7 Alternative Plasma Protein Products: Albumin and Human Immunoglobulin Therapy

Nicole Spurlock
Small Animal Specialist Hospital, North Ryde, New South Wales, Australia

Introduction

The field of veterinary transfusion medicine is rapidly expanding beyond replacement of basic blood components and is moving to target supplementation of more specific molecules. As we develop a broader understanding of physiology, immunology, and critical care, the isolation and transfusion of specific plasma proteins becomes increasingly desirable. Albumin and immunoglobulin replacement therapy is considered commonplace in human medicine and has been for decades. Historically, transfusion of these proteins has been less available to the veterinary community as only human products have been available. Although xenoprotein transfusion carries increased risks over standard transfusion procedures, there is a growing body of literature to support the use of human protein transfusion to companion animals. Furthermore, some animal-specific proteins are available and decrease the risk associated with therapy.

This chapter provides a summary of the body of information describing the use of alternative plasma proteins in veterinary medicine, focusing on albumin transfusion and human intravenous immunoglobulin (hIVIG) therapy in companion animals. The physiologic role of plasma proteins, adverse effects of therapy, and applications for veterinary patients are reviewed.

Albumin

The albumin molecule plays an integral role in both health and disease states (Box 7.1). This protein is most widely known for its importance in maintaining colloid osmotic (oncotic) pressure (COP), but albumin also functions as a carrier of drugs and exogenous substances, an antioxidant, a modulator of coagulation, and a buffer in the extracellular fluid. Albumin also has immunoprotective properties and helps to maintain endothelial cell viability (Mathews 2008).

Box 7.1 FUNCTIONS OF ALBUMIN *IN VIVO* (MATHEWS 2008)

- Maintains colloid osmotic pressure
- Transports and binds substrates
- Functions as an antioxidant
- Contributes to primary and secondary hemostasis
- Buffers extracellular fluid
- Maintains microvascular permeability
- Provides amino acids for protein synthesis
- Assists with immunoprotection
- Aids in wound healing

Structure and function: colloid osmotic pressure

Albumin is a small but highly charged molecule with a molecular weight of 69 kD. Although it represents 50–60% of all plasma proteins in the body, it is responsible for generating 80% of COP in healthy animals (Mathews 2008). COP is one of the forces preventing fluid from exiting the intravascular space and moving into the interstitium. COP is generated by macromolecules located in the intravascular space, most importantly albumin. Albumin's large contribution to COP is mostly due to Van't Hoff's law, which states that the COP generated by a particle is indirectly proportional to its molecular weight. In other words, the smaller the particles contained within the solution, the higher the COP of the solution. The strong charge of the albumin molecule also plays a smaller role in the generation of COP as described by the Gibbs–Donnan effect: the negative charge of the protein attracts sodium cations, which in turn attract water across the semipermeable vascular endothelial membrane (Figure 7.1). Together, the size and charge of the albumin molecule create the majority of the COP in the intravascular space and help to ensure that fluid stays within the vasculature (Throop *et al*. 2004).

Carrier function and antioxidant properties

Albumin molecules have a strong binding capacity for many endogenous and exogenous substances (Table 7.1). Albumin functions as a carrier protein for many pharmacologic agents and effectively transports several drugs to sites of action, metabolism, or excretion. That same carrying capacity allows albumin to further function as a drug reservoir because substances that are protein bound are not free to interact with target tissues. Conversely, hypoalbuminemic patients will have an increased level of unbound agents circulating that are free to generate physiologic action. Increased availability of active drug compounds can result in toxicity and also decrease the drug half-life. As such, dose reduction should be considered when administering

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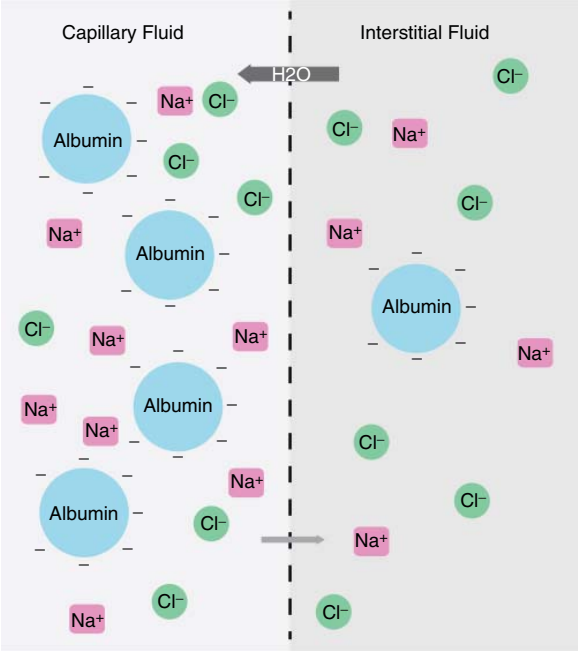

