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CONTINUING EDUCATION

INTERNAL MEDICINE

Fluid Therapy in Critical Care

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Intravenous (IV) fluid administration is probably the most frequently used therapy in veterinary hospitals. Aggressive IV fluid resuscitation in emergent patients and continuous IV fluid administration in hospitalized patients have long been considered fundamental in the management of critically ill animals. However, research into whether the type and volume of fluids infused can contribute to comorbidities and decrease the chances of a favorable outcome continues. This article reviews new trends in fluid therapy in human and veterinary critical care medicine and provides some clinical guidelines for fluid administration based on these trends (**FIGURE 1**).

TRENDS IN CRITICAL CARE MEDICINE

Avoidance of Synthetic Colloid Solutions

Colloid fluids include natural colloids (e.g., plasma products, purified albumin solutions) and synthetic colloids (e.g., hydroxyethyl starch [HES], dextrans, gelatins). Colloid solutions contain large molecules (molecular weight <10,000) that do not readily filter across the vascular membrane, an effect that increases the colloid osmotic pressure (COP) of the intravascular space and leads to fluid retention within the vasculature. The most commonly used synthetic colloid products are composed of HES molecules suspended in an isotonic crystalloid solution.

The use of colloids has been very popular in critical care because these fluids persist longer in the vasculature and require less volume than crystalloids to achieve hemodynamic goals. Based on their effect on COP, it was also believed that synthetic colloids could draw edema fluid from the interstitium and extravascular spaces into the intravascular space in patients with edema secondary to hypoalbuminemia or vascular leakage due to endothelial dysfunction.

PRIMUM NON NOCERE
When used appropriately, IV fluids can improve outcomes in the most critically ill animals. However, inappropriate IV fluid therapy can have harmful effects.

Despite the promising perceived benefits of colloid use, revision of the Starling forces and the effect of the endothelial glycocalyx in vascular permeability has shown that the benefits of natural and synthetic colloids do not apply to critically ill human patients with perfusion abnormalities at the capillary level.[1] Several studies in people have shown that colloids are not superior to crystalloids for intravascular fluid replacement in critical illness.[2-4] In people with severe sepsis, the use of synthetic colloid solutions is associated with higher mortality rates and higher incidence of acute kidney injury (AKI),[5] increased need for renal replacement therapy,[3] and coagulopathies. Over the past decade, the body of literature against the use of synthetic crystalloids in critically ill people, particularly those with sepsis, has grown extensively. The 2016 Surviving Sepsis Campaign has published a strong recommendation against the use of HES solutions for intravascular volume replacement.[6] Despite the lack of studies evaluating the effects of colloids in critically ill animals, a recent international study evaluating the use of synthetic colloids in veterinary practices showed that 70% of the survey respondents have limited the use of these products because of safety concerns.[7]

Use of Chloride-Restrictive Fluid Therapy

Given the current controversy and body of literature in human medicine against the use of colloids in the critically ill, crystalloids have been selected as the main fluid type for intravascular volume replacement and initial resuscitation in people. The next question for the veterinarian is, what type of crystalloid fluids is most beneficial in critical illness? Normal (0.9%) saline, lactated Ringer's solution (LRS), Normosol-R (pfizer.com), and Plasma-Lyte A (baxter.com) are among the most common isotonic fluids used for fluid replacement. The chemical composition of these fluids is described elsewhere,[8] but the chloride concentration of isotonic crystalloid solutions has been a major emphasis of research in critical illness.

