Respiratory acid-base disorders

Respiratory acidosis: Respiratory acidosis results from an increased CO₂ in the blood (hypercapnea). Hypercapnea can be caused by anything that prevents normal gas exchange in the lungs, including impaired pulmonary circulation, reduced respiratory rate, circulation of blood to nonventilated portions of the lung, or an impairment to gas diffusion. Diffusion impairment is the least likely cause of hypercapnea, since CO₂ is approximately 20 times more diffusible than oxygen. Disorders in which respiratory acidosis occur include circulatory failure from cardiopulmonary arrest, central nervous system disease, respiratory muscle failure, physical impairment to ventilation (pleural space disease, pain, thoracic wall disease or external constriction), or primary pulmonary disease (alveolar flooding, interstitial disease, pulmonary thromboembolism). Iatrogenic respiratory acidosis results from inadequate ventilatory monitoring and assistance under general anesthesia. Clinical signs of hypercapnea are consistent with the underlying disorder. Situations that might cause respiratory acidosis must be anticipated and diagnosed with appropriate monitoring.

Treatment for respiratory acidosis involves correcting the underlying disorder by increasing alveolar ventilation. Chronic respiratory acidosis should be corrected slowly. Sodium bicarbonate should not be administered since this drug will exacerbate hypercapnea. Increasing inspired oxygen concentration may be lifesaving; however with severe hypercapnea, stimulation for respiration becomes driven by hypoxia. Resolving hypoxia may result in decreased voluntary respiration. The hypoxic drive for respiration remains adequate below a PaO₂ of 60 mmHg.

Respiratory alkalosis: Respiratory alkalosis results from an increase in ventilatory rate, resulting in elimination of more CO₂ than is produced by normal metabolic function. Hypocapnea develops, and alkalemia is generated. Causes of respiratory alkalosis include hypoxemia caused by pulmonary or circulatory abnormalities, primary pulmonary diseases that stimulate ventilation independent of hypercarbia, central nervous system disorders, and iatrogenic tachypnea with assisted ventilation. Most disorders of respiratory alkalosis result in hyperventilation. Chronic respiratory alkalosis is usually well compensated.

Treatment for respiratory alkalosis should be directed at normalizing the underlying disorder. Clinical signs are minimal, and no other therapy should be needed if the first treatment goal can be achieved.

Metabolic acid-base disorders

Metabolic acidosis: Metabolic acidosis results from gain of H⁺ from addition of an acid into the body, increase of production of an endogenous acid, or failure of elimination of an acid load at the renal tubular cells. Metabolic acidosis can also be caused by a loss of HCO₃⁻ buffering ability. When acid accumulates in circulation, H⁺ combines with HCO₃⁻ to buffer the acid load. When the acid dissociates, the anion remains in solution. Since electroneutrality must be maintained, another anion in circulation must decrease correspondingly. Anion gap (AG) is a formula created to classify disorders causing metabolic acidosis. Anion gap is calculated from four common cations and anions from a serum chemistry profile, and states: AG = [Na⁺ + K⁺] – [Cl⁻ + HCO₃⁻]. In normal animals, AG is 16 +/- 4. Elevated anion gap metabolic acidosis is caused by a gain of acid, while normal anion gap metabolic acidosis (hyperchloremic metabolic acidosis) is caused by loss of bicarbonate buffers and corresponding increase of chloride to maintain electroneutrality. Causes of anion gap metabolic acidosis include ethylene glycol intoxication, uremia, tissue hypoxia, diabetic ketoacidosis, salicylate intoxication, and other unusual intoxications (drugs, alcohol). Hyperchloremic metabolic acidosis is less common, and is caused by renal tubular acidosis...
(failure of the renal bicarbonate buffer system), severe diarrhea and loss of intestinal bicarbonate, or iatrogenically following administration of an alkali-free chloride containing solution for intravenous volume replacement. As an alternate method to evaluate the source of acidosis, SID can be utilized. (Table 1) By this method, alterations in the normal proportion of sodium to chloride ions are interpreted. If the proportion of sodium to chloride is less than 30 mEq (typically from chloride elevation), the animal is said to have a hyperchloremic metabolic acidosis, while a difference of greater than 40 reflects an organic acidosis. This approach takes into account excessive losses or gains of chloride relative to sodium as indications of acidosis, and may permit more complete evaluation of the underlying causes of acid-base abnormalities for the clinician.

Clinical signs associated with metabolic acidosis include lethargy, decreased cardiac output, decreased blood pressure, and decreased hepatic and renal blood flow. These signs may be referable to the acidemia, or to the underlying cause of the acid-base disorder. Compensatory mechanisms would cause an increase in respiratory rate to eliminate CO₂ generated by carbonic acid formation.

Treatment should be aimed at correcting the underlying disorder by improving tissue perfusion with intravenous fluid therapy, eliminating ingested toxin, and correcting metabolic, renal, or gastrointestinal disease. With severe metabolic acidosis (pH, 7.1, HCO₃⁻ < 12mEq/l), sodium bicarbonate may be administered judiciously by the following formula: Bicarbonate dose = (0.3) (Body weight in kg) (Base excess). Half of this dose should be administered slowly intravenously over six hours, and the acid base status reevaluated prior to continuing therapy. Chronic metabolic acidosis should be corrected slowly to avoid undesired side effects including hyperosmolality, hypernatremia, hypokalemia, hypocalcemic tetany from shift of calcium from the ionized to the protein-bound form, and iatrogenic metabolic alkalosis.

