Feline Urethral Obstruction
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Pathogenesis of obstruction
Urethral obstruction (UO) has been reported to occur in 22% of cats with feline idiopathic cystitis (FIC), and is a potentially life-threatening disease. Male cats are more likely to develop a urinary obstruction because their urethra is much longer and narrower than a female’s. It has long been believed that this obstruction is secondary to the physical presence of something occluding the lumen of the urethra, such as a calculus or urethral plug (or much less commonly stricture or neoplasia). However, there is evidence to suggest that mechanical obstruction secondary to urethral spasm and edema may play an equally important role. These conditions in the urethra are thought to be brought about by FIC, a sterile inflammatory process. Attempts to isolate a bacterial or viral cause for this disease have not been successful. It appears to be caused by an imbalance in the neurohormonal systems (cortisol, sympathetic nervous system) that are activated under stressful conditions. This imbalance is thought to result in impaired blood flow to the lower urinary tract, and release of inflammatory mediators which cause edema, smooth muscle spasm and pain. Pain, in turn, can contribute to worsening of urethral smooth muscle dysfunction and urethral inflammation, thereby creating a vicious cycle. These conditions are ultimately what lead to urethral obstruction in cats.

Pathophysiology of obstruction
Complete obstruction of the urethra leads to the build-up of pressure within the urethra and urinary bladder, which will result in pressure necrosis and mucosal injury. Pressure within the bladder is then transmitted up the ureters to the kidney and ultimately through the entire length of the nephron to Bowman’s capsule. As the pressure within Bowman’s capsule starts to exceed glomerular filtration pressure, GFR is essentially reduced to zero. Within 24-48 of obstruction the kidney’s excretory ability ceases.

Uremia can cause depression, nausea, vomiting and anorexia. UO cats tend to present dehydrated due to lack of drinking and GI losses. Severe hyperkalemia is considered to be the most life-threatening aspect of UO because of slowed rate of cardiac depolarization and bradycardia. If the serum potassium level gets high enough, electrical activity in the heart can cease altogether resulting in asystole. Severe metabolic acidosis can lead to denaturing of proteins, enzymatic dysfunction and catecholamine hyposensitivity. Given these changes, it seems likely that hypotension and cardiovascular collapse could develop in the latter stages of urethral obstruction. However, a study assessing blood pressure at the time of presentation in 28 blocked cats found no incidence of hypotension despite having some patients that were significantly ill. Instead it was found that more severely affected patients (having higher blood urea nitrogen, creatinine, and potassium concentrations) tended to be normotensive whereas less severely affect patients tended to be hypertensive. The authors suggested that a number of factors (such as pain, stress, and upregulation of the RAA system) may have served to offset any tendency toward hypotension.

History and clinical signs
The classic history associated with UO involves a male cat which has been vocalizing and straining unproductively in the litterbox. However, these signs might be difficult to distinguish from a cat with idiopathic cystitis. It would be ideal for the owner to know whether or not the cat is urinating. Unfortunately, cystitis cats will often urinate very small amounts frequently, and sometimes outside the litterbox. One distinguishing feature of UO versus cystitis is that affected cats start to show signs of systemic illness. This could include vomiting, lethargy, anorexia and abdominal pain progressing to changes in mentation and recumbency. Obstruction should be considered as a differential for ANY sick male cat!

Clinical signs vary depending on the stage at which the patient is presented. Patients that present early (the “healthy” blocked cat) are distinguished from the non-obstructed FIC cat on the basis of bladder palpation. The blocked cat will have a large, firm, painful bladder that cannot be expressed, while the cystitis cat will have a small or unpalpable bladder. If the obstruction has been present for greater than 24 hours, the patient may be showing signs of systemic illness. Cats which have not previously obstructed are much more likely to be sick at the time of presentation as the owners are unaware of the potential for the disease. Systemic signs
could include dehydration, bradycardia, and hypothermia. The presence of bradycardia (<160bpm) in male cats should always raise concern for hyperkalemia as stress should result in tachycardia (though cats in septic or cardiogenic shock can also demonstrate bradycardia). In fact, the combination of bradycardia (HR < 140) and hypothermia (T < 96.6°F) has been found to be 98% predictive of serum potassium level greater than 8 meq/L in cats with urethral obstruction.

**Initial diagnostics and stabilization – “Sick” blocked cat**

Fluid therapy should be started immediately to support vascular volume and help dilute serum potassium concentration. Many people prefer to hold off on IV fluids until the bladder has been emptied, but there is no physiologic reasoning to support this. Do not hesitate to give IV fluids to these cases. While 0.9% NaCl seems like the obvious fluid choice because it contains no potassium, it is also acidifying. A recent study comparing 0.9% NaCl and Normosol-R showed no difference in outcome (survival, length of stay) or in reduction of serum potassium levels, though acid-base abnormalities corrected more rapidly in the Normosol-R group. Overall it does not appear that the type of fluid matters as long as an adequate volume is administered. If cardiovascular collapse is present it may be necessary to administer crystalloid shock doses (40-60 ml/kg for the cat) in bolus fractions. Remember to give boluses in these fractions. A good rule of thumb is to multiply body weight in kg times 10, which gives ¼ of the total shock volume. If resuscitation is not necessary, fluid rate should be based on replacement of dehydration added to the maintenance fluid requirement. In a pinch, it is reasonable to start at a rate of 10 ml/kg in the initial stages, provided there is no indication of underlying heart disease.

An ECG should be placed even if the patient is not bradycardic. Classic ECG changes associated with hyperkalemia include tall tented T waves, prolonged P-R interval, diminished to absent P waves, and widened QRS. As hyperkalemia worsens, ECG changes can progress to atrial standstill, ventricular fibrillation or asystole. The best way to reduce serum potassium levels is to de-obstruct the cat; however, this process takes time. IV fluid therapy (even without deobstruction) will help to reduce potassium concentrations. If the patient is significantly bradycardic (HR < 140) then immediate intervention to protect the heart (calcium gluconate) and promote intracellular shift of potassium (insulin, dextrose, and/or sodium bicarbonate) should be employed. If insulin is administered, it is essential that dextrose also be given to prevent hypoglycemia.

Though controversial, cystocentesis can also be a part of initial stabilization by allowing immediate resumption of glomerular filtration. Only minimal sedation is usually necessary to perform cystocentesis and a “pure” urine sample can be obtained for urinalysis or urine culture. Finally, relieving the back-pressure against the obstruction (whether stone, plug or spasm) may make for easier passage of a urinary catheter. The major argument which is made against performing cystocentesis is the potential for bladder rupture. In a study presented in abstract at IVECCS this year (publication in progress), 45 cats with UO underwent brief abdominal ultrasound to look for effusion, then cystocentesis, then repeated ultrasound to look for an increase in abdominal effusion. 33% of cats had “scant” effusion prior to cystocentesis, and 49% had “scant” effusion following cystocentesis. Within 24 hours, all cats but one had no peritoneal effusion. This study shows that peritoneal effusion is a common finding in cats with UO, and although more cats had effusion following cystocentesis, it was a transient finding that did not cause complications. The conclusion was that cystocentesis is a safe procedure for male cats with UO.

**Urethral catheterization**

Passage of a urinary catheter to relieve a physical obstruction is generally considered to be essential in the management of UO. In order optimize the likelihood of successful catheterization and minimize damage to the urethra, heavy sedation/analgesia or anesthesia is recommended. A combination of injectable agents (ketamine [4-6 mg/kg] and diazepam [0.25-0.5 mg/kg], buprenorphine [0.01-0.02 mg/kg] and acepromazine [0.01-0.02 mg/kg], +/- propofol [1-4 mg/kg, to effect]) or general inhalant anesthesia may be used in the stable patient. A combination of buprenorphine or hydromorphone (0.05-0.2 mg/kg) and diazepam are often sufficient in the unstable patient depending on the degree of metabolic derangement. Vocalizing or movement during catheterization attempts is likely to be associated with urethral spasm and an increased risk of urethral trauma. Under these circumstances higher doses or additional medications should be given. Once the patient is sedated, an open-ended tomcat catheter can be used to initially relieve the obstruction. Creating a mixture of saline and sterile lubricant (3:1) as the flush solution can serve to deposit lubricant the entire length of the
urethra, rather than just at the tip. This will help decrease damage to the urethra. Another helpful technique is to pull the prepuce caudally once the catheter is seeded in the penile urethra. This will serve to straighten out the urethra, thus making passage of the catheter easier and less traumatic. Once the tomcat is in place the urinary bladder can be emptied and flushed. Given that a tomcat catheter is rigid and can cause significant urethral irritation, it should be withdrawn and replaced by a softer indwelling catheter which is sutured in place. This catheter should then be connected to a sterile collecting system. Open collection systems (i.e., just a catheter hanging out of the cat not attached to anything) is an open invitation to a severe urinary tract obstruction and is not considered standard of care. A closed collection system can be made with an empty IV fluid bag and a drip set. Simply plug the drip set into the open end of the urinary catheter. Once the patient has been stabilized and the obstruction relieved, it is important to obtain abdominal radiographs (even a single lateral view encompassing the entire lower urinary tract) to assess catheter placement as well as the presence of calculi.

