratory laparotomy is needed.

Hemoabdomen in cats

Hemoabdomen in cats is relatively rare compared to dogs. In a study that evaluated hemoabdomen in cats, 46% had abdominal neoplasia and 56% had non-neoplastic causes. Hemangiosarcoma was diagnosed in 60% of the cats with neoplasia with the spleen being the most common site. Unfortunately, only 12% of the 65 cats survived to discharge suggesting that the overall prognosis of hemoabdomen in cats is poor.

Summary

In theory, surgery is a consideration for every non-coagulopathic hemoabdomen patient, especially in patients that do not stabilize medically. Specifically regarding the traumatic hemoabdomen, the author believes that most patients can be stabilized with medical therapy within two hours of presentation. If appropriate resuscitation efforts are not successful and do not achieve cardiovascular stabilization within 2 hours, it is unlikely further medical therapy will be successful. Traumatic hemoabdomen patients that do not stabilize with aggressive and appropriate medical therapy should be considered surgical candidates. Surgery will not only achieve hemostasis but also provide an underlying diagnosis.

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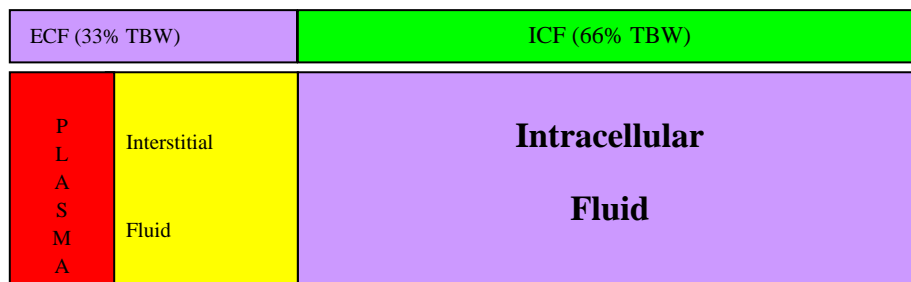
Practical Fluid Therapy: It's More Than Just Water and Salt

Garret Pachtinger, DVM, DACVECC
Veterinary Specialty and Emergency Center
Levittown, PA

Fluid therapy is one of the most commonly used therapies for the small animal practitioner. Despite a large amount of research the general consensus is that there is not one fluid type that is better than another for resuscitation. This is often why there is debate as to what fluids a practice should purchase to have on the shelf. Moreover, the type of fluid desired may vary based on the underlying disease process.

The reason that fluid therapy is so important in medicine is that living organisms are comprised predominantly of...fluid!. Total body water content is approximately 60% of body weight in a non-obese, adult dog or cat. Total body water is further distributed between two major compartments: the intracellular (ICF) and extracellular (ECF) fluid.

Total body water (TBW) fluid compartments



The ICF compartment is the larger of the two compartments and comprises 66% of the total body water and 40% of body weight. It is separated from the ECF compartment by a cell membrane that is permeable to water but impermeable to most solutes. The ECF comprises the remaining 33% of the TBW and 20% of body weight. The ECF is subdivided into the plasma (25% of ECF) and interstitial (75% of ECF) fluid compartments.

The need for fluid therapy is often divided into 2 main categories:

1. Restoring the patient's intravascular volume (hypovolemia)
2. Replacement of extravascular fluid (dehydration)

There are 4 types of hypoperfusion commonly recognized in veterinary practice:

1. Hypovolemia (i.e., loss of intravascular volume)
2. Maldistributive / Septic (i.e., loss of vascular tone, fluid shifting, third spacing)
3. Cardiogenic (i.e., myocardial dysfunction leading to lack of cardiac output and perfusion)
4. Obstructive (i.e., decreased venous return to the right side of the heart as a result of obstruction, e.g., due to gastric dilatation and volvulus or pericardial effusion)

It is important to distinguish which type of hypoperfusion is present as their initial treatment as well as long term therapy will differ based on the underlying disease process. As compared to cardiogenic causes, when clinical signs of hypovolemia are present (pale mucous membranes, prolonged capillary refill time, dull mentation, poor pulse quality, cold extremities, and tachycardia (or bradycardia in cats) intravascular fluids must be replaced for emergency resuscitation. The estimated shock volumes of fluids are 90 ml/kg in dogs, and 60ml/kg for cats. The author initially replaces 1/4 to 1/3 of the calculated volume as rapidly as possible, the reassess perfusion parameters, notably heart rate, mucous membrane color, CRT, pulse quality, blood pressure, and eventually urine output. The reason the volumes calculated seem high is that approximately 75% of the crystalloid fluid administered with redistribute out of the intravascular space within 30-60 minutes of administration.