Metabolic alkalosis: Metabolic alkalosis is generated by loss of chloride in excess of extracellular fluid volume, either due to upper GI fluid loss or sequestration, or by administration of a thiazide diuretic causing chloride wasting. Rarely, metabolic alkalosis may be caused by overzealous administration of sodium bicarbonate or another organic anion, or by hyperaldosteronism causing sodium retention in excess of chloride. The most commonly associated clinical disease in small animal practice is gastric obstruction, with loss of chloride-containing gastric fluid. Renal compensation prevents an acid base disorder until hypovolemia causes aldosterone release. Aldosterone increases renal uptake of sodium. During normal renal function, sodium is reabsorbed with bicarbonate or chloride, or exchanged for potassium. Since gastric fluid has high chloride and potassium concentrations, when these are depleted, sodium can only be reabsorbed with bicarbonate.

Clinical signs associated with metabolic alkalosis depend upon the predisposing disorder. Muscle twitching and seizures have been reported. Signs associated with concurrent potassium depletion may include weakness, cardiac arrhythmias, renal dysfunction, and gastrointestinal motility disturbances.

Treatment for metabolic alkalosis is directed at resolving the predisposing disorder. Intravenous fluids (0.9% NaCl) should be initiated to restore intravenous volume. Fluids should not contain buffer. If vomiting is the underlying cause, use of drug therapy to minimize gastric HCl excretion may be warranted. Intravenous potassium therapy should be utilized to treat the hypokalemia frequently encountered with metabolic alkalosis.

<table>
<thead>
<tr>
<th>Difference between sodium and chloride</th>
<th>Normal anion gap</th>
<th>High anion gap</th>
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</thead>
<tbody>
<tr>
<td>Na - Cl &lt; 30</td>
<td>Hyperchloremic metabolic acidosis</td>
<td>Hyperchloremic and increased anion gap metabolic acidosis</td>
</tr>
<tr>
<td>Na - Cl &gt; 30 but &lt; 40 (Normal)</td>
<td>Normal</td>
<td>Increased anion gap acidosis</td>
</tr>
<tr>
<td>Na - Cl &gt; 40</td>
<td>Metabolic alkalosis</td>
<td>Metabolic alkalosis and increased anion gap acidosis</td>
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Acute respiratory emergencies

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Acute respiratory distress occurs from two broad categories of disease: failure to ventilate (pump failure) or failure to oxygenate (lung failure). Ventilatory failure is caused by abnormalities in neuromuscular control of respiration, airway obstruction, or impairment of appropriate functioning of the thoracic pump. Causes of neuromuscular failure include brain and central nervous system disease (trauma, encephalopathy, encephalitis), cervical spinal cord injury, and lower motor neuron diseases causing paralysis of muscles of respiration. Upper airway obstruction can occur from an acute change such as a laryngeal foreign body, or from chronic progressive disease such as brachycephalic airway syndrome, laryngeal paralysis, neoplasia, or tracheal collapse. Loss of chest wall integrity from trauma or presence of fluid or air in the pleural space also cause an inability to ventilate. Severe thoracic pain, excessive sedation, or thoracic bandaging can cause ventilatory compromise.

Hypoxemic lung failure and failure to oxygenate constitutes the second broad category of respiratory failure. Causes of lower airway disease include trauma and pulmonary contusions, pneumonia or pneumonitis, pulmonary hemorrhage, pulmonary thromboembolism, smoke inhalation, interstitial lung disease, and cardiogenic or non-cardiogenic pulmonary edema. The four basic causes of hypoxemia include hypoventilation, diffusion impairment from decreased alveolar area and increased thickness (uncommon in veterinary medicine compared to human medicine), shunting in which venous blood bypasses areas of gas exchange in the lungs, and ventilation-perfusion mismatch in which areas with no blood circulation are being ventilated.

Diagnosing respiratory compromise: Physical examination should begin with a brief period of hands-off observation since an animal in respiratory compromise can develop an acute deterioration with routine handling. Respiratory rate and visual inspection of the character of respiration should be identified prior to handling. Tachypnea is defined as an increased respiratory rate, while panting is a normal thermoregulatory mechanism in dogs. While tachypnea can signal respiratory compromise, it can also be a response to fear, pain, hyperthermia, central nervous system disease, metabolic acidosis, hypercapnea, or inhaled irritants. In addition to tachypnea, other clinical signs of respiratory compromise include orthopnea (head and neck extended to breathe), cyanosis (blue mucous membranes), stertor (sounds from the nose), and stridor (sounds from the upper airway). Mucous membranes only show cyanosis with severe hypoxemia (PaO₂ < 50 mmHg), and many of the other signs listed can be identified prior to the development of cyanosis to allow for a more rapid response.

Visual inspection of the movement of the chest wall can identify neuromuscular failure of the muscles of respiration. The dog should breathe with an inspiratory:expiratory ratio of 1:1, spending about the same amount of time inhaling and exhaling. In a non-excited animal, the third phase of the inspiratory cycle is a pause or rest period which follows exhalation. A prolongation of the inspiratory phase is consistent with an upper airway obstruction, while a prolongation of the expiratory phase is consistent with a lower airway obstruction or “air-trapping” (most commonly seen in cats presenting for asthma with reflex bronchospasm).

Animals experiencing respiratory distress can become fractious and can injure the veterinary team. The reflex response to the person providing restraint is to increase the level of restraint which creates a vicious cycle of worsening distress leading to respiratory failure. Placing the animal in a quiet, oxygen-rich environment prior to exam can help to alleviate distress. In addition, some oxygen enclosures have ports through which tracheal
and thoracic auscultation can be performed with minimal restraint. During initial physical examination, evaluation of the respiratory system should take priority over other body systems. Cardiac auscultation and simultaneous palpation of the femoral pulses will reveal any obvious murmurs or arrhythmias to increase the suspicion of heart failure. Following cardiovascular evaluation, pulmonary evaluation is completed to identify any abnormal sounds throughout the entire respiratory cycle. In canine chronic lower airway disease, fine crackles are typically ausculted best on deep inspiration. Pleural space fluid or air causes lung sounds to be muffled. If upper airway noise is confounding the ability to localize lung sounds, the trachea and upper airway should also be ausculted. Upper airway sounds will be more intense when ausculting the trachea, while lower airway sounds will become quieter. Other helpful physical examination tools are identification of jugular pulses, observation of the abdominal effort involved in breathing, and assessing air movement through each of the nares. A complete physical examination of all body systems should be performed at the earliest opportunity that is safe for the patient.