A rat model of sepsis that compared 0.9% saline with the more balanced crystalloid Plasma-Lyte A for fluid therapy identified worse kidney function in the saline group (83% versus 28%).[9] The concentration of chloride in 0.9% saline solution (154 mEq/L) is higher than that of plasma in healthy animals (average: 110 mEq/L [dogs], 120 mEq/L [cats]) and other balanced crystalloids (e.g., LRS, 109 mEq/L; Plasma-Lyte, 103 mEq/L; Normosol-R, 98 mEq/L). In human and animal studies, supraphysiologic concentrations of chloride delivered to the renal tubules induce renal afferent vasoconstriction with a subsequent decrease in renal blood flow and glomerular filtration rate (GFR).[10,11] Such concentrations also increase the risk of AKI in the critically ill.[12]

The mortality rates in people with sepsis and septic shock have been demonstrated to be lower when chloride-restrictive resuscitation is implemented.[13,14] A study that evaluated the use of balanced crystalloids compared with 0.9% saline solution in trauma patients showed that resuscitation with Plasma-Lyte A resulted

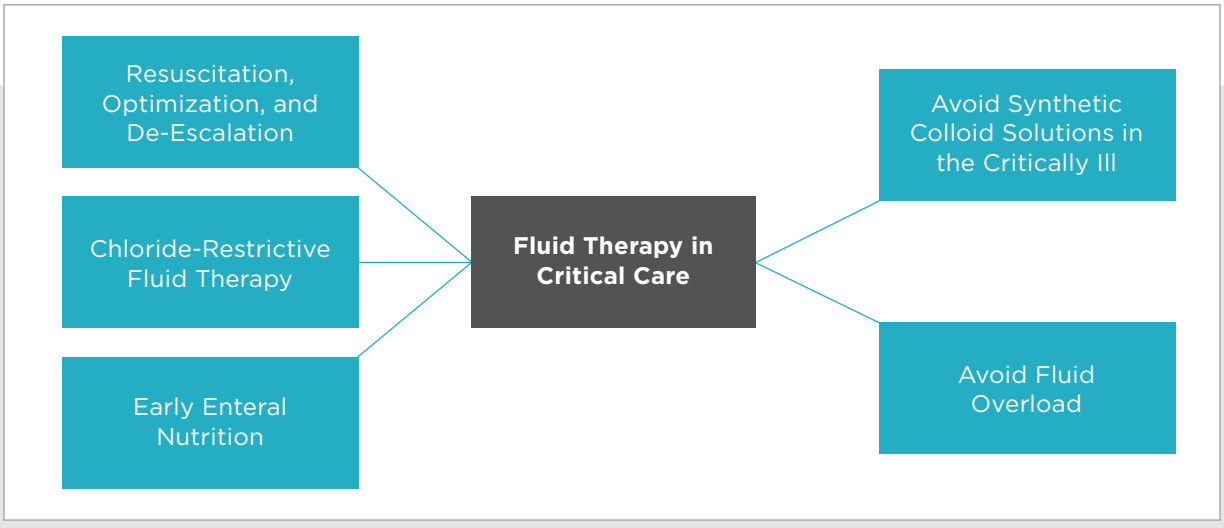

FIGURE 1. New trends of fluid therapy in veterinary emergency and critical care.

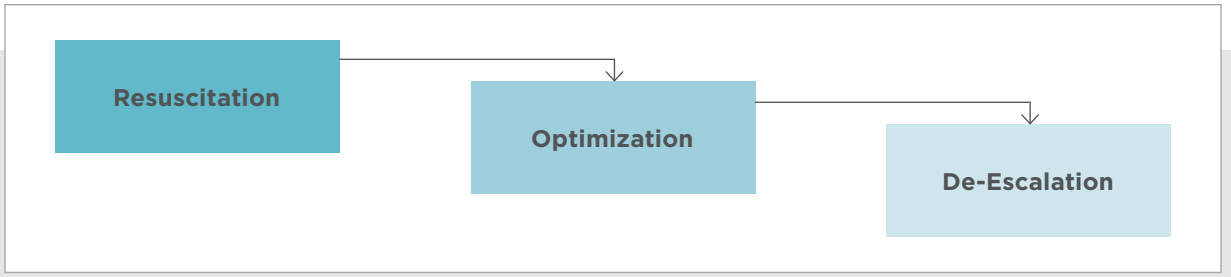

FIGURE 2. Stages of fluid resuscitation in critically ill animals.

in more rapid correction of systemic acidosis, persistent clearance of base deficit, and higher urine output than did saline.[15] The acidifying effects of 0.9% saline solution should therefore be considered when choosing the type of resuscitation fluid for the critically ill. Among replacement crystalloid fluids, 0.9% saline has no buffer capacity and the most acidifying effects.

