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Complications of Fluid Therapy

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The administration of intravenous fluids is one of the most important aspects of patient care in hospitalized animals. Intravenous fluids are administered to replace or prevent dehydration, treat hypovolemic shock and intravascular volume depletion, correct acid-base and electrolyte abnormalities, and maintain vascular access for administration of drugs, blood product components, and parenteral nutrition. Intravenous catheterization also can provide a means of blood sample collection, thus avoiding frequent and uncomfortable venipunctures in critically ill animals. Although the benefits of intravenous catheterization and fluid administration are numerous, there are inherent risks associated with the procedures, and care must be taken to avoid potential complications.

INTRAVENOUS CATHETERIZATION

Avoidance of catheter-induced complications begins with careful assessment of the animal and appropriate selection of the intravenous catheter site. Contamination of the catheter site by the animal's body fluids or excretions (urine or feces) and invasion by nosocomial organisms in the animal's hospital environment are common potential sources of infection. If an animal is vomiting or has epistaxis or ptyalism, forelimb catheters are inappropriate because of the risk of contamination and the frequent need for replacement of the catheter bandage to prevent wicking of bacteria from the environment. Similarly, placement of a medial or lateral saphenous catheter is contraindicated in animals with diarrhea or urinary or fecal incontinence. Elizabethan collars should be placed on inquisitive animals to prevent them from chewing the catheter or intravenous fluid line, which can break sterility and predispose the animal to a catheter-related infection. In animals with coagulopathies, such as disseminated intravascular coagulation or vitamin K antagonist rodenticide intoxication, the use of large-bore central venous catheters should be avoided to prevent excessive hemorrhage from venipuncture sites. Similarly, in animals with hypercoagulable states (eg, immune-mediated hemolytic anemia, hyperadrenocorticism, disseminated intravascular coagulation, protein-losing enteropathy, protein-losing nephropathy), placement of a central venous catheter can induce

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thromboembolism and lead to edema of the site drained by the thrombosed vessel. One report documented cranial vena caval thrombosis from catheterization of the jugular vein in a dog with chylothorax [1].

During placement of an intravenous catheter, careful aseptic technique should be used at all times to decrease the risk of bacterial contamination of the catheter site. Besides the animal itself, one of the most common sources of catheter-induced infection is the hands and equipment of hospital personnel. Hand washing is by far one of the most important tasks that a veterinary technician and veterinarian can perform to prevent catheter-related infections. In one study, the incidence of *Enterobacter* spp bacterial contamination of intravenous catheters decreased significantly when personnel in the critical care unit changed [2]. The authors concluded that lack of hygiene and hand washing between patients contributed greatly to positive bacterial cultures of intravenous catheters.

After carefully clipping and scrubbing the catheter site with an antimicrobial scrub solution, hospital personnel should wear gloves to decrease the risk of sepsis, particularly in immunocompromised animals. The incidence of bacterial contamination of intravenous catheters in puppies with parvoviral enteritis can be as high as 22% [3]. Most bacterial pathogens isolated were from either gastrointestinal or environmental sources and were resistant to multiple antibiotics [3]. Because of the high incidence of bacterial resistance, the environment was thought to be a likely source of contamination, possibly transferred from the environment to the animal by the hands of caretakers. Carefully scrubbing a distal extremity, such as the forelimb, with a 4% chlorhexidine solution followed by a contact time of 1 minute greatly reduces bacterial colonization of skin at intravenous catheter sites [4]. A gauze square 4×4 should be placed over the animal's hair distal to the proposed site of catheterization to prevent dragging the intravenous catheter through contaminated hair. Nonsterile technique during emergency vascular access and vascular cut-down procedures also can predispose an animal to catheter-related infection. Even when strict adherence to aseptic protocols has been used, the catheter site should be evaluated at least once daily for evidence of problems, which may include pain upon injection, erythema, "ropiness" or thickening of the vessel, heat, or any discharge from the catheter site. If any of these abnormalities is noted or if fever develops in a previously afebrile patient, the catheter should be removed, and the tip should be cultured for aerobic bacteria.