Other diagnostics to evaluate the respiratory system include assessment of blood gases or hemoglobin saturation, thoracic radiography or ultrasound, and diagnostic thoracocentesis. Thoracic radiography should not be attempted in an animal with severe respiratory compromise until the patient has been stabilized. Hemoglobin saturation with oxygen can be determined with a pulse oximeter. This device provides a value for SpO₂, which is related to PaO₂ or the dissolved oxygen content in blood. Based on the oxyhemoglobin dissociation curve, an SpO₂ of 90% equates to a PaO₂ of 60 mmHg, and values below 90% represent the rapid decline phase of oxygenation. Any SpO₂ value of less than 95% should generate concern for deterioration of respiratory status.

**Treating respiratory emergencies:** In animals in which respiratory failure is imminent, rapid anesthetic induction of anesthesia and placement of an endotracheal tube for manual ventilation can be life-saving. It is much easier to capture the airway and prevent cardiopulmonary arrest than it is to return an animal to life after cardiopulmonary arrest. An intravenous catheter should be placed at initial presentation, and all supplies for intubation and ventilation should be close at hand. Intravenous propofol works well as a rapid anesthetic induction agent. The larynx can be briefly evaluated for foreign objects, tumors, or laryngeal paralysis.

When the respiratory distress patient is not at immediate risk of death, oxygen therapy to achieve an oxygen environment with an FiO₂ of >40% is indicated. Oxygen can be delivered in an oxygen cage, or with nasal cannulas, oxygen tents, oxygen baggies, or masks. Flow-by oxygen is easy and non-invasive, but typically is expected to provide a 30% environment due to mixing with room air. Human nasal prongs work well in minimally responsive patients, and allow for hands-off delivery of oxygen.

Animals with mild to moderate upper airway obstruction often respond to anxiety reduction with acepromazine at 0.005 mg/kg IV, IM, or SQ as a starting dose. If thoracic wall pain is causing ventilatory compromise, analgesics can help. Likewise, removing thoracic bandages from postoperative recovery patients can be helpful. For animals with hypventilation secondary to excessive sedation or anesthesia, drugs should be discontinued, and reversal agents administered. Significant pneumothorax or hydrothorax should be resolved with therapeutic thoracocentesis. Persistent or recurrent air or fluid may require thoracostomy tube placement, with intermittent or persistent suction to manage the condition.

Animals that fail to respond to conservative management may require assisted ventilation for prolonged periods with a critical care ventilator. Critical care ventilators differ from anesthetic ventilators in that the fraction of inspired oxygen can be reduced below 100% to prevent oxygen toxicity for delivery of more than 8 hours in duration. Mechanical ventilation requires 24-hour care given by experienced personnel. Complications associated
with the underlying disease include failure to respond to therapy, no cure available, and co-morbidities associated with dysfunction or failure of other body systems as a result of the primary disease. Complications associated with mechanical ventilation include pneumothorax, pneumonia, acute airway obstruction from mucus plugs, prolonged general anesthesia, and the necessity for all bodily functions to be managed in the anesthetized patient.

Client communication is vital in cases of respiratory compromise. Animals can deteriorate and die rapidly even when everything is being done to manage the condition. Frequent communication can provide the client a realistic picture of the expected outcome for each patient. Given the life-threatening nature of respiratory compromise, clients may benefit from brief visits with their pet prior to decompensation. Likewise, anesthetizing an animal and capturing the airway for assisted ventilation can allow a client a brief period of time to choose advanced therapy or euthanasia in a controlled setting, while patient distress is alleviated.

Prognosis for any animal with acute respiratory distress for any reason is guarded to poor in the short term. If definitive therapy can resolve the distress or cure the disease, prognosis might improve for the long-term. Rapid, accurate localization of the problem is the most valuable tool to determine prognosis.
Recognizing and treating acute kidney injury

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Acute kidney injury (AKI) is the abrupt, sustained decline in glomerular filtration (GFR) resulting in azotemia. AKI occurs from ischemic events, nephrotoxicity, hypovolemia, drugs, or secondary to the systemic inflammatory response. Acute kidney injury develops through a series of steps that include initiation, extension, maintenance, and recovery. The initiation phase occurs with exposure to the toxicant, ischemic event, or other predisposing cause (Table 1). Extension occurs during the response to injury and the subsequent renal damage that exacerbates the response to the initial insult. The maintenance phase consists of established tubular lesions and nephron dysfunction, and recovery occurs with nephron repair and return to function if possible. In general, renal recovery occurs over 6-8 weeks following establishment of renal failure. Recognizing the possibility of renal injury and administering appropriate therapy during the initiation phase prevents the establishment of ARF or lessens the severity of injury.