Indications for the use of chloride-rich solutions such as 0.9% saline in veterinary medicine are to correct hypochloremic metabolic alkalosis in patients with upper gastrointestinal (GI) obstruction, to promote calciuresis in patients with hypercalcemia, and to correct mild hypernatremia when rapid correction may have neurologic consequences.

Use of Resuscitation, Optimization, and De-escalation

When used appropriately, IV fluids can improve outcomes in the most critically ill animals. However, overzealous or inappropriate IV fluid therapy can have harmful effects. Based on human medicine guidelines, fluid therapy in an emergent patient should be considered as a drug therapy with a dose-response relationship and side effects.[16]

Prompt resuscitation with IV fluid therapy to correct hypoperfusion of vital organs is indicated for animals that present with acute onset of illness and systemic signs of shock (hypovolemic, distributive, or septic) and that do not have cardiac disease. Optimization of macrovascular parameters such as heart rate, systemic blood pressure, capillary refill time, and mentation changes, or other clinical markers such as lactate, is used in techniques such as goal-directed therapy to guide administration of IV fluids in the management of life-threatening conditions. Tissue perfusion can then be optimized and maintained by using fluid titration, with conservative use of fluid boluses as needed during the first hours of hospitalization, and early use of vasopressors as indicated by the underlying etiology leading to cardiovascular collapse. This is followed by de-escalation of IV fluids after the initial hours of hospitalization and once the patient has been stabilized (**FIGURE 2**).[16]

Veterinarians should aim to maintain their patients at a zero fluid balance. Daily fluid balance can be measured by calculating the difference between all intakes (IV fluids, IV constant-rate infusions, enteral/parenteral nutrition) and all outputs (urine production, GI losses), not including insensible losses. In human patients with severe pulmonary disease, the use of a negative fluid balance or restrictive fluid therapy has been associated with decreased mortality and improvement of pulmonary function.[17,18]

Avoidance of Fluid Overload

Fluid overload is defined as a >10% increase in basal body weight during hospitalization. In several studies of critically ill people, a positive fluid balance has been associated with increased mortality, longer hospitalization periods, and requirement of renal replacement therapies.[19,20] Critically ill dogs have also

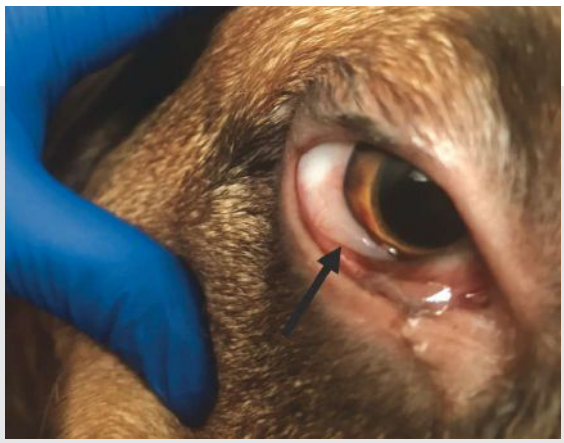

FIGURE 3. Chemosis in a dog with fluid overload.

been identified to have a greater risk of fluid overload with subsequent increased risk of mortality. In one study, dogs that developed fluid overload had a 50% mortality rate.[21]