Figure 7.1 The Gibbs–Donnan effect describes how molecular charge can generate an increase in intravascular colloid osmotic pressure. Intravascular albumin molecules do not cross the endothelial membrane during health. The negatively charged albumin proteins attract sodium cations, which move across the semi-permeable endothelium into the vascular space. Water molecules follow sodium cations across the endothelial membrane and lead to an increase in intravascular volume. (Illustration courtesy of Brandon Mugar.)

albumin-bound drugs to hypoalbuminemic patients (Ikenoue *et al*. 2000). Unfortunately, a predictable relationship between albumin concentration and pharmacologic action does not exist, and choosing appropriate dose alteration can prove difficult. Currently, no guidelines exist regarding dose reduction of protein-bound medications in hypoproteinemic patients (Koch-Weser and Sellers 1976; Ikenoue *et al*. 2000).

Endogenous material is also bound by albumin. Many harmful bacterial toxins and carcinogens are neutralized when binding to the protein, although the albumin molecule is often destroyed as a result. Albumin also exhibits antioxidant properties and is thought to limit ischemia-reperfusion damage to inflamed tissue. By directly scavenging reactive oxygen species and binding iron molecules, albumin prevents iron-dependent lipid peroxidation and truncates oxidative damage (Watts and Maiorano 1999).

Coagulation mediation

The albumin molecule plays a role in coagulation by binding arachidonic acid and enhancing antithrombin (AT) activity (Doweiko and Bistrian 1994). In basic terms, arachidonic acid molecules are metabolized into prostaglandins, which activate platelets that aggregate and cause thrombosis. Low serum albumin concentrations result in higher levels of circulating arachidonic acid and a prothrombotic state. Furthermore, albumin

Table 7.1 Substances bound by albumin (Mazzaferro *et al*. 2002; Mathews 2008).

Endogenous	Exogenous
Arachidonic acid	Amitriptyline
Bilirubin	Cephalosporins
Calcium	Diazepam
Cysteine	Digoxin
Fat-soluble vitamins	Furosemide
Fatty acids	Glipizide
Glucocorticoids	Hydralazine
Iron	Ibuprofen
Reactive oxygen species	Penicillins
Thyroxine	Phenobarbital
Tryptophan	Propanolol
	Radiocontrast iodine
	Salicylic acid
	Sulfonamides
	Tetracyclines
	Thiopental
	Warfarin

demonstrates heparin-like activity by enhancing AT activity *in vitro* (Jørgensen and Stoffersen1979; Doweiko and Bistrian 1994). The combination of increased platelet aggregation and decreased anticoagulant activity in hypoalbuminemic patients might contribute substantially to thromboembolic events in the critically ill (Jørgensen and Stoffersen1979).

Miscellaneous functions

Beyond those already described, the albumin molecule fulfills a multitude of other roles in the body (Figure 7.2). Albumin acts as a buffer in the extracellular fluid compartment and provides amino acids for protein synthesis in catabolic states (Throop *et al*. 2004). It exhibits immunoprotective activity by inhibiting endothelial cell apoptosis and limiting activation of inflammatory cytokines (Kremer *et al*. 2011). Additionally, albumin supports microvascular integrity by occupying space in vessel walls and repelling macromolecules (Emerson 1989). Finally, albumin plays a role in wound healing. When the albumin protein extravasates from "leaky" vessels to sites of inflammation, it carries with it substrates vital for collagen crosslinking and tissue repair (Mazzaferro *et al*. 2002).

Synthesis and distribution

Albumin is synthesized in the liver in response to low COP and hypoalbuminemia. Synthesis is influenced by several factors,

Figure 7.2 The albumin molecule has many roles in human and veterinary physiology. Egg whites are made primarily of the albumin protein.

including nutritional status, serum electrolyte concentrations, and hormonal balance (Beathard 1975). Simply stated, albumin production begins after a significant decrease in COP is detected at the level of the hepatic interstitium. This generally occurs when albumin levels are at 33% of maximum capacity and when adequate nutrients are available. Albumin has a serum half-life of approximately 8 days in healthy dogs, but is slightly prolonged in states of hypoalbuminemia (Powell 2008).