Table 1: Common causes of canine and feline acute renal failure

<table>
<thead>
<tr>
<th>Common nephrotoxic agents</th>
<th>Common ischemic events</th>
<th>Other events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Shock</td>
<td>Leptospirosis</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Hypovolemic</td>
<td>Pyelonephritis</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Cardiogenic</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Distributive</td>
<td>Hypercalcaemia</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Obstructive</td>
<td>Ureteral obstruction</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Decreased cardiac output</td>
<td>Urethral obstruction</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Trauma</td>
<td>Systemic immune- mediated disease</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Radiographic contrast agents</td>
<td>Hyperthermia/hypothermia</td>
<td></td>
</tr>
<tr>
<td>Nontherapeutics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy metals</td>
<td>Extensive cutaneous burns</td>
<td></td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Renal vessel thrombosis</td>
<td></td>
</tr>
<tr>
<td>Pesticides</td>
<td>Hyperviscosity syndromes</td>
<td></td>
</tr>
<tr>
<td>Herbicides</td>
<td>Nonsteroidal anti-inflammatory agents inhibiting renal prostaglandins</td>
<td></td>
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<tr>
<td>Envenomination</td>
<td></td>
<td></td>
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<tr>
<td>Hemoglobin/Myoglobin</td>
<td></td>
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<tr>
<td>Raisins / Grapes</td>
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<tr>
<td>Easter lily</td>
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Diagnosis of acute kidney injury: Evaluating the serum biochemical profile and urine specific gravity prior to fluid administration is essential to diagnosing AKI. Urea nitrogen and creatinine provide an indication of renal function and urine specific gravity is used to determine pre-renal from renal azotemia. A complete chemistry profile can also reveal electrolyte and protein changes that occur as a result of kidney disease. Urine sediment should be examined for tubular casts. Granular casts are created by debris from acute tubular necrosis, but are fragile and deteriorate within 15-20 minutes of passage.
Treatment of AKI: Treatment strategies are aimed at correcting, hypovolemia, restoring hydration, establishing urine output, and managing uremia. Renal recovery following establishment of AKI will continue for several weeks; therefore, dehydration or hypovolemia should be prevented during and after hospitalization. Fluid therapy should be initiated with an isotonic sodium-based, electrolyte solution such as lactated Ringer’s solution. Fluid dose should be calculated to include maintenance fluid needs, dehydration, and contemporary losses from vomiting or diarrhea. Maintenance fluid requirement can be initiated at a dose of 50-60 ml/kg/day, and adjusted based upon response of the individual patient.

Volume of fluid needed for correction of dehydration is based upon the estimate of percent dehydration from clinical parameters by the following formula:

**Dehydration Dose = (％ estimated dehydration) (Body weight in kg) (1000 mL/kg)**

The dehydration dose should be administered over 12-24 hours, in addition to the maintenance fluid dose. Contemporary losses from vomiting or diarrhea should be estimated, and added to the calculated fluid requirement. Fluid should be administered via constant rate infusion pump if available, and overhydration avoided.

Assessment of urine output is essential in AKI. Polyuric AKI is easier to medically manage that oliguric or anuric AKI. Indwelling urinary collection systems provide the most accurate measure of urine output. If oliguria or anuria is confirmed, continuation of fluid therapy at a standard maintenance rate will result in overhydration, causing peripheral edema, pulmonary edema, or pleural effusion. Fluid therapy should be altered to an “ins and outs” method for the oliguric/anuric patient. This type of fluid dosing specifically determines the amount of fluid based on the volume of urine plus an additional quantity to account for “insensible losses” such as metabolic water needs and respiratory losses. Before initiating “ins and outs” therapy, the patient should be euvoletic and hydrated. Insensible losses are 20 mL/kg/day. Urinary output is measured over a set period of time (typically 4-6 hours), and the intravenous fluid dose calculated to exactly replace urine output plus insensible losses.

Oliguria or anuria causes hyperkalemia, which leads to life-threatening cardiac arrhythmias and cardiac arrest. Restoring urine output or initiating renal replacement therapy resolves hyperkalemia. Temporary management of hyperkalemia can be performed by administration of intravenous bolus of 25% dextrose at 0.7 to 1 gram/kg,. Calcium gluconate may be given by slow intravenous injection to protect myocardial function. Approximate volume of a 10% calcium gluconate is 0.3-0.4 mL/kg intravenously. This treatment does not lower serum potassium, but makes the myocardium less sensitive to the effects of hyperkalemia until other therapy is initiated.

If oliguria or anuria persists despite restoration of vascular volume and resolution of dehydration, drug therapy may be initiated to promote urine output. Traditional choices for this therapy include mannitol or furosemide. Prior to initiating these therapies, confirmation of appropriate hydration is indicated. Inappropriate administration of diuretic agents while a renal failure patient is dehydrated will exacerbate renal injury. Mannitol produces an osmotic diuresis to cause more urine to remain in the tubules. Typically, one bolus dose is administered at 250-500 mg/kg intravenously. Repeated administration of mannitol can cause hypervolemia and subsequent pulmonary edema.

Furosemide inhibits the Na-K-2Cl transport pump in the ascending limb of the loop of Henle. Recommended dose for initiation of therapy is 2 mg/kg as an IV bolus, and can be increased incrementally every 2-4 hours. Alternatively, furosemide may be administered via constant rate infusion at 0.25-1.0 mg/kg/hr. Constant rate infusion therapy may be more effective by causing vasodilation in addition to diuresis. If drug therapy is successful in increasing urine output, fluid rates must be adjusted accordingly to avoid dehydration and repeated renal
injury. If the patient remains oliguric despite diuretic therapy, life-threatening hyperkalemia and third-spacing of fluid into the pulmonary space will occur. The only options for ongoing therapy include renal replacement therapy with dialysis. Dialysis reduces uremic waste products by promoting passage of uremic waste across a semipermeable membrane (an artificial dialyzer for hemodialysis, or the peritoneal surface for peritoneal dialysis). Peritoneal dialysis is technically difficult and labor-intensive, however is more widely available than hemodialysis. Hemodialysis is available at some veterinary academic institutions and specialty referral centers in the United States. Dialysis does not cure kidney failure but can “buy time” to avoid life-threatening consequences of azotemia while waiting for renal recovery to occur.

Serum biochemical values should be monitored at 24-48 hours to evaluate azotemia and electrolyte abnormalities. When azotemia has resolved or is no longer changing, fluid therapy should be gradually reduced. The patient should be eating and drinking freely during fluid taper so that water consumption will increase to meet physiologic needs. Renal recovery usually takes 4-8 weeks following establishment of renal failure. However if the patient compensates for polyuria by increased drinking, the patient may be able to maintain and recover at home. Repeat episodes of dehydration should be strictly avoided during this time.