**Post-obstructive care**

Fluid therapy and monitoring urine output are important aspects of post-obstructive care. Patients which have had prolonged obstruction (as signified by severe azotemia) are at risk for a post-obstructive diuresis resulting in massive urine production. This diuresis is thought to occur secondary to the accumulation of osmotically active substances in the blood, pressure necrosis, medullary washout and/or anti-diuretic hormone resistance brought about during the obstructive process. It is very important to keep up with urinary losses in these patients as urine production could be as much as 100-150ml/hr (about half a blood volume in one hour!). If the fluid rate does not match urine output the patient can quickly become severely dehydrated and hypovolemic. To determine urine production, measure the amount in the bag produced over a 4 hour period. Divide this by 4 to determine the ml/hr produced. You will then add this to the cat’s maintenance plus dehydration rate to determine the total fluid rate for the next 4 hours.

Another important aspect of post-obstructive care is analgesia and treatment for urethral spasm. Cystitis and obstruction, in addition to urethral catheterization, are painful and could be associated with risk of re-obstruction. Buprenorphine (0.01-0.02 mg/kg q6-8h) generally provides sufficient pain control and has the benefit of oral administration. If buprenorphine is not sufficient, a fentanyl CRI (2-4 mcg/kg/hr) or hydromorphone CRI (0.005-0.02 mg/kg/hr) is recommended. Acepromazine (0.05 mg/kg IV/IM or 0.5 mg/kg PO) can provide adequate sedation to decrease stress and agitation as long as the patient is stable. Prazosin (an α-1 antagonist) is frequently used at 0.5 mg per cat q8h to decrease urethral spasm. Prazosin has been shown to significantly decrease the incidence of re-obstruction.

Electrolytes and renal values should be monitored every 12-24 hours and should rapidly correct to normal. Antibiotics are often not necessary as very few cats with lower urinary tract disease (<2%) have a UTI at presentation and antibiotics will not prevent infection secondary to catheterization. The urinary catheter should remain in place until the cat is clinically improved, blood work has normalized, post-obstructive diuresis has resolved, and urine is “running clean” in order to help minimize the risk of immediate re-obstruction. Performing a urine culture and sensitivity at the time of catheter removal is recommended to determine if a UTI has been introduced. Given the significant potential for contamination while the catheter is removed, the practice of submitting the catheter tip for culture should be avoided.

**Alternative management protocols**

Unfortunately, the optimal treatment course outlined above may be limited by owner financial constraints. In addition, there is evidence that UO is as much a mechanical obstruction (urethral edema and spasm) as a physical one (plug or stone). A recently published study (Cooper et al, JAVMA 2010) demonstrated that pharmacological manipulation (analgesia and sedation), a low stress environment, and intermittent cystocentesis can result in spontaneous urination without the need for catheterization. This less invasive approach was offered in lieu of euthanasia when traditional treatment for UO was prohibited by financial constraints. Cats in need of emergency stabilization based on significant physical exam/metabolic derangements (heart rate < 120, temperature < 96°F, potassium > 8.0 meq/L, pH < 7.1) were excluded. Treatment involved administration of standardized doses of acepromazine and buprenorphine, and decompressive cystocentesis as needed for up to 4 days. The cats were also placed in isolated housing with minimal handling. Treatment success was defined as resumption of spontaneous urination and discharge.
from the hospital. Fifteen cats were treated using this protocol with successful outcome in the 11 cases (73%). Major complications resulting in euthanasia included the development of uroabdomen or hemoabdomen; though there was no evidence of overt bladder tear/rupture on postmortem examination. Patients with severe azotemia appeared to have a greater risk of complications. There did not appear to be a greater risk of immediate or long-term re-obstruction with this protocol when compared historically to traditional management.

**Prognosis**

Depending on the underlying cause, there is an approximately 20% incidence of recurrence with UO within the first 30 days. The majority of these (~75%) will occur within the first 48 hours following urinary catheter removal. Overall, about 1/3 of cats with urethral obstruction will have a second episode of obstruction at some point in their life. Recently, two studies looked at factors affecting recurrence of urinary tract obstruction (rUO) within 30 days of discharge.

Eisenberg *et al* (JAVMA 2013) studied 83 cats with UO. Following urinary catheter removal, 15% of cats developed rUO within 30 days of discharge. Factors associated with increased rates of reobstruction included: Increased age (8.2 yrs vs 4 yrs) and less time with an indwelling catheter (24 hrs vs. 26.5 hrs). Factors not found to affect the incidence of rUO included: medications used, use of a prescription diet, urinary catheter size, amount of fluids given, initial USG, the presence of crystalluria, or the degree of azotemia at presentation.

Hetrick *et al* (JAVMA 013) studied a similar population of 192 cats. In this study, the incidence of rUO within 30 days was 23.6%. Cats treated with prazosin plus buprenorphine had a lower incidence of recurrence compared to cats treated with meloxicam, tramadol, phenoxybenzamine or other medications. A smaller urinary catheter size (3.5fr vs. 5fr) was found to be associated with decreased rUO as well, but the authors also note that medical management had changed to prazosin and buprenorphine during the time that 3.5fr red rubbers became more frequently used. This study did not find a relationship between rUO and duration of catheterization.

The Eisenberg study also looked at at-home changes and the rate of rUO. Environmental modification, defined as increasing water intake, increasing the number of litterboxes and frequency of cleaning, or providing a more “cat-friendly” environment was found to significantly decrease the rate of rUO. Increasing water intake was achieved by switching to wet food, flavoring the water, increasing number of water bowls, or using a running-water bowl.

Regardless of how these patients are treated in hospital, at-home care is extremely important to help decrease the likelihood of re-obstruction either immediately or in the future. Continued analgesia and anti-spasmodics after discharge can be helpful, continuing treatment with prazosin and buprenorphine for 5-7 days. Antibiotics should only be dispensed based on results of urine culture taken at the time of catheter removal. Given the questionable role that urinary crystals play in the pathogenesis of obstruction, it is unclear whether dietary manipulation of urinary pH to address crystalluria is beneficial.
Traumatic brain injury (TBI) can lead to rapidly expanding intracranial bleeds, brain contusions, edema and vasospasm. Primary brain injury is the injury that occurs at the time of impact (both coup and counter-coup lesions) and is unalterable. Secondary brain injury is the anatomical or physiological alteration of brain tissue which occurs after the impact. Secondary injury results in further vasoconstriction, cerebral excitation, edema and elevated intracranial pressure, and can potentially be avoided or ameliorated by optimal supportive care.

The intracranial contents are composed of 1) brain tissue (80%), CSF (10%) and blood (10%). This is housed in a non-distensible bony encasing (aka, the skull). An increase in volume of any one of the components that make up the brain will result in a rapid, exponential increase in intracranial pressure.

Brain volume = Tissue volume + CSF volume + Blood volume

Remember that water is non-compressible, therefore, brain tissue volume will be changed very little even with massive increases in pressure. (For example, even at the bottom of the ocean your body tissue will not be crushed. However, the gases in your body would come out of solution in a lively, albeit distressing, fashion). Therefore, compression results in decreases in blood and/or CSF volume. Initially, CSF fluid is displaced. Once this compensatory mechanism is exhausted, further increases in pressure lead to rapid decreases in blood flow, followed by anaerobic metabolism of the brain. This in turn leads to further edema and vasoconstriction, resulting in a vicious cycle. The rate of pressure rise is far more important than the total elevation in pressure. Contusions, hematomas, intracranial bleeds and edema are the most common culprits behind pressure-volume decompensation.

The brain makes up only 2% of total body mass, but uses 20% of total body oxygen. Despite these requirements, it has minimal oxygen storage capacity and few recruitable capillaries. Brain metabolism may vary from area to area, but total brain oxygen consumption is usually a constant.
Brain tissue can only utilize glucose as an energy source, but has little storage capacity. During periods of hypoxemia or reduced cerebral blood flow, the brain cannot meet its energy demands.

Cerebral blood flow (CBF) is regulated by: PaCO2, neuronal stimulation, PaO2, and pressure regulation. Of these, PaCO2 is the most important. As PaCO2 increases by 1mmHg, CBF increases by 3-4%. In contrast, PaO2 must fall below 50 mmHg before major changes in CBF occur. At a mean arterial pressure between 50-150 mmHg, CBF is maintained through autoregulation. Below and above this range, CBF is linearly dependent on blood pressure. The true driving force of CBF is Cerebral Perfusion Pressure (CPP). CPP is described by the equation:

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\text{Cerebral Perfusion Pressure} = \text{Mean Arterial Pressure} - \text{Intracranial Pressure}
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\[
\text{CPP} = \text{MAP} - \text{ICP} \text{ (or CVP when ICP is within normal ranges)}
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When ICP is elevated, CPP falls in a linear fashion. However, cerebral vasodilation maintains CBF, until the lower limit of autoregulation is reached. Damaged tissue lacks the ability to autoregulate, making CPP dependent on MAP. A combination of cerebral vasodilation and decreased MAP will result in patchy or uneven perfusion.

**At the Cellular Level**
Changes within the brain occur in a matter of seconds to minutes. Lack of oxygen delivery to the brain will deplete high energy substrate and ATP scores within seconds.

**Cellular injury (cytotoxicity)** is caused by:
1) Intracellular acidosis
2) Loss of Na-K-ATP pump – promotes cell swelling
3) Glutamate release – causing release of the excitatory neurotransmitter, depolarization and increased neuronal activity.
4) Astrocyte swelling – Astrocytes are the main glucose uptake and storage sites for neurons. Cell swelling reduces the ability of the astrocyte to maintain neuronal glucose levels.