One of the major pitfalls in veterinary medicine is the lack of close monitoring of body weight in the most critically ill. In the author's experience, many cases of oligo-anuric AKI that are referred for hemodialysis have a positive fluid balance from overzealous fluid therapy and lack of close monitoring for body weight increase or other clinical signs of edema (**FIGURE 3**). The physiologic consequences of aggressive fluid therapy, even in patients with renal dysfunction, range from disruption of important cellular processes to severe multiorgan dysfunction (**BOX 1**).[22]

Use of Early Enteral Nutrition

The systemic benefits associated with early enteral nutrition in critically ill animals are incalculable. It cannot be emphasized enough that early nutrition plays a key role in the management of animals with acute illness. Delaying enteral nutrition is recommended only in critically ill people with uncorrected shock, persistent hypoxia and acidosis, ongoing upper GI bleeding, GI obstruction, severe gastric fluid retention, or abdominal compartment syndrome.[23]

The use of nasogastric/nasoesophageal tubes in small animals has been increasing in clinical practice and is improving the management of the most critically ill. These tubes do not require general anesthesia or heavy sedation for placement and for the most part do not cause major discomfort to the animal. When calculating fluid balance, enteral nutrition should be included in the sum of all the intakes. In patients without fluid losses and a zero or positive fluid balance, enteral nutrition can replace IV fluid supplementation and provide a more physiologic delivery of daily water requirements.

BOX 1 Major Physiologic Consequences of Fluid Overload

- Disruption of phosphorylation and membrane polarization
- Increased production of tumor necrosis factor-α and interleukins
- Altered glucose metabolism and insulin release
- Decreased cardiac output
- Increased pulmonary vascular leakage
- Increased renal edema and decreased GFR
- Increased gut permeability and ileus
- Decreased soft tissue healing
- Dilution of coagulation factors and increased risk of hemorrhage

FLUID ADMINISTRATION IN SPECIFIC DISEASE CONDITIONS

BOX 2 lists some of the most common reasons for IV fluid resuscitation in veterinary medicine. Despite the recognized benefits of fluid therapy in these situations, evidence-based medicine is rarely applied, and the fluid choice and volume administered are often inappropriate. In many cases, inappropriate fluid regimens do not lead to overt harmful effects because the kidneys and cardiovascular system compensate for the excessive volume or supraphysiologic load of electrolytes delivered, but in some cases, inadequate fluid therapy leads to exacerbation of cardiovascular, respiratory, and renal dysfunction in the critically ill.

A major mistake in veterinary medicine is the inappropriate replacement of fluid deficits by delivering fluid to the patient in terms of maintenance rates and not calculated volume over a target of time. For example, giving an animal 2 times the maintenance rate of fluids for replacement of a 6% volume deficit may take over 24 hours. Instead, the desired volume to be replaced should be divided in a short period of time (6 to 12 hours), in addition to maintenance rate of fluids and calculated ongoing losses.

Increasing evidence in the human and veterinary literature demonstrates that specific disease conditions require appropriate prescription fluid therapy and an understanding of the possible adverse effects of fluid therapy. Following is some information regarding the approach to IV fluid therapy in common disease states observed in critically ill small animal patients.

Anemia

Correction of intravascular volume deficits is essential in stabilizing anemic animals. Normally, oxygen delivery to cells exceeds oxygen consumption by a factor of 3 or 4 under resting conditions. If lower hemoglobin concentrations lead to decreased oxygen

delivery, oxygen consumption can remain constant because the cells can increase the amount of oxygen extracted from each hemoglobin molecule.

However, in anemic animals with fluid deficits, oxygen delivery is compromised by not only low concentrations of hemoglobin but also the decreased ability of red blood cells to reach hypovolemic tissues. Although many veterinarians consider dilution of the circulating cell mass an indication for delaying fluid therapy in anemic animals, volume deficits should be corrected to allow the remaining red cells to deliver oxygen. Fluid therapy must be used as described above with goal-directed resuscitative efforts and rapid de-escalation until blood products become available.