Uremia causes injury to various organ systems such as the gastrointestinal tract, pulmonary system, hematologic system, cardiovascular system, and central nervous system. Managing azotemia is the best way to limit damage of other organ systems. While azotemia is severe, a variety of ancillary therapies can be used to limit nausea and protect the GI tract. Nutritional support is important. If there is no appetite, a feeding tube may be placed. If phosphorous remains elevated following rehydration and the patient is eating, oral phosphate binders (aluminum hydroxide, calcium carbonate) may be administered to bind intestinal phosphorous.

Prognosis of AKI: Overall mortality from AKI is approximately 60%, despite best efforts to treat. Of animals that survive, approximately 20% progress to chronic, stable kidney disease, and 20% become non-azotemic. Certain causes of AKI such as ethylene glycol toxicity carry a grave prognosis if renal failure has become established.
Transfusion products and managing hemorrhage

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When planning a transfusion medicine program, available products should include whole blood or packed red blood cells to provide oxygen-carrying capacity, and plasma products to provide coagulation factors. In small practices, needs might be met by having one or two large dogs and cats “on call” as blood donors; however, component therapy allows larger practices to provide targeted treatment for specific medical problems. Component therapy provides exactly what is needed at the time it is needed. For example, if a dog is actively bleeding from vitamin K inhibition following rodenticide intoxication, providing fresh frozen plasma will supply vital coagulation factors for immediate use. If the same dog was also anemic from the bleeding episode, administering packed red blood cells after the clotting factors were delivered would increase the usefulness of the red cells since bleeding would decrease following the plasma therapy. Component therapy also maximizes the usefulness of one donor to conserve this limited resource.

Animals enrolled as blood donors should be large enough to donate a standard amount of blood. A standard collection volume for a cat is 55 mL (+ 5 mL of anticoagulant to equal 60 mL), so donor cats should be >4.5 kg. Dog collection volume is 400 mL, which when mixed with anticoagulant is the volume to fill a standardized collection system used in human medicine, therefore, dogs should be >25 kg. Donor animals should be friendly, accepting of regular phlebotomy and restraint, and free from transmissible disease. Greyhounds are commonly used as canine donors since that breed has a higher red blood cell production and produces a larger quantity of packed red blood cells; however, plasma volumes will be smaller. Donors should have known blood type. Donor dogs that are considered “universal donors” are DEA 1.1, 1.2, and 7 negative. Cats more commonly have blood type A in the United States, so most donors in a program should be type A. Type B cats should be identified and screened for availability to address transfusion need for B-type cats.

Blood should be collected atraumatically from the jugular vein through a large-bore needle. Dogs can be trained to allow venipuncture and collection without sedation while most cats require sedation. Once the collection is complete, the fresh whole blood can be used as a whole blood transfusion, or can be separated into components. Centrifugation causes the red blood cells and plasma to separate. The oxygen-carrying component is called packed red blood cells with a volume of ~200-250 mL. Depending on the type of anticoagulant used, this product can be refrigerated and used within 4-5 weeks. To extend transfusion utility, the 250 mL unit can be subdivided into two ~125 mL units. A dose of PRBC of 10 mL/kg should increase patient PCV by 10%, so a 125 mL unit would provide appropriate therapy for a 10-15 kg dog.

Plasma that is separated and frozen within 6 hours of collection is referred to as “fresh-frozen plasma”. All coagulation factors are active in fresh frozen plasma for a year after collection if frozen in a household freezer and not allowed to thaw. If fresh frozen plasma is >1 year old, or if plasma was not frozen within 6 hours of collection, factor 8 and von Willebrand’s factor become inactive; however, the factors affected by vitamin K inhibition (factors 2, 7, 9, and 10) remain active for up to 5 years. Therefore, these products still have clinical utility for treating most common causes of acquired coagulopathy in dogs.
TRANSFUSION THERAPY: OXYGEN-CARRYING CAPACITY: Moderate to severe anemia or rapid, large-volume blood loss are the primary indications for red blood cell transfusion therapy. The main products containing red blood cells are whole blood or packed red blood cells. By convention, in veterinary medicine, transfusion is generally withheld until the animal is showing clinical signs of anemia, and the therapeutic target for transfusion is to resolve clinical signs referable to anemia (tachypnea, tachycardia, weakness).

Transfusion can be helpful in all causes of anemia – loss, destruction, and lack of production; however, transfusion is merely a bridge to improve clinical outcomes while a definitive diagnosis for anemia is established. When administering packed red blood cells (PCV = 80%), a dose of 10 mL/kg should increase patient PCV by 10%. Whole blood transfusion dose is 20 mL/kg to increase patient PCV by 10%. Reasons to consider fresh whole blood transfusion include lack of availability of component therapy, need for both oxygen carrying capacity as well as coagulation factor therapy, and acute, fulminant blood loss. In an emergency setting where hemorrhage is active, acute, rapid blood loss can be severe before the PCV decreases since all blood components are being lost equally. Total protein declines before PCV decreases.

There are distinct blood types in dogs, but dogs do not have naturally occurring alloantibodies. Any dog that has never received a transfusion can receive blood from any other dog. Dogs produce antibodies to proteins in transfused blood, and should be cross-matched if in need of a second or subsequent transfusions to insure compatibility. Cats have three distinct blood types: A, B, and AB, and have naturally occurring antibodies. If a B-type cat receives type A blood, a fatal reaction occurs in 30% of cases. If an A-type cat receives type B blood, the reaction is not typically fatal; however, the blood will undergo hemolysis and not provide effective oxygen-carrying capacity. There are breed associations with blood types, and test kits are readily available to identify feline blood type. If test kits are not available, crossmatch can be performed to identify type incompatibility. Type AB cats are rare. These cats can receive either type A or B packed red blood cells; however, should not receive plasma from either type A or B cats since the plasma will contain antibodies that can cause allergic reaction. Cross-match is not technically difficult but does involve several steps. A commercial cross-match kit test is available to facilitate the procedure in a practice setting.