With regards to total body albumin, 40% is located in the intravascular space and 60% is present in the interstitial compartment (Mathews 2008). During health, there is constant flux between the two compartments, at a rate of 4% hourly. During times of acute protein loss or decreased synthesis, a more rapid exchange occurs between the two compartments until the extravascular supply is depleted (Doweiko and Nompleggi 1991). The increased exchange rate helps to preserve COP in the short term, but is not sustainable as there is no true storage pool for albumin in the body. Importantly, measured serum albumin concentrations might not accurately reflect total body depletion because of the flux between the intra- and extracellular spaces (Mathews 2008).

Causes and consequences of hypoalbuminemia

Hypoalbuminemia is almost always a component of critical disease, secondary to increased loss and degradation, decreased synthesis, and increased use during catabolic states (Box 7.2).

Box 7.2 CONDITIONS ASSOCIATED WITH HYPOALBUMINEMIA (THROOP *ET AL*. 2004; MATHEWS 2008)

Adrenal disease	Lymphangectasia
Burns	Neoplasia
Diabetes mellitus	Pancreatitis
Dilution of plasma proteins (fluid retention or fluid therapy)	Panleukopenia
Enteritis: bacterial, hemorrhagic, parvoviral, parasitism	Peritonitis
Ehrlichia canis	Polytrauma
Glomerulonephritis	Cardiogenic or non-cardiogenic pulmonary edema
Heat stroke	Pyothorax
Hemorrhage	Sepsis
Hepatic damage	Toxins
Immune-mediated disease	Vasculitis
Inflammatory bowel disease	Any disease causing systemic inflammatory response syndrome (SIRS)

Albumin can be lost via the kidneys or gastrointestinal tract. Extravasation can also occur secondary to vascular leak from damaged or inflamed endothelium. Circulating toxins contribute to destruction of available albumin and protein can also be denatured by cytokines present in inflamed tissue.

Decreased synthesis of albumin can also significantly contribute to hypoalbuminemia. Albumin is a negative acute phase protein: during times of metabolic stress or illness, albumin synthesis is downgraded as cytokines shunt amino acids towards production of acute phase proteins vital to the inflammatory process (Mathews 2008). Liver insufficiency can also contribute to low serum albumin. Although albumin concentrations are sometimes used as a marker of liver function, plasma albumin concentration will remain normal until liver function decreases below 10–25% (Beathard 1975). During end-stage liver disease, low protein concentration occurs not only as a result of decreased production, but also as a sequela of third spacing into ascites.

Although a mild decrease in serum albumin concentration results in few clinical concerns, moderate hypoalbuminemia compromises hemostasis and can result in edema, decreased perfusion, and tissue hypoxia. If vascular integrity is intact, fluid extravasation rarely occurs when serum albumin concentrations are over 1.5 g/dL (15 g/L) (Willard and Tvedten 2012). However, systemic inflammation from any cause can lead to endothelial compromise and vascular leak, thus exacerbating the effects of existing

albumin deficits. Hypoalbuminemic patients are at high risk of hypotension, hypoperfusion, and multiple organ dysfunction syndrome. Edema and fluid accumulation within body cavities occurs, leading to a variety of complications; these are largely dependent on the location and extent of fluid accumulation and can include discomfort, decreased gastrointestinal absorption, gastrointestinal ileus, feeding intolerance, ascites, intra-abdominal hypertension, pulmonary edema, pleural effusion, respiratory compromise, delayed wound healing, and surgical dehiscence (Doweiko and Nompleggi 1991; Woods and Kelley 1993). As previously discussed, moderately to severely hypoalbuminemic patients are also prone to thromboembolic events (Jørgensen and Stoffersen 1979; Doweiko and Nompleggi 1991).

Albumin transfusion in human medicine

Despite the intuitive benefits of albumin transfusion for the support of protein-depleted patients, the efficacy of albumin supplementation in human medicine has faced significant debate. Multiple studies have been published with differing outcomes and a consensus regarding albumin supplementation has not been reached. The benefits of albumin transfusion appear to vary between population subsets and more research is needed before firm conclusions can be drawn regarding the practice of albumin transfusion in the critically ill.