The approach to fluid therapy in patients with anemia from hemorrhagic shock (**TABLE 1**) takes into account the cause of hemorrhage and the cause and timing of blood loss. For example, in animals with acute hemorrhage and risk of exsanguination from trauma, rupture of an intracavitary neoplasm (e.g., splenic hemangiosarcoma), or coagulopathy, permissive hypotension and volume-restricted resuscitation strategies are advocated to prevent blood clot dislodgment and exacerbation of hypovolemic shock.[13] These strategies are implemented after a surgical plan has been established to stop the source of bleeding or blood products become available to replace the components lost.

In animals with ongoing causes of anemia (e.g., immune-mediated hemolysis, chronic inflammation, chronic kidney disease, GI or external parasitism), initial fluid therapy should be guided to rapidly correct fluid deficits or percent dehydration over several hours. If the patient requires a blood transfusion, the use of separate IV access lines (2 IV catheters) is encouraged to rapidly correct both anemia and intravascular volume deficits, with rapid optimization of macrovascular parameters and correction of decreased oxygen delivery to tissues. If the patient is hypotensive or has severe signs of hypovolemic shock due to the combination of anemia and decreased intravascular fluid volume, a bolus of crystalloids (LRS, Plasma-Lyte 148, or Normosol-R 10-20 mL/kg IV over 10 minutes) can be given to more rapidly correct clinical signs of hypovolemia.

Cardiomyopathy

Although patients with underlying cardiomyopathies may require fluid therapy because another systemic process is causing volume loss, the use of fluid therapy in animals with cardiomyopathies and evidence of pulmonary edema or concern for congestive heart failure is absolutely contraindicated.

Patients that are being treated for congestive heart failure, especially geriatric animals, tend to have an increase in kidney values during hospitalization, most likely due to unmasked chronic renal disease and ongoing cardiorenal syndrome. It is imperative to recognize that increases in renal functional markers such as creatinine are not an indication for IV fluid therapy in animals currently undergoing treatment for congestive heart disease. In these situations, worsening of the pulmonary function leads to decreased oxygen delivery to tissues, especially the kidneys and heart.

BOX 2 Common Reasons for Intravenous Fluid Resuscitation

- Hypovolemia (traumatic or nontraumatic hemorrhage or GI/renal fluid loss)
- Distributive shock from sepsis or other noninfectious causes of systemic inflammation such as pancreatitis or endocrine emergencies (e.g., diabetic ketoacidosis, addisonian crisis)
- Perioperative hemodynamic optimization
- Acute or chronic renal disease
- Severe GI disorders

Sepsis and Septic Shock

No specific guidelines are available for IV fluid therapy in animals with signs of systemic inflammatory response syndrome or sepsis; therefore, fluid therapy recommendations (**TABLE 1**) are extrapolated from the international guidelines for management of sepsis and septic shock in people.[6] Some of the recommendations from the Surviving Sepsis Campaign are based on animal studies of sepsis.[6]

Acute Kidney Injury and Renal Dysfunction

Fluid therapy in hypovolemic patients with AKI is aimed at optimizing cardiac preload and stroke volume to restore systemic blood pressure, cardiac output, and, as a result, renal perfusion pressure (**TABLE 1**). Unfortunately, overzealous fluid therapy without close