Blood should be warmed to body temperature prior to administration, and an appropriate blood delivery set and filter should be used. Blood can be delivered via gravity flow through a drip-set or delivered by infusion pump, but not all infusion pumps will deliver blood without injuring the red blood cells. Blood pumps used for human medicine must undergo specific testing to be approved for this procedure. For cats, use of a syringe pump and in-line filter is common; however, recent studies have shown that the inline filter creates some damage to the red blood cells. There is currently not a better alternative.

Acute transfusion reactions are rare in veterinary medicine. Blood should be administered slowly for the first 15 minutes while monitoring patient temperature, respiratory rate, and other vital signs to identify acute transfusion reaction. The transfusion should be discontinued if reaction occurs. Delayed reactions cause the red blood cells to break down within 2-4 days following administration. These have not been reported in veterinary medicine, but are difficult to identify since an abrupt change is not seen and the main effect is that the patient PCV does not increase which might be attributed to the patient disease.

TRANSFUSION THERAPY: COAGULATION FACTORS AND PLATELETS: Hemorrhage from coagulopathy is treated by administration of either coagulation factors or platelets. All coagulation factors are contained in fresh-frozen plasma, and appropriate transfusion therapy can be life saving. Secondary coagulopathy - absence of one or
more clotting factors - can be either inherited or acquired. Inherited coagulopathy that causes clinical bleeding is rare, and includes hemophilia A (absence of factor 8) or B (absence of factor 9). These disorders typically present in pediatric or juvenile patients at first diagnosis, and cannot be cured. Acquired coagulopathy is more common, with vitamin K inhibition coagulopathy from rodenticide toxicity (inhibits factors 2, 7, 9, or 10) being the most common. Conditions that cause absorption failure of vitamin K, such as feline hepatic lipidosis, can also cause coagulopathy. Acquired coagulopathy can also occur in the late stages of disseminated intravascular coagulopathy. As with red blood cell transfusions, plasma transfusion for coagulopathy is performed concurrently with identifying and resolving the underlying disease process.

Plasma should be kept frozen until ready for use. The plastic transfusion bags are fragile when removed from the freezer, and should be left to sit at room temperature for 20-30 minutes before being handled or actively thawed. Active thawing can be performed with a warm water bath by placing the transfusion bag inside a watertight plastic bag to avoid contamination of the unit. Once completely thawed, the product should be delivered over a 4-hour period. Therapeutic dose of plasma is ~20 mL/kg. Plasma has been advocated for treatment of acute pancreatitis in the past under the theory that plasma alpha-2 macroglobulins in plasma can limit activity of activated pancreatic enzymes, but this practice has largely fallen out of favor.
Food is love: inappetance in the critical patient

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Malnutrition is detrimental to health and healing; however, dogs and cats with critical illness requiring hospitalization are frequently inappetant. Inadequate nutritional intake in critically ill patients can lead to “stressed starvation”. “Simple starvation” from lack of food intake is characterized by multiple adaptations resulting in a decreased metabolic rate and energy conservation to maintain body mass. These adaptations include increased production of inactive triiodothyronine (T3) compared to active thyroid hormones, and utilization of glucose and fat as the primary sources of energy. “Stressed starvation” occurs during illness or injury. Counter-regulatory hormones such as glucagon, epinephrine and inflammatory cytokines are released during serious illness, altering physiologic response to starvation. Energy expenditure does not decline appropriately, and tissue catabolism results.

Determining energy intake: Energy requirement is determined by estimating the resting energy requirement (RER, the energy requirement at rest in a thermoneutral environment and in a post-absorptive state), and then adjusting that figure to meet unique patient needs based upon the type of illness or injury present. The RER is calculated by the exponential formula: 70 x the body weight in kg (BWkg)\(^{0.75}\). A linear formula \([30 \times BWkg + 70]\) can be used for animals between 2 and 30 kg. Feeding can be initiated at the RER in most veterinary patients, and adjusted to maintain body weight as needed. For moderate to severe illness, the RER can be multiplied by an illness factor of 1.2 to 1.5 in dogs, and 1.1 to 1.25 in cats.

Food intake in hospitalized patients: Dogs and cats often refuse to eat in the hospital, or have inadequate food intake even if they do eat. Animals that are completely anorexic due an underlying disease process are unlikely to eat enough to support tissue maintenance and recovery from illness. These patients will benefit from enteral feeding via feeding tube, or supplemental parenteral nutrition, while the clinical disease process is managed. Once the animal transitions from anorexia to hyporexia (reduced appetite), various modifications in feeding techniques may enhance voluntary food intake.

Environmental and behavioral aspects of appetite: An often-overlooked aspect of food intake in hospitalized animals includes eating habits with regards to physical environment, time of day, food placement, and comfort level. When food is offered in a small kennel environment with constant bright lighting conditions and unfamiliar noises, the stress level created might overwhelm any desire to eat. In addition to taking a diet history, the owner of the hospitalized pet can be questioned with regards to the time of day the animal typically consumes most of its food, and feeding location within the home in case feeding outside of the kennel is attempted. Some animals prefer to eat in the morning or evening, and some will graze throughout the day. Locations found in many veterinary practices to simulate at-home feeding areas include the kitchen, laundry room, office, or outdoor area. Some animals prefer to eat in relative seclusion, and some cats are nocturnal eaters. Finally, food placed next to a litter pan or soiled kennel area will generally not be enticing.