Previously it was recommended to empirically change the intravenous catheter every 3 days to avoid catheter-induced infection. A prospective study investigated the risk of bacterial contamination of intravenous catheters left in place for less than 72 hours with those left in place for more than 72 hours. The investigator documented that the risk of bacterial contamination of the catheters was similar in both groups and overall the risk of bacterial contamination was low [5]. Bacteria that were cultured from the catheters included *Enterobacter aerogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Pasteurella multocida*, and *Bacillus* spp. The source of *Bacillus* spp contamination was the gauze sponges used to prepare the catheter sites. Once the source of contamination

was found, the incidence of catheter-related bacterial contamination decreased dramatically. This report emphasized the importance of clean technique and clean supplies. The study determined that it is costly and not necessary to change catheters every 72 hours. In another study, the incidence of bacterial contamination of intravenous catheters was not related to the length of time catheters were in place or other catheter complications [2]. Currently, I recommend using a catheter for as long as necessary and for as long as it is functioning properly without any of the complications listed previously. A larger scale observational study of more than 600 intravenous catheters in human patients documented no increased risk of infection, thrombophlebitis, or mechanical complications with prolonged catheterization [6]. As a general rule, once the catheter is no longer needed, it should be removed because it always can be a potential source of infection and thrombophlebitis.

CRYSTALLOID FLUIDS

A wide variety of crystalloid fluids is available for veterinary use. Ideally, the choice of crystalloid fluid is based on the patient's acid-base and electrolyte status. For example, the administration of a fluid that contains bicarbonate precursors as buffers may be inappropriate for an animal with hypochloremic metabolic alkalosis caused by pyloric outflow obstruction. A better fluid choice in this situation would be 0.9% sodium chloride, which contains a high concentration of chloride (154 mEq/L) and no bicarbonate precursors. Administration of 0.9% sodium chloride, however, can cause an additional increase in serum chloride concentration in a patient that already is hyperchloremic. Administration of a solution with no bicarbonate precursors (eg, 0.9% saline, 5% dextrose in water) can exacerbate metabolic acidosis, although in patients with severe hypovolemic shock, administration of these fluids can help restore perfusion and correct lactic acidosis by replacement of intravascular fluid volume alone. Administration of lactated Ringer's solution (which contains calcium) may be inappropriate in an animal with hypercalcemia. Similarly, administration of a potassium-containing fluid to an animal with severe hyperkalemia places that patient at risk for an additional increase in its serum potassium concentration. In many cases, however, administration of intravenous fluids (regardless of composition) improves perfusion and causes dilution of the patient's serum electrolytes. The administration of large volumes of dextrose-containing fluids as a bolus may result in hyperglycemia, which can worsen the prognosis in animals with head trauma [7]. Rapid administration of hypotonic fluids, such as 5% dextrose in water, also potentially can cause intravascular hemolysis. Similarly, overly rapid administration of a hypertonic solution, such as hypertonic saline, can result in crenation of red blood cells if inappropriate volumes are administered too rapidly [8]. Hypertonic saline infusion also can be associated with vagally mediated hypotension and bradycardia and is contraindicated in animals that are hypernatremic or dehydrated [8,9]. Calcium-containing fluids should not be administered concurrently with blood products because of the risk of calcium citrate precipitation in the fluid line.

ACID-BASE AND ELECTROLYTE IMBALANCES

Electrolyte abnormalities are common in a wide variety of illnesses that affect small animal patients. Sodium and potassium are among the most important electrolytes to consider, because imbalances in these electrolytes can dramatically affect neuromuscular function and maintenance of cellular homeostasis. Animals that lose water in excess of solute or animals that have hypothalamic lesions can develop a free water deficit that manifests itself as hypernatremia. Animals that have an aldosterone deficiency cannot reabsorb adequate amounts of sodium and can become profoundly hyponatremic as a result. Abrupt changes in sodium concentration can cause substantial shifts in intracellular or interstitial fluid and lead to cerebral edema or central pontine myelinolysis, particularly in states of severe hyponatremia (ie, serum sodium concentration $<$ 120 mEq/L) [10,11]. To avoid excessively rapid correction or normalization of serum sodium concentration during states of either hyper- or hyponatremia, the following calculations can be used.