Table 1. Approach to Fluid Therapy for Common Conditions

ANEMIA (HEMORRHAGIC SHOCK)	SEPSIS	ACUTE KIDNEY INJURY OR DYSFUNCTION
1. Administer bolus of hypertonic saline (7.2% or 7.5%): 4 to 5 mL/kg IV over 10 minutes. 2. Administer bolus of balanced isotonic fluid (LRS, Plasma-Lyte 148, Normosol-R): 10 mL/kg IV over 10 minutes. 3. Target blood pressure: ≤90 mm Hg 4. Reassess after boluses. 5. If severe hypotension is persistent (systolic pressure <60 mm Hg), repeat once, then consider blood component therapy.	■ Administer bolus (10-20 mL/kg) of balanced crystalloids for initial resuscitation. ■ Administer fluid boluses (10-20 mL/kg) of balanced crystalloids for optimization of hemodynamic variables (e.g., blood pressure, lactate, urine output). ■ Use balanced crystalloids rather than 0.9% saline to avoid hyperchloremia. ■ Avoid use of HES solutions for volume replacement. ■ Consider the use of vasopressors early if hypotension is persistent	■ Avoid fluid overload at all costs. ■ Use fluid resuscitation to restore blood pressure in the acute phase of management, then optimization based on urine output and/or frequent body weight assessment. ■ Avoid synthetic colloids and chloride-rich solutions (e.g., 0.9% saline). ■ Closely monitor for polyuria in patients recovering from AKI or postobstructive diuresis. ■ Use balanced solutions in cases of obstructive disease for rapid correction of pH and electrolyte abnormalities.

monitoring of body weight and daily fluid intake is common, with deleterious effects on GFR[11,22] and other organ systems. The choice of fluid also appears to have a pivotal role in renal function and mortality, especially in critically ill and septic human patients, where chloride restriction and avoidance of synthetic colloids may improve outcome and reduce the requirement for extracorporeal blood purification.[2,3,5,9,12-15]

Another major pitfall in the management of animals with AKI or ureteral/urethral obstructions is the lack of identification of polyuric (high-output) phases associated with diuresis. During the recovery phase of AKI, animals can quickly go from an oligo-anuric urine output state to a polyuric phase with sometimes excessive fluid loss. The polyuric phase can be easily missed if urine output and body weight are not monitored in the hospital, or when animals are sent home after functional renal markers such as creatinine and urea start improving.

Similarly, cats commonly develop postobstructive diuresis after alleviation of urethral obstruction.[24] In cases of urinary obstruction, especially in the acute resuscitation phase, the fluid choice should be one that rapidly corrects electrolyte and acid-base imbalances. Two studies have demonstrated that the use of balanced crystalloids (e.g., LRS, Plasma-Lyte) instead of 0.9% saline solution leads to a more rapid correction of electrolyte and pH abnormalities in obstructed cats.[25,26]

Pulmonary Disease

No specific guidelines exist in veterinary medicine to help guide fluid therapy in animals with lung disease, so fluid therapy should be judicious and tailored to each patient. Pulmonary conditions such as infectious or aspiration pneumonia and noncardiogenic pulmonary edema can worsen without judicious use of fluids. In these cases, fluid therapy should be titrated on an individual basis.

Fluid therapy can exacerbate pulmonary dysfunction by increasing hydrostatic pressure and endothelial dysfunction caused by inflammation at the level of the pulmonary capillaries, ultimately leading to fluid extravasation and impaired gas exchange.[22] Based on human studies showing better outcomes and decreased need for mechanical ventilation, fluid therapy in an animal with suspected or diagnosed pulmonary disease should be restricted, with the aim of having a zero or negative fluid balance.[27] If a cardiogenic cause of pulmonary edema is suspected, fluid therapy should not be initiated until underlying heart conditions are ruled out.

Hypoalbuminemia

Albumin is responsible for up to 80% of the oncotic pull within the intravascular compartment. The use of crystalloids in severely hypoalbuminemic animals can lead to further extravasation of water into the interstitial space and worsening of edema in vital organs. As mentioned above, the use of colloids to increase oncotic support and reverse edema is now in question. Crystalloid therapy should be considered as a resuscitation strategy in a hypoalbuminemic animal with severe cardiovascular collapse only when plasma

products or albumin are not available.

When used, the effects of IV crystalloid fluids are short lived, as 80% of the fluid volume infused leaves the intravascular space within 20 to 30 minutes of administration. The long-term approach for fluid therapy in hypoalbuminemic patients should include early enteral nutrition, which not only can optimize water balance but also improve oncotic support through increased delivery of nutrients to the GI tract.