Depletion of glucose stores and derangement of synaptic transmission occurs within seconds. Energy states and ionic gradients deteriorate within minutes. After 10 minutes, lactic acid accumulation plateaus and irreversible nerve damage occurs unless oxygen is restored immediately.
The two most important factors to treat are hypotension and hypoxia. In human medicine, 90% of deaths from TBI are attributable to hypotension and hypoxia. In another study, 70% of patients with TBI developed elevated ICP early, and 50% of the patients with medically uncontrollable elevations in ICP died. Any cause of elevated ICP must be sought out and effectively treated early in the course of TBI! Cerebral edema is the result of cytotoxic and vasogenic injury. Cytotoxic injury was discussed above. Vasogenic injury is from either platelet plugging or physical disruption of the endothelium, allowing accumulation of plasma proteins and electrolytes in the subendothelial space. It is thought that cytotoxic injury is more important in the development of cerebral edema.

The neurologic survey
The ABC’s of resuscitation must be addressed first. Ensure or provide an adequate airway, oxygen, ventilation, blood volume and peripheral perfusion prior to moving onto assessment of the neurologic system. Examine for skull fractures causing significant compression. Hematomas and intraparenchymal hemorrhage usually cannot be diagnosed without an MRI.

Level of consciousness: trauma anywhere from the thalamus to the cortex will result in altered mentation. Categories include: awake, depressed, delirium, stupor and coma. Stupor is defined as unconsciousness except in the face of noxious stimuli. Coma implies non-responsiveness.

Respiratory patterns: Cheyne-Stokes respirations are seen with cortical or diencephalic injury, but in animals are most commonly seen with massive diffuse cortical injury. Cheyne-Stokes respirations are a rhythmic waxing and waning in respiratory rate in response to altering cerebral CO2 levels. Hyperventilation is seen with lesions of the midbrain or pons, although metabolic acidosis, hypoxemia and pain must be ruled out. Apneustic breathing is associated with brainstem lesions, and causes deep, irregular respirations. Severe bradycardia and arrhythmias can be seen with brainstem damage.

Decerebrate rigidity occurs with complete transection of the brainstem from the cortex. It usually occurs with severe midbrain trauma. The animal is comatose, and displays opisthotonus and rigidity of all 4 limbs. Pupils are fixed and dilated. The prognosis is extremely poor.

The Three Tenets of Head Trauma Treatment:
1) Maintaining a normal blood pressure: CPP should be maintained above 60 mmHg at the least, and more ideally above 65-70 mmHg. In the face of elevated ICP, MAP should be maintained at or above 90 mmHg. Volume resuscitation and improvements in perfusion are generally achieved through intravascular volume expansion. However, crystalloid fluids rapidly distribute out of the intravascular space, and can lead to worsened cerebral edema and increased ICP. Hypotonic or dextrose containing fluids should always be avoided.

There has been much research into which resuscitation fluid is the best. Is it mannitol with conservative crystalloids or hypertonic saline with colloids (HTS-Colloid)? There is evidence to support both sides. Recent multi-center randomized trials showed a slight but insignificant advantage for HTS-Colloids over mannitol. The systemic resuscitation effects of colloids have not been shown to be superior to crystalloids, but lower volumes are required. Therefore… if you need to get an animal out of shock AND treat head trauma, it might be better to use HTS-Colloids rather than mannitol-crystalloids. However, if you want to use mannitol, it has been shown that a single large dose (1 g/kg) is better than several small doses. You may also hear that mannitol is contraindicated for patients with a hematoma. The answer is: how do you know the patient has a hematoma?

2) Maintain $P_aO_2$: providing supplemental oxygen is indicated in all patients with head trauma. If the patient is unable to maintain $P_aO_2 > 60$mmHg even with supplemental oxygen, mechanical ventilation is required.
3) **Maintain PaCO2:** Hypoventilation will lead to cerebral vasodilation, which in turn increases ICP. Hypoventilation can be caused by thoracic cage disease, pain, or from the head trauma itself. **PaCO2 should be maintained at 40-45 mmHg.** While hyperventilation will cause cerebral vasoconstriction and decrease ICP, it can also cause cerebral ischemia from excessive vasoconstriction. If hyperventilation is required to acutely decrease ICP, the target PaCO2 is 35-40 mmHg.

**Treatment Priorities**

1) **Decrease ICP:** Osmotherapy results in shrinkage of normal but not abnormal brain tissue. The brain volume changes in response to osmotherapy tend to persist even after the osmotic drug has been eliminated. Mannitol requires an intact blood-brain barrier to work, as does HTS.

2) **Increase venous drainage:** Facilitate CSF drainage by maintaining a **head elevation of 20-30 degrees** (whole body elevation, not just the neck). Avoid increases in venous pressure – do not use jugular catheters, avoid jugular blood draws and avoid coughing if intubation is necessary.

3) **Maintain semi-normoglycemia:** Both humans and animals with hyperglycemia have a worse prognosis. It is unknown if hyperglycemia is simply an indicator of the severity of injury and physiologic stress, or if hyperglycemia contributes directly to cytotoxic injury by being more readily available for anaerobic metabolism. There is evidence that BG >200g/dl is detrimental to recovery. **Administration of insulin is recommended for severely hyperglycemic (>200) patients.** Use ½ the typical dose of regular, short acting insulin IM.

4) **Maintain normothermia:** While fever is associated with increased CMRO2, hypothermia will lessen systemic response to catecholamines and can decrease MAP. **Keep the body temperature in the normal range. Avoid fever, consider permissive hypothermia (i.e., if they come in cold, do not actively warm them quickly).** A target body temperature of 94-96F is recommended in human patients. The recommended range has not been established in veterinary patients but I shoot for 96-98F. If the body does not want to be cold, do not force it to be cold.

5) **Maintain serum osmolarity:** Dehydration should be avoided. Monitor serum sodium concentrations and avoid rapid changes in serum osmolality.

6) **Use appropriate analgesic therapy:** The argument that pain medications should be avoided in patients with head trauma so that neurologic exams can be performed is barbaric at best. At worst, pain is associated with catecholamine release, hyperglycemia, hyperventilation, and cerebral ischemia.

   1) **Barbiturates** – Always indicated. They are neuroprotective through decreased oxygen demand, cerebral vasoconstriction, and anti-glutaminergic actions. They provide superior protection against edema and elevations in ICP.

   2) **Benzodiazepines** – Always indicated. The benzodiazepines are the least likely to depress the cardiovascular system, but do not provide analgesia. However, they will lessen the dose needed for other analgesic drugs.

   3) **Opioids** – Are almost always indicated. However, monitor carefully for respiratory depression. Hypoventilation will result in cerebral vasodilation and increased ICP. The use of mixed or partial agonists (Buprenorphine or Butorphanol) may lessen the risk of respiratory depression.

   4) **Lidocaine** – Indicated for dogs. Lidocaine prevents sodium influx into ischemic neurons, acts as a free radical scavenger and stabilizes lysosomal membranes to decrease oxidative burst from activated WBCs. While we usually use it at low doses (20-30 mcg/kg/min), anti-arrhythmic doses (1.5-2 mg/kg) have been associated with decreased neuronal death and improved outcome.
5) Propofol – Controversial. Propofol acts as an antioxidant and also modulates GABA receptors. However, hypotension frequently occurs with use, and decreased MAP will decrease CBF. If you chose to use this drug, monitor BP very carefully.

6) Ketamine – Controversial. At anesthetic doses, it is known to increase CMRO2 likely through inhibition of GABA. However, blockade of NMDA receptors may be beneficial. See more below.

7) Etomidate – Do not use. Use of Etomidate is associated with cerebral hypoxia and ischemic injury, possibly through NO scavenging.

8) Inhalant anesthetics – Do not use. At low concentrations, inhalants may decrease CMRO2. However, at higher (therapeutic) doses, decreases in MAP and increased $P_aCO_2$ will override any beneficial effects.

Therapies to consider...

1) Ketamine – at low doses, NMDA receptor antagonism may be a good thing. Neuronal hyperexcitability is likely the most important cause of increased CMRO2 and ischemia. However, higher doses of ketamine will increase CMRO2. Thus far, studies on use of low-dose ketamine in human TBI patients have been unrewarding. If used, ketamine doses should be 2-5 mcg/kg/min.

2) Magnesium – Supraphysiologic doses of magnesium may displace Ca2+ from the NMDA receptors and allow closure. However, administration of supraphysiologic magnesium has not been shown to penetrate into the CSF... but this does not necessarily reflect intracellular levels. The dose is 0.75 meq/kg/day of magnesium sulfate—this should be supplemented into the patient’s fluids and never given as a bolus.

3) Steroids? Do not use. Steroids have been shown to significantly worsen outcome. In the large scale, multi-center CRASH II trial, patients treated with methylprednisolone were significantly more likely to die, develop complications, or sustain long term neurological damage compared to patients where steroids were withheld.

Long term care:

Even with very severe head trauma, most patients that make it through the initial 24 hours will survive. The animal brain is amazingly plastic, and even with massive cortical injury, these animals can live normal lives. Young animals tend to adapt to brain injury far better than older animals because of the ability to form new synapses.

1) Nutrition – ensure that the patient has a normal gag reflex if oral nutrition is used. Force feeding should always be avoided due to risk of aspiration and food aversion. Feeding tubes may be required for short term nutrition in these cases.

2) Mobility – Some animals will need to be taught how to walk again. Ensure good footing and support for these patients. Slings and carts can help. Frequent, short physical therapy sessions should be started early.