CORRECTION OF HYPERNATREMIA

$$\text{Free water deficit} = 0.6 \times \text{kg body weight} \times \left(\left[Na^{+}_{current} \Big/ Na^{+}_{desired}\right] - 1\right) \text{ [11]}$$

Controversy exists as to which fluids should be used to decrease serum sodium concentration. Infusion of 5% dextrose in water actually represents administration of free water because the dextrose is metabolized to carbon dioxide and water. In cases of severe hypernatremia, however, reduction in serum sodium concentration can be achieved by first using solutions with higher concentrations of sodium such as 0.9% saline (154 mEq/L), progressing to lactated Ringer's solution (130 mEq/L) and, ultimately, to 5% dextrose in water to avoid excessively rapid correction of hypernatremia. Severe hypernatremia can occur when an animal has chronic free water or hypotonic fluid loss, such as an animal with chronic diabetes mellitus or renal insufficiency whose serum sodium concentration may approach 200 mEq/L.

A second formula determines the effect of 1 L of a solution (infusate) on the decrease in serum sodium concentration:

$$\text{Change in serum sodium (mEq/L)} = \left[Na^{+}_{infusate} \Big/ Na^{+}_{patient}\right] \Big/ [(\text{kg body weight} \times 0.6) + 1] \text{ [11]}$$

Ideally, the change in serum sodium concentration should not exceed 0.5 mEq/kg/h or 10 to 12 mEq/kg/d. By using this calculation, one can estimate how quickly to administer 1 L of fluid. This formula predicts what the animal's serum sodium concentration should be after administration of a liter of the infusate solution.

When faced with an animal with severe chronic hyponatremia, the same approach of careful and slow correction of serum sodium concentration should be followed. Although it may seem reasonable to administer a fluid that contains large amounts of sodium (eg, 0.9% NaCl with 154 mEq/L) to an animal with a serum sodium concentration of less than 120 mEq/L, gradual administration of a fluid with a moderate amount of sodium (eg, lactated Ringer's with 130 mEq/L or Normosol-R with 140 mEq/L) is more appropriate to avoid overly rapid correction of serum sodium concentration and the risk of central pontine myelinolysis.

HYPOKALEMIA

Unless an animal has been rapidly infused with a fluid that contains added potassium chloride, hyperkalemia and resultant atrial standstill rarely are complications of intravenous fluid therapy. Severe hypokalemia can promote refractory ventricular arrhythmias, muscle cramping, muscle weakness, lethargy, ileus, and cervical ventroflexion [11]. Many isotonic crystalloids used for replacement fluid therapy contain small quantities of potassium (3–4 mEq/L). Hypokalemia, however, is a common occurrence during fluid therapy, and unless commonly used crystalloid replacement solutions are supplemented with potassium chloride, an animal can become hypokalemic as a result of intravenous fluid administration. As a rule, potassium supplementation should not exceed 0.5 mEq/kg/h. Potassium supplementation typically is performed according to the animal's serum potassium concentration (Table 1). If an animal (eg, a patient with diabetic ketoacidosis) has refractory hypokalemia despite appropriate potassium supplementation, magnesium chloride also should be administered at a rate of 0.75 mEq/kg/d by constant rate infusion. Hypomagnesemia is a common occurrence in critical illness and can lead to dysfunction of sodium-potassium-ATPase with resultant refractory hypokalemia.

INTRAVASCULAR VOLUME OVERLOAD

In normal individuals, total body water comprises approximately 60% of the animal's body weight. Most of this water (67% of total body water) is located intracellularly, whereas the rest of it is located in the intravascular and

Table 1
Serum potassium concentration and recommended amount of potassium supplementation (mEq/L)

Serum potassium (mEq/L)	KCl (mEq/L) supplementation
< 2.0	80
2.1–2.5	60
2.6–3.0	40
3.1–3.5	30
3.6–5.0	20
> 5.0	0

interstitial spaces. Of the 33% of water that is located extracellularly, 24% of total body water is located in the interstitial space and 8% to 10% of total body water is located in the intravascular space. Fluid flux between compartments is determined by the balance between hydrostatic and oncotic forces within each compartment and vascular endothelial pore size. Hydrostatic force is the pressure exerted by water on either side of a blood vessel wall. Increases in hydrostatic forces favor extravasation of fluid from one fluid compartment to the other, especially if oncotic forces are suboptimal. Conversely, oncotic forces favor retention of fluid within a fluid compartment, helping to avoid interstitial edema if a healthy vasculature is present.

Starling's Law of Diffusion largely determines the movement of fluid from one compartment to another and states that

$$\text{Fluid flux} = k[(P_c+\pi_i) - (\pi_c+P_i)]$$

where k is filtration coefficient, P_c is hydrostatic pressure in the capillary, P_i is hydrostatic pressure in the interstitium, π_c is capillary oncotic pressure, and π_i is oncotic pressure of the interstitial space.