Fluid resuscitation

Although not often used for fluid resuscitation in veterinary patients, 4% albumin has historically been employed as a resuscitative fluid in human patients. A commonly cited meta-analysis conducted in 1998 examined a large number of heterogeneous studies and concluded that critically ill human patients receiving 4% or 5% albumin solution for volume replacement had a 6% increase in mortality compared to those patients not receiving albumin (Cochrane Inquiries Group Albumin Reviewers 1998). Many clinicians questioned the conclusions of the group and further studies were subsequently conducted evaluating the use of albumin in human patients.

The Saline versus Albumin Fluid Evaluation (SAFE) study was published in 2004 and was designed to evaluate risk in human patients administered 4% albumin versus 0.9% NaCl during fluid resuscitation. Initial albumin concentrations or reasons for hospital admission were not recorded. In direct contrast to the original meta-analysis, administration of albumin for volume replacement in critically ill patients did not result in increased mortality. In fact, both protocols resulted in equivalent death rates within the 28-day trial period (Finfer *et al*. 2004).

In 2012, another meta-analysis compared multiple randomized clinical trials and evaluated outcome in critically ill patients receiving different colloid solutions for fluid resuscitation. Although the analysis found no increase in mortality associated with albumin administration, no clear benefits could be demonstrated with albumin supplementation in the overall patient population. However, the evidence suggested that patient response to albumin therapy varied between specific patient populations. The authors concluded that while albumin therapy might be beneficial during resuscitation of septic patients, it might increase mortality in patients suffering from burns, traumatic brain injury, or hypoalbuminema (Bunn and Trivedi 2012). To date, a consensus has not been reached on the use of albumin-containing fluids during fluid resuscitation of critically ill patients, as subsequent studies have not found significant advantages with the use of albumin over crystalloids (Perel *et al*. 2013).

Septic patients

The trend towards improved survival after albumin administration in septic patients raises the possibility that albumin might be beneficial in this population. A meta-analysis comparing the use of albumin versus crystalloids for fluid resuscitation of human patients with severe sepsis or septic shock demonstrated a reduction in 90-day mortality in patients with septic shock that were administered albumin (Xu *et al*. 2014). However, another meta-analysis was unable to demonstrate any advantage of using albumin-containing fluids for resuscitation of patients with sepsis of any severity (Jiang *et al*. 2014).

Unfortunately, because albumin is so much more expensive than crystalloids, it can be difficult to justify its use as a first-line resuscitative fluid. However, albumin supplementation might improve outcome in septic patients when used as an adjunct to standard resuscitative therapy. Current Surviving Sepsis Campaign Guidelines recommend crystalloids as the initial fluid choice in the resuscitation of sepsis and septic shock, but advise addition of albumin to the treatment protocol for patients who persistently require high-volume crystalloid therapy to maintain adequate mean arterial pressure (Dellinger *et al*. 2013).

Acute lung injury and acute respiratory distress syndrome

Hypoproteinemia is one of the strongest independent predictors for the development of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) in the critically ill, and several studies have focused on the benefit of albumin therapy in this subset of patients. One such study investigated the use of furosemide and albumin in patients with ALI or ARDS. Decreased morbidity and fewer days of mechanical ventilation occurred in hypoalbuminemic patients who received a 5-day standardized regimen of 25% albumin and furosemide. The authors concluded that albumin and furosemide therapy decreases pulmonary edema and improves fluid balance, oxygenation, and hemodynamics in patients with ALI (Martin *et al*. 2002). A follow-up study was conducted comparing the administration of furosemide and albumin to furosemide therapy alone. Combination therapy was more effective as patients receiving albumin had greater increases in oxygenation and serum protein concentrations (Martin *et al*. 2005). Improvement in overall mortality has not been demonstrated at this stage, but emerging trends suggest that albumin therapy might be beneficial in patients with ALI or ARDS (Martin *et al*. 2005; Calfee and Matthay 2007).

Current human recommendations

Although promising new research is being generated, the controversy regarding albumin transfusion in human medicine

continues. Albumin is not currently recommended as a standard resuscitation fluid for all patients as no clear benefit has been demonstrated when used in this capacity. Additionally, existing studies do not clearly demonstrate a decrease in morbidity and mortality associated with albumin supplementation in non-resuscitative situations (i.e., as maintenance fluids), and the cost of therapy is significantly higher when compared to synthetic colloids. Serious adverse effects are rare in humans receiving albumin and occur with an incidence of 1.29 per 10^6 doses (Vincent 2003). Regardless, data garnered from current literature is inadequate to justify routine administration of albumin to all hypoalbuminemic critically ill patients. However, the use of albumin transfusion might be advantageous in specific patient populations and is generally considered a reasonable adjunct to standard therapy.