3) Turning – avoid pressure sores by turning the patient every 4 hours, and provide appropriate cushioning. The all body surfaces (including the inguinal and axillary regions) should be inspected twice daily for development of moist dermatitis or pressure sores. Silver sulfadiazine, A and D ointment, and other skin barrier treatments can be used to help prevent wound infections.

4) Urination and defecation - if the patient is non-ambulatory, urinary catheters can be placed. Urinary catheter care should be performed every 8 hours, and includes flushing the vulva or prepuce with dilute chlorhexidine followed by saline. Lines and bags should be changed every 24 hours, and the entire collection system cleaned every 8 hours (or sooner if soiled).

5) Hydration – IV fluids should be used if the patient is unable to drink, but monitor serum sodium concentration to avoid cellular dehydration.
Dyspnea is defined as the sensation of difficulty with breathing, or is often referred to in human medicine as shortness of breath. Since veterinary patients cannot report sensations, we commonly use the term respiratory distress. Patients in respiratory distress have an exaggerated work of breathing. Normally, only 3% of the total energy expend by the body goes towards breathing. In patients with severe respiratory distress, that percentage can climb to upwards of 40%.

There are 4 major categories of respiratory distress etiology. These include: upper airway disease, lower airway disease, parenchymal disease and pleural space disease. Many other disease conditions, such as pain, stress, hyperthermia, anemia, CNS disease or compensation for a metabolic acidosis, can mimic dyspnea without true pulmonary pathology. The hallmark signs of dyspnea are open mouth breathing, cyanosis, abdominal effort, increased respiratory rate and effort, flaring nostrils, and orthopneic stance. More subtle signs can include hiding, weight loss, loss of appetite, decreased activity, and lethargy.

**Upper Airway Disease**

*Clinical Signs:* Upper airway disease can often be diagnosed by its classic obstructive breathing pattern. The obstructive pattern is associated with long, slow inspiration, stridor or stertor (depending on whether the obstruction is fixed or dynamic), increased effort +/- abdominal component, and orthopnea. Severe hyperthermia may be present, especially in dogs. Thoracic auscultation usually reveals referred upper airway sounds, found best by ausculting over the trachea. Obstruction can also cause non-cardiogenic pulmonary edema, resulting in pulmonary crackles.

*Pathophysiology:* While most upper airway obstruction is associated with inspiratory dyspnea, intrathoracic upper airway obstruction can cause expiratory distress. Narrowing of the airway is responsible for reduced and turbulent air flow. As the patient works harder to breathe against the obstruction, further edema and inflammation result, creating a viscous cycle. Airway obstruction reduces the amount of exhaled CO2 and inhaled O2, and hypercapnemia with hypoxemia is a common feature.

*Etiologies:* In dogs, the most common reasons for airway obstruction are laryngeal paralysis, brachycephalic airway syndrome and collapsing trachea. In cats, nasopharyngeal polyps, severe nasal disease, and tracheal masses are more common. Both species can have airway obstruction as a result of foreign bodies, intraluminal or extraluminal masses, abscesses or granulomas, or strictures.

*Treatment:* The primary treatment for upper airway obstruction is sedation and supplemental oxygen. Sedation lessens the work of breathing, reduces airway collapse and lessens obstruction. Butorphanol 0.1-0.2 mg/kg IV or IM is a good choice for the unstable patient. If the patient is cardiovascularly stable, acepromazine 0.02-0.05 mg/kg IV or IM can be used with or instead of butorphanol. Sedation should be titrated to effect. Upper airway obstruction tends to be oxygen responsive, but hypercapnemia may still be present. If the patient does not respond to initial sedation and oxygen, or if it is in severe distress, induction and intubation are appropriate. Emergency tracheostomy may also be indicated if a mass is present in the upper airways and the patient cannot be intubated.

*Diagnostics:* Once the patient is stable, appropriate diagnostics include sedated upper airway exam (looking for elongated soft palate, nasopharyngeal polyps, laryngeal paralysis or masses),
and otic exam, and thoracic and cervical radiographs. CT, rhinoscopy or tracheal fluoroscopy may be required for difficult to diagnose cases or to determine the extent of lesions.

**Lower Airway Disease**

*Clinical signs:* Lower airway disease is associated with expiratory distress, defined by normal inspiration and exaggerated, prolonged expiration. Expiratory wheezes are usually present on thoracic auscultation. A marked abdominal "push" may be present. Cats may present with a history of coughing. A heart murmur is usually not ausculted unless severe airway disease has led to cor pulmonale.

*Pathophysiology:* In lower airway disease, edema and cellular infiltration of the bronchiole walls leads to thickening and weakening of the bronchial walls, excessive secretion and mucus plugging. Further narrowing is caused by acute bronchospasm. As the patient inhales, radial traction on the lungs pulls the airways open and allows air to enter the alveolus. During expiration, negative intrathoracic pressure causes the airways to collapse, trapping air inside the alveolus. Since the alveolus is already full on the next Inspiratory cycle, the result in decreased gas exchange and hypoxemia. These changes are further complicated in the presence of secondary bacterial infections.

*Etiologies:* Expiratory dyspnea is most common in cats, and is pathognomonic for feline asthma. These cats typically have a history of a non-productive cough, "coughing up hairballs", or open mouth breathing after exercise, and are typically young to middle aged. Dogs can develop chronic bronchitis with secondary bacterial infections.

*Treatment:* The initial therapies are sedation and supplemental oxygen. As above, opioids should be used in the non-stable patient. Butorphanol is more sedating than other opioids, and a dose of 0.1-0.2 mg/kg IV or IM can be administered. Physical exam should be very brief to minimize stress. If the patient struggles, stop! This is not the patient you want to fight with to place an IV catheter. Albuterol 2 puffs via facemask should be administered. Albuterol is a fast-acting local agonist. If an albuterol inhaler is not available, terbutaline 0.01 mg/kg SQ can be administered. Aminophylline and theophylline are much slower to act, and the negative effects of atropine and epinephrine outweigh their benefits. Steroids are a feature of long-term asthma control, but take time to work and are not immediately indicated in asthma treatment. Once the patient has been stabilized, steroid therapy can be initiated.

*Diagnistics:* Thoracic radiographs should be taken only once the patient is stable. Cats with asthma will have a flattened diaphragm, over-inflated lungs, and may have right middle lung lobe atelectasis secondary to airway trapping. The hallmark of lower airway disease in both cats and dogs is the presence of the bronchiolar pattern on thoracic radiographs, including the presence of "doughnuts" and "tramlines" that indicate infiltration of bronchiolar walls. Airway cytology and culture can be used to rule out secondary bacterial infections. *Mycoplasma* is a common infectious agent, but requires special growth media. Doxycycline is the antibiotic of choice for treatment. Most times, lower airway disease is based on the presence of compatible clinical signs, radiographic findings, and the absence of cardiac disease.

**Pulmonary Parenchymal Disease**

*Clinical Signs:* Parenchymal disease does not have a specific respiratory pattern. Respirations are usually short, rapid and deep, but may mimic any of the other respiratory patterns. The patient may be in severe distress, cyanotic, and/or have a marked abdominal component. The best way to diagnose parenchymal disease on physical exam is to auscult the presence of crackles. A heart murmur may be ausculted in patients with cardiogenic edema, however, not all cats with severe heart disease will have a heart murmur. Dogs will commonly have a history of a cough (productive or not), while cats rarely cough with parenchymal disease. Bradycardia and hypothermia may be noted in the cat with congestive heart failure. Fever may be present in the patient with pneumonia. A thorough history should be taken to cover the most common causes of
parenchymal disease, including any history of vomiting or recent boarding (pneumonia), potential trauma (contusions or non-cardiogenic edema), or heart disease (cardiogenic).

**Pathophysiology and Etiology:** Crackles are the sound of collapsed alveoli and lower airways “popping” open at the end of inspiration, and indicate fluid filled alveoli. There are only a few types of fluid that can be present: blood (pulmonary contusions or hemorrhage), pus (pneumonia), or water (cardiogenic or non-cardiogenic edema). Pulmonary contusions are most commonly the result of blunt force trauma to the lungs, which causes rupture of vessels and bleeding into the alveoli. Pulmonary hemorrhage can occur as a result of coagulopathy. Pneumonia can be spread by the hematogenous route, but is more commonly associated with aspiration and vomiting. Cardiogenic edema is caused by left sided heart disease and increased pulmonary venous pressures. Non-cardiogenic edema is associated with severe seizures, head trauma, strangulation, airway obstruction and electrocution. Cardiogenic edema is low in protein and is caused by increased hydrostatic pressure within the pulmonary veins and capillaries. Non-cardiogenic edema is thought to be caused by endothelial injury and vascular leak of protein-rich fluid into the alveolus.

**Treatment:** As above, the initial treatments of choice are sedation and supplemental oxygen. Since these patients are more likely to be cardiovascularly unstable, butorphanol is preferred over acepromazine. However, trauma patients may require stronger analgesia than that offered by butorphanol. In those cases, I will reach for methadone 0.2-0.5 mg/kg IV or hydromorphone 0.1-0.2 mg/kg IV. If a heart murmur is present, or if heart disease is strongly suspected, a single dose of furosemide 2 mg/kg (dogs) or 1 mg/kg (cats) IV or IM is not likely to cause harm. Once further history and diagnostics have been collected, additional treatment may be indicated. The goal of initial treatment is to get the patient stable enough for radiographs. If that patient is severely dyspneic and does not quickly respond to treatment, then the patient should be anesthetized, intubated and mechanically ventilated. Positive end-expiratory pressure (PEEP) of 5 cmH\textsubscript{2}O can help to recruit alveoli.