The filtration coefficient is determined by the capillary fenestration or pore size. The oncotic pressure is the force that attracts fluid or water and is determined by the size and number of particles in solution relative to the size and number of particles in the interstitial space. Forces that favor filtration of fluid out of the vessel into the interstitial space are the interstitial oncotic pressure and the capillary hydrostatic pressure. Forces that favor retention of fluid within the intravascular space are the intravascular oncotic pressure and the interstitial hydrostatic pressure. The balance between the forces that favor filtration versus forces that favor fluid absorption determines the net direction of fluid flux.

Interstitial edema occurs when intravascular hydrostatic forces exceed intravascular oncotic forces. Infusion of crystalloid fluids alone (which do not contribute to intravascular oncotic pressure) can dilute serum albumin and other proteins and increase the risk of interstitial edema [12]. This is particularly true in the lungs when pulmonary capillary pressures exceed 25 mm Hg and the pulmonary lymphatic drainage system becomes overwhelmed. The use of direct cardiac output monitoring and measurement of pulmonary capillary occlusion pressures is not advocated in all critically ill animals. Central venous pressure measurements, however, are simple and easy to perform with minimally invasive equipment and can be used indirectly to measure trends in intravascular fluid volume, provided that right heart function, vascular compliance, and intrathoracic pressures are normal [13]. Colloid osmometry also is a useful monitoring technique to determine a patient's colloid osmotic (oncotic) pressure (COP) and response to colloid therapy [14]. Although attempts have been made to extrapolate serum oncotic pressure from total serum protein concentration in animals, results are variable and do not correlate well [15–17]. Intravascular oncotic pressure and intravascular fluid volume must be

carefully titrated to meet the patient's fluid therapy needs. Consequences of edema include impaired cellular oxygen delivery and enzyme function, impaired cellular oxygen exchange, cellular swelling, and cellular lysis [13]. Clinical signs of overhydration include shivering, restlessness, serous nasal discharge, chemosis, tachypnea, cough, and pulmonary crackles. An important component of monitoring includes frequent assessment of the animal's respiratory status, because tachypnea and cough often occur before clinical signs of serous nasal discharge, chemosis (Fig. 1), peripheral edema (Fig. 2), and fulminant pulmonary edema [8].

ALBUMIN

Albumin is an important contributor to COP in the body. Unless severe hyperglobulinemia is present, albumin contributes approximately 50% of the patient's total protein concentration and contributes 80% to the serum COP. Extrapolation of COP using serum albumin concentration has been reported, but this method is largely inaccurate in animals [15–17]. Use of a colloid osmometer is considered the gold standard for assessment of COP if an animal is at risk of developing interstitial edema. When severe hypoalbuminemia (serum albumin concentration < 2.0 g/dL) is present, an animal is at risk for extravasation of fluid from the vascular space and development of interstitial edema. This degree of hypoalbuminemia has been associated with a significantly increased risk of mortality in critically ill dogs [18], enteral feeding intolerance, and delayed wound healing [19]. Consequently, increasing serum albumin concentration to 2.0 g/dL may improve clinical outcome. Increasing serum albumin concentration potentially can be accomplished by use of fresh frozen or regularly frozen plasma; administration of plasma is largely an inefficient method of increasing serum albumin concentration. Approximately

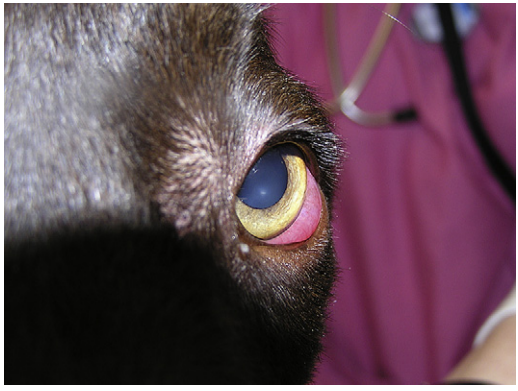

Fig. 1. Chemosis secondary to overzealous intravenous fluid administration in a dog with vasculitis. (*From* Mazzaferro EM. Fluid therapy: the critical balance between life and death. NAVC Clinician's Brief 2006;73–5; with permission.)