Indications for albumin therapy in veterinary patients

Administration of albumin-containing solutions is not warranted for all critically ill patients and should be used conservatively in hypoalbuminemic patients. A niche population of animals might benefit from albumin therapy, but each patient must be considered individually prior to transfusion. Current research suggests that albumin supplementation could be considered in hypoalbuminemic dogs with serum albumin concentrations <2.0 g/dL (20 g/L). Septic patients or those with vasculitis, systemic inflammatory response syndrome (SIRS), or edematous manifestations of disease might also benefit from albumin therapy (Mathews and Barry 2005). Despite the potential benefits associated with therapy, note that critical patients with ongoing refractory protein loss (e.g., protein losing enteropathy or nephropathy [PLE/PLN]) might quickly lose any albumin transfused (Mathews 2008). Likewise, albumin products are not appropriate for routine fluid resuscitation and should not be used to increase serum albumin concentrations >2.0–2.5 g/dL (20–25 g/L) so as not to suppress endogenous albumin production (Barton 2005; Mathews 2008). Albumin transfusion can be considered as an adjunct to standard therapeutics and might improve global perfusion and oxygen delivery in hypoproteinemic patients.

Albumin supplementation in small animals

In veterinary patients, intravenous albumin can be provided in three forms: species-specific plasma, human serum albumin (HSA), or canine-specific albumin (CSA). While synthetic colloid administration is effective for support of COP, hydroxyethyl starches do not possess the same physiologic benefits of albumin and have associated risks such as coagulopathies and acute kidney injury (Myburgh *et al*. 2012). The use of species-specific plasma is generally not recommended as a method for resolution of hypoalbuminemia due to the large volume of product required, associated cost of administration, and added risk of transfusion-associated complications. In order to increase the plasma albumin concentration by 0.5 g/dL (5 g/L) in a hypoalbuminemic dog, a minimum dose of 22.5 mL/kg of plasma is needed (Throop *et al*. 2004).

Human serum albumin in canine patients

The body of literature describing the use of HSA for transfusion in veterinary patients is limited, but several studies documenting the use of HSA transfusion in healthy and critically ill veterinary patients are available (Table 7.2). Early studies focused on transfusion of 25% HSA to combat conditions including sepsis, peritonitis, trauma, neoplasia, pancreatitis, gastric dilation volvulus, hepatic disease, PLE/PLN, gastric ulceration, hypotension, and hypoalbuminemia (Figure 7.3). In these studies, serum albumin concentrations and total protein measurements were up to 45% higher post-transfusion (or at discharge) in most patients. Only subjects in the PLE/PLN group showed decline in albumin levels post-transfusion, indicating that HSA transfusion offers only transient benefit in animals suffering from ongoing protein loss. Almost no adverse effects were noted in transfused animals and the authors concluded that HSA can be safely administered to select critically ill animals and might improve outcome (Chan *et al*. 2004; Mathews and Barry 2005; Mathews 2008).

More recent studies have evaluated the application of 5–10% HSA transfusion in critically ill patients with the same conditions outlined above. Potential benefits of transfusion with more dilute HSA include provision of a more physiologic approach to albumin supplementation, decreased risk of volume overload, and development of fewer transfusion reactions. As with administration of 25% HSA solutions, significant increases in serum albumin levels were achieved with transfusion of 5% and 10% solutions. No adverse effects were reported when an isotonic (5% HSA) solution was transfused. When administered 10% HSA, 6.8% of patients suffered severe complication peri-infusion (Trow *et al*. 2008; Vigano *et al*. 2010). Importantly, achievement of a serum albumin level of 2.0 g/dL (20 g/L) with 5% and 10% HSA administration appears to take up to 7–10 days compared to 1–2 days when 25% HSA solutions are administered.

Although these studies support the use of HSA transfusion as a safe and useful intervention in critically ill hypoalbuminemic animals, most research describing HSA use in veterinary patients is retrospective in nature and lacks patient follow-up. Caution should be used when interpreting available data and drawing practical conclusions.

Adverse effects in dogs

Significant concerns have been raised regarding adverse effects associated with the administration of a human protein to companion animals. As with any xenoprotein transfusion, there is an inherent risk of hypersensitivity after initial or repeated exposures. Several studies have demonstrated that the administration of HSA to healthy dogs results in non-immune anaphylaxis and type III hypersensitivity reactions (Cohn *et al*. 2007; Francis *et al*. 2007; Martin *et al*. 2008). Clinical signs of acute reactions during HSA transfusion include facial edema, tachypnea, vomiting, and fever. In some cases, manifestations of immune-mediated hypersensitivity appear 10 days to 2 months after transfusion and

Table 7.2 Albumin use in veterinary patients.