**Diagnostics:** A thorough history is often the first step in diagnosis. Physical exam will also aid in making the diagnosis. Look carefully for other signs of trauma (bruising, especially episcleral or in the inguinal region) or injury. A burn at the lip commisures indicates electric shock. As above, the presence of a heart murmur is helpful, but does not always mean that cardiogenic edema is present. Fever may indicate infectious disease.

Thoracic radiographs are the best way to help determine the underlying cause. An interstitial to alveolar or alveolar pattern suggests parenchymal disease. The following radiographic distributions can be useful in helping to determine the underlying cause:

- **Perihilar pattern:** Indicates cardiogenic edema in dogs. Additional helpful findings include pulmonary venous dilation (veins are ventral and central to arteries), enlarged cardiac silhouette and left atrial dilation. In cats, pulmonary veins are usually distended, but cardiogenic edema in cats does not have a typical radiographic distribution.

- **Cranioventral distribution:** Indicates aspiration pneumonia. The right cranial, right middle and left cranial lung lobes are most commonly affected. Aspiration pneumonia is very uncommon in cats, but common in dogs. Predisposing conditions in dogs include vomiting, laryngeal paralysis, or upper respiratory tract infection.

- **Caudodorsal distribution:** Usually indicates either hematogenous spread of pneumonia or non-cardiogenic edema. History and physical examination are useful in differentiating the two causes.

- **Nodular (Structured interstitial) pattern:** Usually indicates either neoplasia or fungal disease. It can be difficult to differentiate between these two disease processes, since both can cause fever, hemoptysis and cough. A search for another site of neoplasia with
abdominal radiographs or ultrasound, or a fundic exam looking for fungal granulomas can be of use.

Cats with any of the above disease processes can have almost any radiographic distribution. Additional diagnostics to consider include airway wash (transtracheal, endotracheal or bronchoalveolar lavage) with cytology and culture, abdominal radiographs and ultrasound, echocardiogram, and fungal titers.

Additional Treatment: Definitive treatment will be dictated by the diagnosis. Furosemide is indicated in cases of cardiogenic edema, but not in non-cardiogenic edema or pneumonia. IV fluid therapy and broad spectrum antibiotics are indicated for treatment of suspected pneumonia. There is no specific treatment for pulmonary contusions and non-cardiogenic edema other than supportive care and oxygen therapy.

Pleural Space Disease

Clinical signs: The restrictive pattern is the hallmark of pleural space disease. This is a short, shallow, rapid breathing pattern. The thorax may take on a “sprung” appearance, where the chest wall seems wider than normal, especially with pneumothorax. On auscultation, lung sounds and/or heart sounds may be dull. If pleural effusion is present, lung sounds will be loudest dorsally and a fluid line may be ausculted. If pneumothorax is present, lung sounds will be loudest ventrally. Borborygmi may be noted on thoracic auscultation in patients with diaphragmatic hernia. A heart murmur or gallop may be ausculted in patients with heart disease.

Pathophysiology: The presence of air, fluid, organs or masses in the pleural space prevents expansion of the lungs by increasing intrapleural pressure above intrapulmonary pressure. As a result, the tidal volume is greatly increased, and animals must breathe must faster than normal to maintain an adequate respiratory minute volume. Progressive collapse of alveoli leads to hypoventilation, VQ mismatching and hypoxemia.

Etiology: There are 4 things that can be in the pleural space: air, fluid, organs and masses. Pneumothorax is usually caused by trauma (either blunt or penetrating), but may be spontaneous due to rupture of bullae or severe parenchymal disease. Pleural effusion can be caused by hemothorax (rare), infection (pyothorax), heart failure, neoplasia or accumulation of chyle. Rarely, overhydration or hypoalbuminemia can cause pleural effusion. Diaphragmatic hernia (congenital or traumatic) and large intrathoracic masses can also cause clinically relevant pleural space disease.

Treatment: Again, oxygen and sedation are the initial treatments. Diuretics are not effective for rapid removal of pleural effusion. Once the patient is appropriately sedated, thoracocentesis should always be performed prior to radiographs if pleural space disease is suspected. A chest tap should be performed at the 7th or 8th rib space, with the needle directed perpendicular to the chest wall. Continue to remove fluid or air until as much as possible is gone. If negative pressure cannot be achieved, if more than 2 taps are required in a one hour period or more than 3 taps are required in a 24 hour period, a chest tube should be placed. Thoracocentesis has a low rate of complications, but can cause hemorrhage, lung injury or introduce infection if not performed steriley. In cases with long-standing pleural effusion, rapid and fatal re-expansion pulmonary edema can occur.

Diagnosis: The presence of pneumothorax should prompt a search for pulmonary disease if there is no history of trauma. Traumatic pneumothorax generally resolves without surgical intervention, although some injuries can take up to a week to heal. The causes of pleural effusion are many, but the etiology can be narrowed with cytology of the fluid. Below is a table of the common causes of pleural effusion and their cytologic characteristics. In cats especially, echocardiogram may be required to differentiate causes of modified transudate. If thoracocentesis is negative, thoracic radiographs looking of an underlying cause of the restrictive
pattern should be performed. Diaphragmatic hernias will require surgery to repair. A blanket waiting period of 24 hours after the onset of traumatic diaphragmatic hernia is no longer recommended – patients should be taken to surgery as soon as they are stable.

<table>
<thead>
<tr>
<th>Category</th>
<th>Total Protein (g/dl)</th>
<th>Cell Count (cells/μL)</th>
<th>Etiology</th>
<th>Cytologic Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transudate</td>
<td>&lt; 2.5</td>
<td>&lt; 2,500</td>
<td>Hypoalbuminemia</td>
<td>Very low cellularity</td>
</tr>
<tr>
<td>Modified Transudate</td>
<td>&gt; 2.5; &lt; 5.0</td>
<td>&gt;2,500; &lt; 5,000</td>
<td>Heart Failure (right sided in dogs, either side in cats) Neoplastic</td>
<td>No specific changes May see large, abnormal cells or mitotic figures</td>
</tr>
<tr>
<td>Exudate</td>
<td>&gt; 5.0</td>
<td>&gt;5,000</td>
<td>Chyle</td>
<td>Characteristic strawberry milk appearance, may see small lymphocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pyothorax</td>
<td>Primarily degenerate neutrophils, may see intracellular bacteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FIP</td>
<td>High total protein, low cell count, predominately macrophages</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neoplastic</td>
<td>Similar to above, may be very cellular</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Similar or higher to peripheral blood</td>
<td></td>
<td>Bleeding masses Anticoagulant rodenticide toxicity Trauma (rare)</td>
<td>PCV will be similar to or higher than peripheral blood</td>
</tr>
</tbody>
</table>
Diabetic Ketoacidosis
Amy Butler, DVM, MS, DACVECC
President – Critical Consults

Pathogenesis:
DKA represents a complication of diabetes mellitus characterized by the combination of hyperglycemia, ketonemia, and acidemia. The development of DKA is related to an absolute or relative insulin deficiency, which causes an insufficient amount of insulin to be produced. At the same time, increased counter-regulatory hormones such as epinephrine, cortisol or growth hormone cause an increase in hepatic glucose production, impaired glucose uptake by tissues, and marked hyperglycemia. Low or insufficient insulin levels combined with increased counter-regulatory hormones lead to activation of lipases which cause breakdown of triglycerides and release of free fatty acids. Diseases that contribute to formation of DKA include infection (pneumonia, UTI, pyelonephritis, even skin infections); inflammatory disease (pancreatitis, immune-mediated processes); neoplasia; endocrine disease (Cushing’s, hyperthyroidism); or insulin deficiency (too low of dose, intra-fur injections, poor insulin handling).

Fatty acids are taken up by the liver and converted to ketone bodies to serve as an alternate energy source, especially under the direction of glucagon. These ketones (β-hydroxybutyrate, acetoacetate, and acetone) are generated at levels that exceed cellular utilization. The ketoacids readily dissociate, producing metabolic acidosis and signs of illness. The hyperosmolar state created by hyperglycemia and ketonemia causes fluid and electrolytes to move out of the cells and interstitium, promoting cellular dehydration. Hyperglycemia also results in a marked osmotic diuresis resulting in volume depletion and electrolyte wasting. Severe hypovolemia can then cause diminished renal perfusion and an impaired ability to excrete glucose, ketones and acid, thus establishing the vicious cycle of DKA.

Physical examination:
Progression to DKA should be considered for any known diabetic (dog or cat) that develops signs of systemic illness. The most common signs include lethargy, weakness, depression, anorexia, weight loss, vomiting and diarrhea. These signs are non-specific for patients not previously diagnosed with diabetes. The owners might also report the development or worsening of polyuria and polydypsia, potentially progressing to decreased urination and water intake. Initial physical exam often reveals depressed mentation, moderate to severe dehydration and potentially signs consistent with poor perfusion/cardiovascular collapse (tachycardia, pale mucous membranes, weak pulse quality, etc.). Patients may be described as in respiratory distress, but often have Kussmaul’s respirations. This is a deep and slow respiratory pattern associated with severe acidosis. It may also be possible to smell ketones on the breath of a patient with DKA.