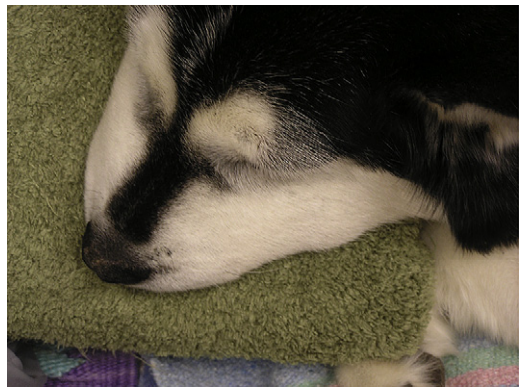

Fig. 2. Patient with severe subcutaneous edema from overhydration and renal failure.

15 to 20 mL/kg of fresh frozen plasma is necessary to increase serum albumin concentration by 0.5 g/dL, provided no ongoing losses are present [19]. Recently, concentrated human albumin has been used with success to increase serum COP and blood pressure in critically ill dogs [20]. Other research has demonstrated that concentrated human albumin and hetastarch were superior to 0.9% saline in fluid resuscitation and resulted in decreased incidence of pulmonary edema compared with saline resuscitation alone [21]. More recently, research has indicated that the use of concentrated human albumin may be detrimental in normoalbuminemic dogs [22,23]. A limitation of this study was that all experimental dogs were normoalbuminemic. The authors acknowledged that immunocompetence in normoalbuminemic dogs may have differed from that of critically ill animals and may place normoalbuminemic animals at risk for developing antihuman albumin antibodies and reactions to albumin infusion. I have used concentrated human albumin (25%) with success and minimal adverse reactions in severely hypoalbuminemic dogs in veterinary clinical practice. The potential benefits associated with the use of concentrated human albumin must be weighed against its potential risks on a case-by-case basis, however. Once serum albumin concentration has increased to 2.0 g/dL, COP can be maintained by administration of a synthetic colloid such as hydroxyethyl starch, Pentastarch, or Dextran-70.

POTENTIAL COMPLICATIONS ASSOCIATED WITH VARIOUS COLLOID FLUIDS

The various colloids available for use in veterinary patients are not without the potential for complications. In general, administration of a colloid causes any infused crystalloid fluid to be retained within the intravascular space for a longer period of time than usual. Normally, up to 80% of an infused crystalloid fluid leaves the intravascular space within 1 hour of administration. When a colloid is administered concurrently with a crystalloid, however, the crystalloid

fluid volume should be decreased by 25% to 50% (ie, only 50%–75% of the crystalloid should be administered) to avoid increased intravascular hydrostatic pressure and interstitial edema, particularly within the pulmonary parenchyma. Clinically and experimentally, an increase in intravascular lung water during resuscitation from hemorrhagic shock has resulted in decreased serum COP and decreased oxygen delivery [24]. Hydroxyethyl starch or dextrans can artifactually cause small dilutional decreases in total solids as measured by refractometer, but they are known to significantly increase COP [25].

Von Willebrand factor and factor VII can be decreased to 40% of normal after an animal has received hydroxyethyl starch [26]. Activated clotting time, activated partial thromboplastin time, and platelet plug formation may be prolonged from normal in animals that have received hydroxyethyl starch [27,28]. These abnormalities likely are not clinically relevant and clinically do not cause bleeding until infusion exceeds the manufacturer's recommended dosage of 20 to 30 mL/kg/d or unless the animal has a hereditary coagulation disorder, such as a factor VII deficiency or von Willebrand's disease [29–31]. Neutrophil counts can be increased in animals that have received Dextran-70 because of neutrophil demargination [31]. Low molecular weight dextrans should be used with caution–if at all–in animals with renal impairment because of the risk of renal failure secondary to tubular obstruction [32]. Dextrans can coat red blood cells and platelets and interfere with tests of coagulation and red cell cross-match procedures. Dextran-40 has been associated with an increased risk of anaphylaxis [9] and should be avoided whenever possible because better options are available for veterinary patients.