Gastrointestinal Disease

GI emergencies are among the most common reasons for prescribing fluid therapy in small animals. Outpatient IV or subcutaneous crystalloid supplementation to correct fluid deficits caused by vomiting, diarrhea, and lack of oral water intake is common practice in veterinary medicine. Appropriate fluid therapy for animals with GI conditions should include calculation of total fluid deficit from physical examination findings along with measurement of ongoing losses and calculation of required daily intake to maintain homeostasis. TVP

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CONTINUING EDUCATION

Fluid Therapy in Critical Care

LEARNING OBJECTIVES

Readers will be able to describe new trends in prescription of intravenous (IV) fluid therapy during critical illness and apply these principles to common clinical scenarios identified in small animals. Readers will also able to identify appropriate monitoring techniques to guide prescription of IV fluid therapy.

TOPIC OVERVIEW

This article provides an overview of the current trends of fluid therapy in critical care, with emphasis in 4 main categories: avoidance of synthetic colloids and chloride-rich fluids, prevention of fluid overload, early enteral nutrition, and staged fluid therapy prescription.

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1. **In people with sepsis and septic shock, the use of synthetic colloids has been associated with:**
   a. Increased risk of acute kidney injury (AKI)
   b. Increased risk of mortality
   c. Coagulopathies
   d. All of the above

2. **Which of the following isotonic crystalloids contains the highest concentration of chloride?**
   a. LRS
   b. Plasmalyte-B
   c. 0.9% Saline
   d. Normosol-R

3. **In critically ill dogs and cats, veterinarians should titrate IV fluid therapy with the aim of achieving __ fluid balance.**
   a. 0%
   b. +10%
   c. +20%
   d. +30%

4. **Chloride-rich IV fluids such 0.9% saline are indicated in cases of:**
   a. Feline urethral obstruction with severe hyperkalemia (K+ >8 mEqL)
   b. Hemorrhagic shock
   c. Upper GI obstruction with hypochloremic metabolic alkalosis
   d. Septic shock with severe lactic acidosis

5. **Fluid overload is defined as __ increase in basal body weight and has been associated with __ mortality in critically ill dogs.**
   a. 0.5%; 100%
   b. 10%; 50%
   c. 50%; 50%
   d. 20%; 30%

6. **Which group of patients can benefit from a negative fluid balance (<0%)?**
   a. Dogs and cats with anemia and hypovolemia
   b. Dogs and cats with septic shock
   c. Dogs and cats with AKI
   d. Dogs and cats with pulmonary disease

7. **In small animals with hemorrhagic shock, what IV fluid resuscitation strategies are advocated?**
   a. Permissive hypotension and volume restriction
   b. Optimization of blood pressure (systolic >90 mmHg) and volume overload
   c. Use of synthetic colloids and blood product restriction
   d. Use of chloride-rich solutions to correct acidosis and increase blood pressure (systolic >120 mm Hg)

8. **Which parameter is often overlooked when monitoring fluid therapy in critically ill veterinary patients?**
   a. Systolic blood pressure
   b. Plasma lactate level
   c. Urine output
   d. Body weight

9. **Which of the following fluid therapy strategies can be recommended for a dog with normal vital signs, anorexia, and severe hypoalbuminemia (albumin <1.2 g/dL)?**
   a. Fresh frozen plasma 45 mL/kg IV over 12 hours to raise the albumin to 2.2 g/dL
   b. Synthetic colloids 20 mL/kg over 24 hours to prevent peripheral edema
   c. Isotonic crystalloids (LRS) at 2 times maintenance
   d. Enteral nutrition via nasogastric tube to meet resting energy requirements

10. **What 3 stages are recommended for fluid therapy prescription in critically ill small animals?**
    a. Maintenance → De-escalation → Subcutaneous fluids
    b. Resuscitation → Optimization → De-escalation
    c. Replacement → Ongoing losses → Maintenance
    d. Optimization → Maintenance → Negative fluid balance