Diagnostic Testing:
Point-of-care testing should be performed in all patients suspected of DKA. The disease is relatively easy to diagnose if the appropriate tools are available.

PCV/TG: May reveal hemoconcentration.

Blood glucose: May be significantly elevated, although ketosis can develop at ANY blood glucose concentration. The presence of hyperglycemia does not necessarily indicate the presence of ketones.

Urine ketones: The presence of urine ketones is considered the standard for diagnosis of DKA. However, cats and dogs with very concentrated urine or with all-meat diets may have traces of ketones. In the presence of hyperglycemia, glucosuria and ketosis, DKA can be diagnosed. However, remember that the urine strips only test for acetoacetate and acetone, but not beta-hydroxybutyrate. In an animal with a pure beta-hydroxybutyrate ketosis, the strip may be negative, although this is very rare.

Plasma ketones: If the urinary bladder is empty, or if urine cannot be obtained, plasma ketones can be used for diagnosis. Plasma ketones have been shown to have good sensitivity and specificity for diagnosis of DKA (98% in dogs, 89% in cats).

Venous blood gas: Is an indispensable tool in treatment of DKA. Severe acidemia (pH < 7.0) may be present, with a compensatory decrease in P\textsubscript{a}CO\textsubscript{2}. The pH serves as a guide for bicarbonate therapy.

CBC: May demonstrate hemoconcentration or a mild non-regenerative anemia and may also reflect changes consistent with any co-morbid disease processes.
Biochemical profile: May reveal mild to moderate azotemia. It can be difficult to determine if this is renal or pre-renal, as DKA patients are usually isosthenuric due to hyperglycemia and glucosuria. Hyponatremia and hypochloremia are common and can occur secondary to urinary and GI losses. In addition, the hyperosmolar state created by marked hyperglycemia and ketonemia can exert a dilutional effect on serum sodium concentration. It has been demonstrated that every 100 mg/dL increase blood glucose over normal will reduce the sodium concentration by 1.6 – 2 meq/L. At the time of presentation, serum potassium, magnesium, and phosphorus levels tend to be normal or elevated. This is secondary to decreased renal perfusion and intracellular shifting. Regardless of the serum level, these patients often have significant total body depletion of these electrolytes from urinary and GI losses. Other significant biochemical abnormalities include hypercholesterolemia and elevations in liver enzymes (especially alkaline phosphatase).

Urinalysis: Isosthenuria is often present secondary to the osmotic diuresis induced by glucosuria. The presence of isosthenuria and azotemia does not necessarily indicate renal disease. Urine sediment should be investigated for signs of urinary tract infection. However, the urine sediment can be inactive even in the presence of infection as diabetics have impaired white blood cell adhesion and chemotaxis. A urine culture should always be submitted for any DKA patient.

The remainder of the diagnostic work-up is contingent upon index of suspicion for co-morbid disease processes but could include imaging (thoracic radiographs, abdominal ultrasound), PLI, adrenal axis testing, thyroid levels, etc. It is important to note that the systemic impact of DKA can make interpretation of testing for hyperadrenocorticism (dogs) and hyperthyroidism (cats) challenging and ideally these tests are performed at a later time.

Treatment:

IV fluid therapy is the cornerstone of treatment. The goal is to restore intravascular volume and replace fluid deficits. Administration of isotonic crystalloid “shock doses” (80-90 ml/kg) in bolus fractions (1/4 – 1/3 shock dose over 10-15 minutes, repeated as necessary) may be necessary for patients experiencing cardiovascular collapse. If resuscitation is not necessary then aggressive replacement of fluid deficit is still warranted. Intravenous fluids alone can have a significant effect of reducing blood glucose through dilution and increased tissue perfusion. Fluid therapy can also decrease concentrations of counter-regulatory hormones, thereby making cells more responsive to the effects of insulin. Rehydration will also promote fluid and electrolyte shifts into the intracellular space which can result in significant reductions in blood levels. Traditionally, 0.9% NaCl has been considered to be the fluid of choice because it allows for more rapid correction of sodium and chloride deficit and may prevent an overly rapid reduction in serum osmolality (and associated neurological sequelae). However, 0.9% NaCl is an acidifying solution which could serve to exacerbate metabolic acidosis. Conversely, balanced electrolyte solutions have an alkalinizing effect and contain potassium but may cause a more rapid reduction in serum osmolality. Despite these arguments, there is no evidence that one fluid type is superior in the treatment of DKA.

Sodium bicarbonate administration remains controversial. No studies have shown a survival or hospitalization time benefit with administration of bicarb. In addition, there are potential adverse effects including rapid reduction in potassium and calcium concentrations, paradoxical CNS acidosis, and overshoot alkalosis. Despite these concerns, in human medicine the use of bicarbonate is currently recommended for patients with a persistent pH < 7.0 after adequate fluid resuscitation. The dose can be calculated as dose (in meq) = 0.3 x BW x (expected change in HCO₃). We typically try to correct bicarbonate to 12-16 meq/L so to avoid overshoot alkalosis. An easier way to calculate this is to give 1 meq/kg. Half of the dose should be given over 30 minutes, and the rest given over 3-4 hours.

Insulin Therapy must be given to stop ketogenesis. However, insulin will also promote intracellular shifting of electrolytes. It is generally recommended that insulin therapy is delayed in the initial stages of treatment. Fluid therapy alone can cause significant reduction in blood glucose and electrolytes. The decision to start insulin therapy should be made after it is evident that fluid therapy alone is not causing any further dramatic changes in these values (generally 6-12 hours). Short-acting (regular) insulin should be administered IM or IV, but not SC since absorption will be delayed in the dehydrated patient. Do not use long-acting insulin since dose reduction in patients that develop hypoglycemia is not possible, and the insulin must be constantly adjusted. Therefore, protocols for intermittent IM or CRI of regular insulin are generally preferred. Ideally the patient’s blood glucose should be checked at least every 1-2 hours in the early stages of insulin therapy as fairly rapid changes can occur.
Potassium supplementation will be needed for most patients. Even if the patient is normo- or hyperkalemia initially, severe hypokalemia can develop once fluid, insulin and bicarbonate therapies are initiated. There are published guidelines for potassium supplementation, with the recommendation not exceed a maximum rate of 0.5 meq/kg/hr. Potassium levels should be checked frequently (every 4-6 hours initially).

<table>
<thead>
<tr>
<th>If Potassium Is…</th>
<th>Supplementation (in meq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5 – 5.0</td>
<td>20</td>
</tr>
<tr>
<td>3.0 – 3.4</td>
<td>30</td>
</tr>
<tr>
<td>2.5 – 3.0</td>
<td>40</td>
</tr>
<tr>
<td>2.0 – 2.4</td>
<td>60</td>
</tr>
<tr>
<td>&lt; 2.0</td>
<td>80</td>
</tr>
</tbody>
</table>

Magnesium supplementation is often required as well. The presence of refractory hypokalemia despite aggressive replacement should alert to the need for magnesium supplementation (0.3-1 meq/kg/day), despite initially normal or even elevated ionized levels. Magnesium sulfate preparations are available, and typically only small amounts are required.

Phosphorous supplementation can be a part of potassium supplementation. As cells begin to replenish severely depleted ATP stores, severe hypophosphatemia can rapidly develop. The most significant consequences of severe hypophosphatemia (typically < 1.0 mg/dL) are hemolytic anemia in cats and seizures in dogs. The easiest way to supplement phosphorous is to calculate the potassium requirement. Half of this should be supplemented as potassium chloride, and the other half should be supplemented as potassium phosphate, dosed on the potassium fraction.

Dextrose therapy is often required to treat hypoglycemia. While it seems counter-intuitive that a diabetic would require insulin and dextrose at the same time, insulin must be given to shut off ketogenesis. If dextrose supplementation is required to continue giving the insulin, then it should be given. The table below is one of many protocols for use of dextrose in DKA patients.

<table>
<thead>
<tr>
<th>If the glucose is…</th>
<th>Dextrose</th>
<th>Insulin Given?</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 250</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>200 – 250</td>
<td>2.5%</td>
<td>Yes</td>
</tr>
<tr>
<td>150 – 200</td>
<td>5%</td>
<td>Yes</td>
</tr>
<tr>
<td>&lt; 150</td>
<td>5%</td>
<td>No</td>
</tr>
</tbody>
</table>

Antibiotic therapy should be initiated until culture results are available, especially if infection is suspected as a cause of DKA. *E. coli* is the most common cause of urinary tract infection in both dogs and cats. Ampicillin, sulbactam-ampicillin and enrofloxacin are all good choices for treatment of community-acquired urinary tract infections. Other antibiotics should be chosen on the basis of site of infection and likelihood of bacterial type.

Monitoring

Blood glucose should be monitored every 1-2 hours initially, and every 2 hours while on the short-acting insulin protocol. A central catheter will prevent frequent needle sticks and improve patient comfort. Be careful to clear the catheter with at least 6ml of blood if the line is also being used to provide supplemental dextrose. Ideally, venous blood gases and electrolytes should be monitored every 4-6 hours initially. At a minimum, electrolyte panels should be performed every 6 hours. Heart rate, respiratory rate and temperature should be checked frequently (every 2-4 hours initially). The continued presence of ketones should be evaluated daily, although the presence of ketones should not delay switching the patient to long term insulin or hospital release. PCV should be monitored at least twice daily to monitor for the development of hemolytic anemia. Cats can easily become anemic with frequent sampling, so the volume of blood draws should be limited in these patients.