HEMOGLOBIN-BASED OXYGEN CARRIERS

Hemoglobin-based oxygen carriers are potent colloids that have an added benefit of increasing oxygen-carrying capacity without the need for blood typing and cross-match procedures. Because hemoglobin-based oxygen carriers are potent colloids, they should be used with caution in animals with marginal cardiac function to avoid interstitial and pulmonary edema [33]. Other complications that have been reported with use of hemoglobin-based oxygen carriers include pleural effusion, discolored mucous membranes, vomiting, neurologic abnormalities, and pigmenturia. Use of hemoglobin-based oxygen carriers also artifactually alters serum and urine chemistry tests that are measured by colorimetric assays.

BLOOD PRODUCTS

Blood products, when administered correctly, can make the difference between life and death in a critically ill animal. Without care and forethought, however, administration of blood products can be associated with potentially life-threatening complications in some animals. In cats, for example, infusion of type A blood into a type B cat can result in rapid hemolysis and death [34]. In dogs, infusion of blood into an animal that has been previously sensitized can result in hemolysis, pigmenturia, and hypotension [35,36]. Other transfusion

reactions that have been described include ionized hypocalcemia, fever, vomiting, urticaria, angioneurotic edema, and hypotension [37]. Ionized hypocalcemia can make the vasculature less sensitive to circulating catecholamines and potentiate vasodilatation, cardiac dysfunction, hypothermia, and hypotension. If an animal develops refractory hypotension and hypothermia after administration of blood products, citrate toxicity and ionized hypocalcemia must be considered. Treatment consists of replenishing calcium by administration of calcium gluconate (1 mL/kg of a 10% solution given slowly) [38]. Dogs that have received massive transfusions, defined as administration of blood products in an amount more than the animal's blood volume (ie, > 90 mL/kg), have been shown to develop ionized hypocalcemia, thrombocytopenia, and coagulopathy [37].

Minimally, blood typing should be performed before administration of any blood product to a dog or cat. Ideally, a cross-match procedure also should be performed to prevent adverse complications [39]. Nausea, ptyalism, and vomiting also can be caused by accumulation of nitrogenous waste products, such as urea in stored blood [40]. Unless severe hemorrhage has occurred, administration of blood products should proceed slowly, and personnel should monitor the recipient carefully for early signs of a transfusion reaction. If a reaction occurs, diphenhydramine (0.5–1 mg/kg intramuscularly) and a glucocorticoid such as dexamethasone sodium phosphate (0.25 mg/kg intravenously or subcutaneously) should be administered and the transfusion rate decreased. Severe reactions that result in collapse and hypotension should be treated by rapid discontinuation of the blood product and prompt administration of epinephrine (0.01 mg/kg intravenously). A rare complication of hemochromatosis (iron toxicity) has been reported in a Miniature Schnauzer with pure red cell aplasia that received multiple red blood cell transfusions over several years' time [41]. Transmission of infectious diseases, such as leishmaniasis, to dogs from infected blood donors also has been reported [42,43].

COMPLICATIONS ASSOCIATED WITH ADMINISTRATION OF PARENTERAL NUTRITION PRODUCTS

Nutrition is one of the most important aspects of therapy in a critically ill or injured patient. Whenever possible, enteral nutrition is preferred, but in some cases, parenteral nutrition must be administrated because of enteral feeding intolerance or a malfunctioning gastrointestinal tract. Many parenteral nutrition products are hyperosmolar and can contribute to thrombophlebitis. As a general rule, parenteral nutrition solutions with osmolalities of 600 mOsm/L or less can be administered short-term though a peripheral venous catheter, whereas solutions with osmolality of more than 600 mOsm/L should be administered through a central venous catheter. Perivascular administration of dextrose-containing fluids, including parenteral nutrition solutions, can cause erythema and pain. Catheter-related complications during the administration of parenteral nutrition include kinks in the catheter, disconnected lines, and clogged catheters [44]. Catheter-related sepsis also can occur, particularly

with frequent disconnection of the fluid line for blood sampling or injection of drugs through a catheter used for parenteral nutrition. Guidelines for avoiding the potential for catheter-induced sepsis include not disconnecting the parenteral nutrition fluid line, designating the catheter and line solely for parenteral nutrition, and changing the parenteral nutrition fluid line every 24 hours (or if it becomes contaminated). Hyperglycemia has been associated with administration of parenteral nutrition and represents an increased risk for morbidity and mortality in critically ill cats [45]. Careful monitoring of the parenteral nutrition catheter and catheter site and acid-base, electrolyte, and glucose monitoring should be performed at least once a day to avoid these potential complications.

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