Animals may be unwilling to eat from a person whose only interactions have been to administer painful or unpleasant treatments. Therefore, veterinarians or veterinary treatment technicians may not be the best persons to offer food. The kennel worker or animal care assistant might have more success at feeding. Additionally,
delivery of health care should also include some positive interactions between the pet and healthcare personnel such as petting or praising without any invasive treatments. In certain instances, owners can attempt to feed animals during patient visits especially if they are visiting in a secluded location; however if the owner is basing a euthanasia decision on whether or not food is consumed at that time, undue stress could be created for both the pet and the owner.

**Palatability:** Methods to increase palatability include increasing dietary moisture, freshness, temperature, protein, fat, or changing flavoring. Moisture is usually increased by changing from a dry to a canned or moist pouch food; however, canned/moist foods are often higher in fat or protein than the same type of dry food. If the nutritional content of the particular dry food diet needs to be maintained, the dry kibble can be soaked in water to increase moisture. Additionally, some cats will refuse kibble with water added if they have never eaten food other than dry kibble.

Increased fat diets are often more readily accepted. Addition of fat also increases the energy density of the food so that a caloric requirement can be met with a smaller food intake. High-fat diets can slow gastric emptying time and transit time, and can exacerbate pancreatitis in dogs. Increased protein diets may also have greater acceptance; however these diets are also typically higher in fat and moisture so the specific role of protein is unclear.

Dogs may show more willingness to eat with foods that are sweet or salty; however cats do not have “sweet” taste receptors and seem insensitive to the addition of salt on food. Increasing the carbohydrate content of food is generally safe; however the clinician should be careful to not exceed the addition of >10% of the total calorie intake with an unbalanced food source since the total diet will be unbalanced at that point.

Fresh foods may be more readily accepted. Freshness is likely tied to aroma, and increasing aroma of foods is more enticing. Therefore, a newly opened can of food might be accepted than one that was opened some time prior, or human fresh or canned foods might have a better aroma and be more palatable than the usual diet.

A “rare” food is one that the animal receives infrequently as a “treat”, and has a history of eagerly accepting at some point in the past. Offering rare foods to hyporexic animals will sometimes promote voluntary food intake. In contrast to rare foods, foods that are completely novel are unlikely to be accepted. Cats develop strong preferences for the shape and consistency of food that is typical for them to consume, and completely novel foods often result in refusal to eat. “Cafeteria” style feeding (exposing the animal to multiple types of foods while in the hospital) can sometimes increase food intake; but can also increase develop a learned food aversion.

**Other aspects of hyporexia in hospitalized animals:** Certain disease processes (e.g. uremia) or medications (e.g. analgesics, anti-inflammatories, anti-fungals, chemotherapeutics) can suppress appetite. Drug therapies should be reviewed periodically, and medications should be discontinued as they become unnecessary. Likewise, appetite will sometimes increase simply because an illness is responding to therapy or time.

**Appetite stimulants:** Drugs to stimulate appetite usually are ineffective unless an animal is on the verge of eating. Low-dose intravenous diazepam has been the traditional in-hospital appetite stimulant in cats (0.05-0.15 mg/kg IV intermittently, once daily to once every few days). Side effects include central nervous system (CNS) depression. Long-term use is not appropriate for home therapy since intravenous dosing cannot be performed
at home. Cyproheptadine is an antihistamine and serotonin receptor antagonist that has been used in cats for appetite stimulation (1-4 mg/total dose per cat PO q 12-24 hrs), but does not stimulate appetite in dogs. Main side effects include CNS depression and anticholinergic effects (dry mucous membranes). Occasionally, cats will become hyperexcitable with administration.

Mirtazapine is a piperacine used as an antidepressant in people that has recently been advocated for use as an appetite stimulant in both dogs and cats. Reported doses in dogs are 15-30 mg PO per dog q 24 hrs; however there is evidence that demonstrates a drug half-life of approximately 6 hours in normal research dogs. (Giori M and Yun H, 2012). Published doses include 1.875 or 3.75 mg PO per cat q 48 hours, but the higher dose causes more side effects (vocalizing, increased interaction). In cats with IRIS stage II, III, or IV chronic kidney disease, the dose is 1.875 mg PO per cat q 48 hours. Mirtazapine was originally sold as a 15 mg tablet for the smallest size, so the doses administered can be recognized as logical divisions of a 15 mg tablet.

**Enteral and parenteral feeding:** If animals are consuming less than their resting energy requirement for more than 3-5 days with no chance of rapid improvement, enteral or parenteral feeding should be administered. The main benefit of enteral feeding is that most devices can be used at home by owners to supplement calorie intake for animals eating less than desired, and most medications can be delivered through feeding tubes which greatly improves the quality of life of the owner and the pet. Resources are widely available that discuss all aspects of enteral and parenteral feeding.
Pain management in the ICU

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Pain is a sensory experience associated with tissue damage or injury. “pain” refers to the conscious realization of pain, while “nociception” refers to specific neurologic signals identified by afferent neurons that transmit information to the central nervous system, which then initiates a physiologic or pathophysiologic response. The differentiation of these two concepts is important when considering when and how to address pain management for critically ill patients. If pain management is only provided following interpretation that an animal is painful, analgesic drugs will be less effective and higher dosages will be required. Additionally, as the central nervous system is processing pain, central sensitization occurs which actually increases sensitivity for future painful events leading to chronic pain syndromes. Therefore, adopting a proactive policy toward pain management will provide better control of pain, and allow for more judicious use of drugs to avoid side effects.

The peripheral and central nervous systems process painful sensations and produce behavioral responses to react to or alleviate pain. Receptors vary by type of receptor and type of stimulus received, with some receptors being triggered by normal sensation, and others being triggered by more noxious events. Once the pain sensation is received, the sensation undergoes transduction into an electrical stimulus, and is transmitted to the spinal cord. The spinal cord modulates the impulse before projecting to the brain which perceives the pain. A combination of various brain centers process sensory information and produce responses including fear, anxiety, aggression, and autonomic, neuroendocrine, and motor responses. The central nervous system is also responsible for generating a memory of a painful event which can change the nervous system response to analgesic medication. The peak intensity of pain is the most important determinant of the memory of pain. Treatment becomes more difficult for patients with a memory of a significant painful event, and in patients in which pain has been experienced for more than 12-24 hours.