Prognosis

The decision to discontinue the short-acting protocol and switch to subcutaneous insulin is typically based on a number of factors. Ideally the patient should be completely rehydrated and clinically
improved with stabilization of electrolytes and without dramatic fluctuations in blood glucose on the insulin protocol. Most importantly, the patient should be willing to eat on their own, though this can be challenging with cats. Resolution of ketonemia and/or ketonuria is not recommended as a guide because presence of ketones can persist well beyond clinical improvement.

The reported rate of survival to hospital discharge for dogs and cats with DKA is approximately 70%. In dogs it has been shown that concurrent hyperadrenocorticism is associated with a decreased likelihood of survival. In addition, non-survivors had lower ionized calcium concentration, lower hematocrit, lower pH and larger base deficit. Each unit increase in base deficit was associated with a 9% greater likelihood of survival to discharge. A study in cats demonstrated that azotemia, metabolic acidosis, and hyperosmolality were more severe in those that did not survive to discharge.
Intravenous Lipid Emulsion Therapy: It's Good for what Ails You!
Amy Butler, DVM, MS, DACVECC
President – Critical Consults, LLC

Treatment with lipid emulsion for acute intoxication is one of the most exciting advances in recent years. It is used to treat toxicosis by lipophilic substances, and has been investigated as a therapeutic for numerous substances. The advantages of ILE include an apparent wide margin of safety, relatively low cost, long shelf-life, and ease of administration.

What are intralipids?
Intralipid® is a brand name for intravenous lipid emulsion (ILE). This is a soy-bean oil based emulsion containing fatty acids, including linoleic, oleic, palmitic, linolenic, and stearic acids. ILEs have been used as a component of parenteral (intravenous) nutrition since the early 1960's. In the 1970s and 1980s, studies were performed on the effect for ILE on pharmacokinetics of cyclosporine and phenytoin. Then, in 1998, a study showed that administration of ILE greatly changed the dose-response of bupivicaine-induced cardiac arrest in rats. This study triggered an explosion of other studies investigating the therapeutic effects of ILE first in local anesthetic toxicosis, then other lipophilic substances. Multiple brand names of ILE are available. While Intralipid® is the most recognized brand name, Liposyn III®, Lipoven® and Lipofundin® are other forms of ILE.

Mechanism of Action
The exact mechanism of action is unknown. Current theories include: formation of a “lipid sink”, or improved myocardial performance. The “lipid sink” theory relies on a separate lipid compartment within the intravascular space where lipophilic toxins are sequestered. Simply put, the infused intravascular lipid binds the offending toxin in sufficient quantity to pull drug from the target tissue, thereby reversing the toxicity. From the blood, the toxin is excreted into the bile or taken up by the reticuloendothelial system. The myocardial performance theory posits that improved myocyte performance is a result of free fatty acid availability, leading to more available energy.

The lipid sink theory (the more popular of the two) requires that the toxin be lipid soluble. The lipid solubility of a drug is predicted by the $\log P$ value. The $P$ stands for partition coefficient, which indicates the drug's solubility in two different solvents. The higher the $\log P$ value, the more lipid soluble the drug is. However, the measured $\log P$ is often related to the pH of the solvents, so the biological behavior of a drug in the body may be different than that predicted by the $\log P$ value.

Toxins treated
ILE have been investigated as an antidote for multiple drug toxicities. In veterinary medicine, published case reports exist for treatment of intoxication with moxidectin, ivermectin, diltiazem, marijuana, lidocaine, pyrethrin and baclofen. The author has successfully used ILE for treatment of intoxication with ivermectin, nicotine, pyrethrin, and a variety of unknown neurotoxins. Realistically, anything that is able to cross the blood-brain barrier and cause neurologic signs is likely to respond to ILE. This is because the blood-brain barrier is typically only penetrable to fat-soluble substances, which are the substances removed with ILE therapy.

Two case series (Kuo, JVECC 2013; Haworth, JVECC 2012) have been published on use of ILE in pyrethrin toxicity in cats. In both series, cats presented with moderate to severe tremors. Most cats improved markedly within a few hours after ILE administration (one cat required a second, longer bolus). The doses used ranged from 0-1.5 mL/kg bolus, then ~0.25 mL/kg/min for 30-45 minutes. One cat did not receive a bolus; only an infusion 0.25 mL/kg/min over 60 minutes was administered. All cats had significant improvement in tremors, although one cat had to have the lipid dose repeated.

One point to remember when administering ILE is that sedatives and anticonvulsants may be reversed or have diminished effectiveness in patients given ILE. Theoretically, ILE administration may decrease serum levels of antiepileptic drugs, but this has not been studied in veterinary or human patients.

Dose
ILE is given as a bolus, followed by a slow infusion. The following doses are for the 20% solution. Published doses for the bolus range from 1.5mL to 4 mL/kg IV over 1 minute, with most case reports using a 1.5 mL/kg dose. The bolus is followed with a slow infusion of 0.25 mL/kg/min IV for 30-60 minutes. These doses may need to be repeated. Maximal doses have not been investigated in veterinary patients, although some sources
suggest a maximum dose of 8 ml/kg/day. Some investigators recommend monitoring for the presence of hyperlipidemia by inspecting the plasma portion of a hematocrit tube prior to delivering additional doses of ILE.

These doses are extrapolated from human data. No safety studies have been performed in veterinary patients.

**Set-up and precautions**
ILE should be handled similarly to parenteral nutritional solutions. The set-up should be handled in a sterile manner to avoid contamination of the solution. A regular drip set is used to spike the bag, and a 1.2µm filter is used between the drip set and the patient. A filter is essential to prevent infusion of lipid globules. Blood filters (such as Hemonate or blood filter drip sets) should not be used as the pores in these filters are large enough to let unsafe sized lipid globules through.

Other medications should not be given in the same line as ILE. Either wait until after the infusion is over, or place another catheter. The IV catheter may be used for fluid and medication delivery before or after, but not during ILE infusion. Once ILE infusion is completed, the line may be steriley unhooked and flushed. While technically ILE should be discarded after 4 hours of opening the bag, the author will store unused ILE for that patient for up to 24 hours in the refrigerator. A peripheral catheter may be used since the osmolarity of the ILE is similar to that of plasma.

Care should be taken to avoid extravasation of ILE. Local tissue pain, swelling and necrosis have been reported. ILE should only be given via an intravenous catheter.

**Adverse Effects and monitoring**
Case reports of patients given recommended doses have not reported adverse effects, however, there are anecdotal reports of hemolysis in cats following intralipid administration. In the Kuo and Haworth case series, packed cell volumes were either not monitored pre- and post-administration or not reported. Currently, I recommend monitoring pre- and post-ILE administration PCV in cats.

Tonkin et al (AJVR 2013) investigated the effects of ILE on hemostatic variables in dogs. Although the maximum amplitude on thromboelastography (essentially, the clot strength) was significantly decreased, this finding was unlikely to be clinically relevant. Their conclusion was that even very high serum lipid concentrations did not significantly affect coagulation. Theoretically, hyperlipidemia is associated with development of pancreatitis, but this has not been reported yet in veterinary patients.

In human medicine, allergic and anaphylactic reactions to ILE have been reported. The potential for reactions exists but has not been reported in veterinary patients.

During infusion, heat rate, body temperature, respiratory rate and mucous membrane color should be monitored 5 minutes after starting the infusion. TPR-mm should be monitored every 15 minutes. Delayed or subacute reactions related to 'fat overload' may be seen. Fat overload syndrome occurs when the body's mechanism for clearing long-chain triglycerides is overwhelmed. Clinical signs reported in humans include fat embolism, hyperlipidemia, hepatomegaly, icterus, splenomegaly, thrombocytopenia, increased clotting times and hemolysis. This syndrome has not been reported in veterinary medicine.

**Cost of Intralipid Therapy**
Intralipids (20%) may be ordered direct from Baxter, or through a supplier such as MWI or Butler Schein. There is currently a national shortage, so it can be difficult to purchase as Baxter is allocating the drug. Intralipids are purchased by the case (10 bags – each 100mL). The hospital cost is ~$25 per bag. The 1.2 micron filters are available for ~$6.00 purchased individually through Butler (or in a box of 50).
Furosemide Nebulization
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Dyspnea is the sensation of shortness of breath or air hunger. While the human medical definition focuses on the self-reported symptoms of dyspnea, our patients are unable to report sensations. The definition in veterinary medicine focuses on the clinical signs of difficulty or labored breathing. Interestingly, both pain and dyspnea share common neural pathways. Activation of pain pathways often results in perceived air hunger, while the presence of dyspnea will frequently decrease reported pain scores, possibly conferring a survival benefit.

The Mechanisms of Dyspnea
Multiple receptors within the bronchial tree and pulmonary parenchyma have been implicated in the sensation of dyspnea. Among these are the slowly adapting receptors (SARs) and rapidly adapting receptors (RARs) present in the lower airways, which respond to pulmonary stretch. SARs are primarily activated by lung inflation. These are myelinated fibers, and carry Aβ and Aδ receptors. An increase in SARs firing has been show to alleviate signs of dyspnea. RARs are polymodal, chemosensitive, and present in both the submucosa and epithelium of small airways. RAR stimulation has the opposite effect of SARs. RARs have also been implicated in the cough response.