The administration of synthetic colloids is another option considered in hypovolemic patients, notably if there is a concern for hypoproteinemia (TP < 4.5) or in combination with crystalloid therapy. Common colloid bolus doses are 10–20 ml/kg in dogs and 5–10 ml/kg in cats followed by rapid and frequent reassessment. Synthetic colloids such as Hetastarch and Vetstarch cause expansion of the intravascular volume by pulling fluid from the interstitial and intracellular spaces into the intravascular compartment and keeping the fluid within the intravascular space longer due to the colloidal properties.

Besides isotonic crystalloids and synthetic colloids, another alternative fluid therapy is hypertonic crystalloids, specifically hypertonic saline. Hypertonic saline is considered for rapid expansion of the intravascular compartment and used in patients that have a normal hydration status. Hypertonic saline is contraindicated for a patient that is dehydrated or hypernatremic. Hypertonic saline has a potent effect, drawing fluids from other compartments into the intravascular space due to its potent osmotic forces. The typical dose

recommended for rapid resuscitation is 4-7 ml/kg of 7.5% HS over 20 minutes. Additionally, hypertonic saline is theorized to have other beneficial properties including improved myocardial contractility, activation of a neurogenic reflex leading to peripheral vasodilation, improving microcirculatory flow by preventing capillary collapse, a reduction of endothelium cell swelling and alterations in function of polymorphonuclear cells (PMN) and endothelial cells. Complications include bradycardia, bronchoconstriction, sodium fluctuations, fluid overload and pulmonary edema, phlebitis and ventricular arrhythmias.

To prolong the effect of fluid resuscitation, the author also considers the combined use of a hypertonic saline/synthetic colloid. To achieve this fluid mixture, 1:2.5 ratio of 23.4% hypertonic saline (sodium chloride) and hetastarch or Vetstarch are used. To easily make this solution, 17ml of 23.4% hypertonic saline and 43ml of the colloid are mixed in a 60ml syringe. 3-5ml are then used as a bolus in the canine patient and 2-3ml are used as a bolus in the feline patient, followed by re-assessment.

Once immediate life-threatening fluid deficits are replaced, the focus then shifts to the patient's dehydration level, maintenance level, and provisions for suspected ongoing losses.

The following chart is commonly used to assess patient dehydration characteristics:

Physical examination findings in dehydrated patients

Percent dehydration	Clinical signs
<5	No detectable abnormalities
5-8	Decreased skin turgor, dry mucous membranes
8-10	Decreased skin turgor, dry mucous membranes, eyes may be sunken in orbits, slight prolongation of CRT
10-12	Severe skin tenting, prolonged CRT, dry mucous membranes, eyes sunken in orbits, possibly signs of shock
>12	All of the above plus signs of shock, often life threatening

Measurement of dehydration is subjective and is not expected to be detected clinically below 5%.

For patients with evidence of chronic dehydration on examination but stable cardiovascular parameters (i.e. no evidence of hypovolemia), fluid deficits are corrected over a 6-24 hour period

Following treatment of hypovolemia, the following formulas are used to create a fluid therapy plan

1. Dehydration fluid replacement = Body weight (kg) x %dehydration x 1000
2. Maintenance daily requirements = Body weight (kg) x 2-4 ml/kg/h.
3. On-going losses = 3-4 ml/kg/vomit or diarrhea

Complications of fluid therapy

While fluid therapy is often considered a benign treatment, it is not without risk. Complications to consider based on the individual patient characteristics include:

- Pulmonary edema
 - Volume overload
 - Increased vascular permeability
- Rapid sodium shifts
 - Neurologic signs
 - Obtundation
 - Cerebral edema
 - Seizures
- Phlebitis
 - Use of hyperosmotic agents

Conclusions

Intravenous fluid therapy can be performed rapidly and can be life saving for the emergency patient. A thorough history, physical examination, and preliminary diagnostics can be used to help differentiate disease processes which may be worsened by fluid therapy (i.e. cardiogenic shock), as well as help the clinician choose the best fluid type to improve the clinical condition.

TABLE: Colloids and their chemical properties.

Colloid	Mean MW (KDa)	Molar substitution	COP (mmHg)
5% Human albumin	69	N/A	23.2± 0.1
25% Human albumin	69	N/A	> 200
Canine fresh frozen plasma	69	N/A	17.1± 0.6
6% Hetastarch in 0.9% NaCl	600	0.7	32.7± 0.2
6% Hetastarch in balance electrolyte solution--Hextend™	670	0.75	37.9± 0.1
6% Voluven™	130	0.4	37.1± 0.8
6% Vetstarch™	130	0.4	40*

In vitro

TABLE: Common crystalloids and their chemical properties.

Solution	LRS	Plasmalyte A; Norm R	0.9% NaCl
Na	130	140	154
K	4	5	0
Ca	3	0	0
Mg	0	3	0
Cl	109	98	154
Gluconate	0	23	0
Lactate	28	0	0
Acetate	0	27	0
Osmolarity	270	294	310

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