In addition to the nervous system response to direct injury, a variety of other factors influence pain and stress responses. In addition to stimulation of nociceptors, direct tissue injury also results in release of inflammatory mediators interleukin 1 and 6, and tumor necrosis factor α which exacerbate local inflammation and response of the autonomic nervous system. As a result of brain processing, pituitary stress hormones are released into systemic circulation. These result in peripheral increase of cortisol, aldosterone, catecholamines, and glucagon which increase response to pain and stress. The combination of neurologic change, release of inflammatory mediators, and release of stress hormones can lead to development of injury at sites which are distant to the original injury. This process is commonly known as the systemic inflammatory response syndrome, or SIRS. Neutrophil activation during this process results in free radical production and protease release, as well as damage to the gastrointestinal mucosal barrier allowing bacterial translocation into systemic circulation. These changes ultimately lead to multiple organ dysfunction syndrome (MODS) which manifests as heart, lung, liver, or kidney failure.

Recognizing pain

Dogs and cats manifest pain in a variety of ways. While several different behavioral manifestations of pain have been recognized, there is also overlap between some signs of pain and other manifestations such as normal behavioral response or anxiety response. Use of a pain scoring system to train all hospital personnel to identify levels of pain can be useful to recognize levels of pain and response to analgesia. (examples published

Treating and preventing pain

Analgesia is defined as a reduction in the intensity of pain perceived. Although it is impossible to distinguish the intensity and quality of pain animals feel compared to that felt by a person following a similar noxious stimulus, any stimulus that causes pain in people will cause pain in animals. The concept of balanced analgesia refers to a multimodal strategy to alleviate pain. Since various classes of analgesic drugs produce an effect at different areas of the pain pathway, utilizing combinations of analgesic therapy will target specific areas of the pain response for an additive or synergistic effect. The simplest example of balanced therapy is provision of local lidocaine anesthetic blocks prior to the onset of noxious stimulus to minimize or eliminate pain transduction, and also providing a systemic medication to control pain. The drugs that are currently available to treat pain fall into 6 broad categories: opioids, salicylates, para-aminophenol derivatives, nonopioid/nonsalycalate, local anesthetic agents, and α₂ agonists. Each group has indications for appropriate use, and favorable and unfavorable characteristics. Unlike other classes of drugs, analgesic medications have high interspecies variability of effect. This variability is determined by species differences in the number and type of pain receptors found in various neurologic centers.

Opioids are natural or synthetic compounds that act on opioid receptors to produce analgesia. There are three types of opioids receptors, namely OP3 (¿), OP2 (κ), and OP1 (δ). Opioid drugs differ in their clinical effects depending on the receptor(s) stimulated and the degree of stimulation. Through various central nervous system effects, opioids raise the pain threshold, reduce the perception of pain, and alter the emotional component of pain to make pain more tolerable. Although used primarily for their central effects, peripheral tissues have opiate receptors that have led to study of locally administered opioids drugs to limit pain transduction. Examples of local administration include intra-articular infusion post arthroscopy, and corneal application for corneal analgesia. Side-effects of opioid therapy include central nervous system depression, respiratory depression, hypothermia, and bradycardia in dogs, or panting, tachycardia, and hyperkinesis in cats. In addition, nausea and vomiting can occur following administration. Opioid administration can result in excitatory effects in any species, but this is unlikely if appropriate species dose recommendations are followed, administration occurs when an animal is in pain, or administration is concurrent with a sedative/ tranquilizer medication. In addition, repeated doses alter motility of the gastrointestinal tract and urinary bladder. Opioids generally have minimal cardiovascular side-effects which make them useful for critically ill animals if the patient can be closely monitored for respiratory depressant effects. Since opioids are administered parenterally and use is subject to governmental oversight, they are typically administered to hospitalized animals. Due to relative safety when used in sick animals that are monitored appropriately, opioids are the analgesic class of choice for controlling moderate to severe acute pain. Specific information on opioid types and doses for dogs and cats are given in Tables 3 and 4.

Nonopioid, non-steroidal anti-inflammatory analgesics (NSAIA) act primarily in the periphery to decrease production of substances which facilitate the generation and conduction of painful impulses. When administered prior to the insult, these drugs produce analgesia by suppressing inflammation and the production of kinins and prostaglandins. The most common toxic effects include gastric and intestinal ulceration, with secondary anemia and hypoproteinemia. Impaired platelet function can also occur. Acute renal failure can occur in hypovolemic animals; therefore use in critically ill animals should be avoided.
α₂-adrenergic agonists are sedative-hypnotic drugs used most frequently for sedation. They also have some analgesic activity which varies by species and drug administered. Analgesic activity results from stimulation of the α₂ adrenoreceptors in the brain, decreasing norepinephrine release. Xylazine is the most commonly used drug in this category; however pharmacokinetics have not been extensively studied. Newer drugs in this class include detomidine, medetomidine, and dexmedetomidine. In addition to sedation and analgesia, these drugs have profound cardiovascular and metabolic effects. Following administration, arterial blood pressure increases and then decreases, and cardiac output decreases. These side-effects limit usefulness of these drugs as analgesics in critically ill patients.

Tramadol is a synthetic, centrally acting analgesic that is not related to opioids analgesics. The primary effect of tramadol is at the μ-opioid receptors. It also inhibits reuptake of norepinephrine and serotonin in a similar manner to α₂-agonists. Tramadol is effective against moderate to severe pain, and effectiveness appears similar between cats and dogs. Tramadol is an oral medication that can be prescribed for at-home use and for long-term control of pain. Side effects include respiratory depression when administered concurrently with other anesthetics, and constipation in dogs with long-term use.