Nebulized furosemide is thought to work by inhibition of the Na⁺/K⁺/2 Cl⁻ (NKCC) receptors creating an antagonistic effect in the RARs. In the SARs, it is thought to work by sensitizing Na⁺ channels through an unknown mechanism. The combined effect is increased firing of SARs and decreased firing of RARs, decreasing the overall response to pulmonary stretch, tidal volume and lung compliance.

History of Nebulized Furosemide
Nebulized furosemide was first investigated in the early 1990’s as an alternative treatment for palliation of dyspnea in end-stage lung cancer patients. Since then, it has been investigated as a treatment for multiple respiratory conditions, including COPD, asthma, congestive heart failure, and neoplasia. In patients with acute allergic asthma and in patients with exercise-induced asthma, nebulized furosemide has been shown to have a protective effect against bronchoconstriction. In multiple studies, patients with terminal neoplasias of the respiratory tract reported improved quality of life, less shortness of breath, and less anxiety related to breathing. Interestingly, these studies have failed to identify any improvement in objective measures of ventilation, including S₂O₂, arterial blood gases, or respiratory rate. In the majority of studies, systemic diuresis was not reported.

What is the Veterinary Evidence?
The veterinary evidence for nebulized furosemide is scant. One study by Nehashi et al in 2001 investigated its use in healthy, anesthetized cats with experimental tracheal tube occlusion. In this study, it was found that nebulized furosemide significantly decreased escape behavior (measured by forelimb and head movement) compared to controls inhaling saline alone. Escape behavior was reduced for up to 3 hours following a single treatment. Another study on airway responsiveness (measured by cytokine and receptor expression) in mice with allergen-induced asthma found that nebulized furosemide significantly decreased basal airway responsiveness.

When to Use Nebulized Furosemide?
Although the scientific evidence is sparse, many anecdotal reports exist which praise the use of nebulized furosemide. Perhaps more important than its effects on bronchoconstriction is nebulized furosemide’s
effects on the sensation of dyspnea. I have used it with intermittent success in patients with non-cardiogenic pulmonary edema, feline asthma, congestive heart failure, and pneumonia. Indications for use include tachypnea, increased respiratory effort, and perceived dyspnea. Remember that this treatment does not correct the underlying problem, but it makes it less unpleasant for the patient to breathe without reducing respiratory drive. Medical management of the underlying cause should be continued.

The difficulty in determining effectiveness lies in our patients’ inability to report improvement in dyspnea. We are left asking ourselves – does the patient seem more comfortable? Does it seem to be breathing easier? Because the answer is so subjective, it can very difficult to determine if it is helping. If the patient is grooming, eating, drinking and otherwise acting normally, there is little reason to give nebulized furosemide as that patient is not likely experiencing dyspnea.

The Mechanics of Nebulized Furosemide

- In nebulization cup, place 5 mg/kg furosemide injectable
- Add 1mL Magnesium Sulfate (0.081meq/mL or 10mg/mL)*** (READ TEXT BELOW)
- Add 1mL sterile water or 2mL 0.45% NaCl
- Nebulize to patient every 3-4 hours or less frequently as needed

***Remember to double check your Magnesium concentration! Magnesium MUST be diluted with either sterile water or 0.45% NaCl to an isotonic solution. If not diluted, serious pulmonary injury and edema can result. You should ensure that the Magnesium Sulfate concentration is 0.081 meq/mL. If your hospital carries the 500mg/mL MgSO₄, then the correct dilution is 0.14mL MgSO₄ in 1.9mL sterile water. The rationale behind use of Magnesium Sulfate is that it is a known bronchodilator.

***Magnesium is not required. You can simply dilute your furosemide dose in 2mL sterile water and not add the magnesium portion.

Adverse Effects

The most reported adverse effect is that it doesn’t work. There appear to minimal side effects associated with nebulized furosemide. One study on a porcine model found an increase in pulmonary endothelium permeability in healthy lungs exposed to nebulized furosemide, but those results were not replicated in multiple other studies. Since less than 10% of the dose is absorbed systemically, diuresis may be seen, but is not common. Monitor the patient to ensure adequate hydration, and make sure that fresh water (or IV fluid therapy, if indicated) is available.
Cleaning protocols
Surface disinfection is one of the most fundamentally important aspects of infection control. Reducing pathogen load helps to prevent bacterial colonization of wounds, surgical incisions and indwelling devices (such as IV and urinary catheters). Colonized surfaces can contaminate personnel and other patients, even without direct contact between patients. Disinfectants are typically used to destroy pathogenic organisms. It is important that disinfection be a two-step process – where gross contamination is removed first using a detergent, and then the disinfectant is used to kill surface organisms. This is important since gross contamination with organic matter will rapidly inactivate most disinfectants.

Despite labeling to the contrary, the majority of quaternary ammonium disinfectants (Parvosol®, Roccal-D®, Zephiran®) do not reliably kill parvovirus or other non-enveloped viruses. Peroxygen compounds and accelerated hydrogen peroxide based cleaners are steadily replacing the older quaternary ammoniums as preferred disinfectants. These are more effective against both enveloped and non-enveloped viruses, fungi, bacterial spores, and are bacteriocidal whereas the quaternary ammoniums are bacteriostatic.

So what is the best protocol for cleaning cages? Most large and academic institutions use a two-step process. The first step is thorough cleaning with a detergent to remove gross contamination. Dish soap, Tide with Bleach, or other laundry detergents are first used with plenty of hot water and a scrub brush to remove any remaining organic matter. Once rinsed and dried, disinfectant is sprayed to coat the area and allowed to air dry or remain in place for the recommended contact time, and then rinsed. This cleaning protocol is used between every patient.

For an excellent review on disinfectants, I highly recommend the following article: Portner JA, Johnson JA. Guidelines for reducing pathogens in veterinary hospitals: Disinfectant selection, cleaning protocols and hand hygiene. Compend Contin Educ Vet. 2010 May;32(5):E1-11

Environmental Surveillance
When environmental contamination is suspected, it is important to identify the source of the bacteria. For example, one of the hospitals where I worked experienced a number of wounds all contaminated with a similar resistance pattern *Serratia marcescens*. This bacteria was resistant to most of the commonly used antibiotics (cephalosporins, penicillins, fluoroquinolones). Eventually, this *Serratia* was cultured from the inside of the drawer where the laceration repair packs were kept and from our saline scrub pots. With new cleaning measures instituted, the outbreak was easily contained.

This example highlights the importance of several things. One, it is important to designate one member of your staff to monitor for emerging bacterial infections within your hospital. Because each of these cases belonged to a different doctor, it would have been easy to miss the entire outbreak. This is as simple as having a copy of all cultures go to one person, who can review them and look for patterns. Two, little cleaned areas are going to be the most likely to harbor bacteria. This includes computer keyboards and mice, phones, drawer and door handles, faucet handles, and cage latches. Your laboratory counter is much more likely to be contaminated than the exam tables and cages. One study in human medicine found the highest levels of pathogens on men’s neckties and on the sleeves of lab coats. Three, develop a surveillance program for your hospital. Most of the larger reference laboratories offer environmental...
cultures to help you to determine which pathogenic bacteria are present in your hospital. Some hospitals perform this task monthly, others every 3-4 months depending on budget.

**Some Best Practices for Your Hospital**

1) **Wash your hands often!** In human medicine, the CDC Guidelines on nosocomial infection prevention mandate routine handwashing between every patient. Make it easy for personnel to perform appropriate hand hygiene by having multiple handwashing stations or alcohol-based hand cleaner readily available.

2) **Wear gloves!** Exam gloves should be worn whenever connecting or disconnecting indwelling devices (such as IV and urinary catheters), cleaning or handling wounds, placing IV catheters, or when examining infectious or immunocompromised patients. Remember that your hands are likely the most contaminated surfaces in the hospital – so it is important to protect your patients from your hands!

3) **Clean scrub pots regularly.** Horror stories abound of pathogens living in scrub pots and cold sterile instrument trays. Scrub pots should be disinfected (or ideally, sterilized) every 24 hours. Metal scrub pots are attractive because they can easily be placed in the autoclave. Never reach in and out of the scrub pots while cleaning a wound as this can introduce bacteria. Instead, remove the amount of scrub you think you will need and then close the container. Scrubs should be made in small batches rather than filling a large container at once.

4) **Discard used IV fluid bags regularly.** In human medicine, the “one bag one patient” rule is strictly followed. Until recently, there was no evidence in veterinary medicine for or against using a fluid bag for multiple days or for multiple patients. In a study we presented at IVECCS last year, it was found that bags of LRS that were punctured three times daily had bag contamination rates of 1.7% within 4 days, and 6.7% within 7 days. From this study, we concluded that multi-use bags should be discarded after 48 hours, maximum.

5) **Do not alternate chlorhexidine scrub and alcohol wipes.** Chlorhexidine effectiveness increases with increased contact time (10 minutes is recommended), and alcohol inactivates chlorhexidine. To scrub more effectively, scrub first with chlorhexidine, allow for appropriate contact time, and then clean the surface with alcohol.

6) **IV catheters do not have to be routinely changed every 3 days.** Multiple studies in human medicine have shown that this practice is unnecessary. However, catheter insertion sites should be checked daily for any evidence of redness, swelling, discharge, or phlebitis. If the catheter insertion site appears questionable or if there is pain on flushing the catheter, then it should be replaced. The use of a “color of the day” system can help you to determine at a glance which patient’s catheters need to be checked.