Condition	Concentration	Dose
Hypotension	25% HSA	500 mg/kg to 1 g/kg slow bolus followed by 25–425 mg/kg/hour over 4–72 hours (Mathews 2008)
Hypoalbuminemia	25% HSA	0.1–1.7 mL/kg/hour over 4–72 hours Maximum volume administered 25 mL/kg (Mathews 2008)
Critically ill population of dogs: sepsis, peritonitis, trauma, neoplasia, pancreatitis, gastric ulceration	25% HSA	Total dose of 380 mg/kg to 3.6 g/kg (Chan *et al*. 2004)
Critically ill population of dogs: septic peritonitis, trauma, neoplasia, hepatic disease, gastric ulceration	25% HSA diluted to 10%	Total dose of 100 mg/kg to 6 g/kg (Trow *et al*. 2008)
Critically ill population of dogs and cats: GDV, peritonitis, nephropathy, pancreatitis, hepatic disease, PLE*	25% HSA diluted to 5%	100 mg/kg/hour for 10 hours, administered daily until serum albumin reached 2.0 g/dL (20 g/L) (Vigano *et al*. 2010)
PLE and PLN	25% HSA	Total dose of 200 mg/kg to 4.2 g/kg (Mathews and Barry 2005)
Liver disease*	25% HSA	Total dose of 350 mg/kg to 6.3 g/kg (Mathews and Barry 2005)
GDV	25% HSA	Total dose of 475 mg/kg to 1.7 g/kg (Mathews and Barry 2005)
Septic peritonitis, hypoalbuminemia	5% CSA	Total dose of 800–884 mg/kg over 6 hours (Craft and Powell 2012)

GDV, gastric dilation volvulus; PLE, protein losing enteropathy; PLN, protein losing nephropathy; HSA, human serum albumin; CSA, canine-specific albumin.
*Indicates studies that include cats, other studies include dogs only.

include polyarthritis, dermatitis, and vasculitis. Delayed (type III) hypersensitivity reactions after HSA transfusion in two healthy dogs even resulted in death (Francis *et al*. 2007). As a result of these studies, it is not recommended to administer HSA to healthy animals (Cohn *et al*. 2007).

Despite several documented and, even lethal, hypersensitivity reactions in healthy dogs administered HSA, studies document HSA transfusions in systemically ill veterinary patients occurring without incident (Chan *et al*. 2004; Matthews and Barry 2005).The dichotomy likely stems from the fact that immunosuppression is an integral component of critical disease. Every patient considered for albumin therapy in a clinical setting is ill and immunocompromised to some extent. It has been hypothesized that critically ill patients suffer fewer adverse effects after albumin transfusion because they are unable to mount an appropriate response against infusion of a foreign protein (Francis *et al*. 2007; Martin *et al*. 2008). While it is indisputable that sick animals tolerate xenotransfusion better than their healthy counterparts, caution is still warranted when considering HSA transfusion. Development of lesions consistent with type III hypersensitivity in two critically ill dogs after treatment with 25% HSA has been documented. Reactions were self-limiting in both dogs that were not seriously compromised (Powell *et al*. 2013). Altogether, HSA transfusion might provide significant benefit to critically ill veterinary patients, but concerning risks exist and should be considered prior to administration. Development of anti-HSA antibodies has been documented after albumin transfusion in both healthy and sick dogs (Martin *et al*. 2008). Although some studies document multiple HSA transfusions without complication, repeat infusion of HSA to canine patients more than 7 days after initial transfusion is not advised (Trow *et al*. 2008).

Available products

Human serum albumin products are created from ultrafiltered pooled plasma and are composed of highly soluble globular proteins (Figure 7.4). Solutions are available as 5% and 25% concentrations (Grifols Therapeutics Inc., Clayton, NC; CSL Plasma, Boca Raton, FL). 5% HSA is isotonic and has a COP of 20 mmHg, while 25% HSA is hypertonic with a COP of 200 mmHg. Most HSA products are stable for 3 years if stored at room temperature (Figure 7.5). Temperatures below freezing and above 30°C (86°F) damage the product and render it ineffective. Once

Figure 7.3 Albumin transfusions can be advantageous to treat a myriad of diseases. This patient received an albumin transfusion, in addition to standard therapies, for the management of septic peritonitis.

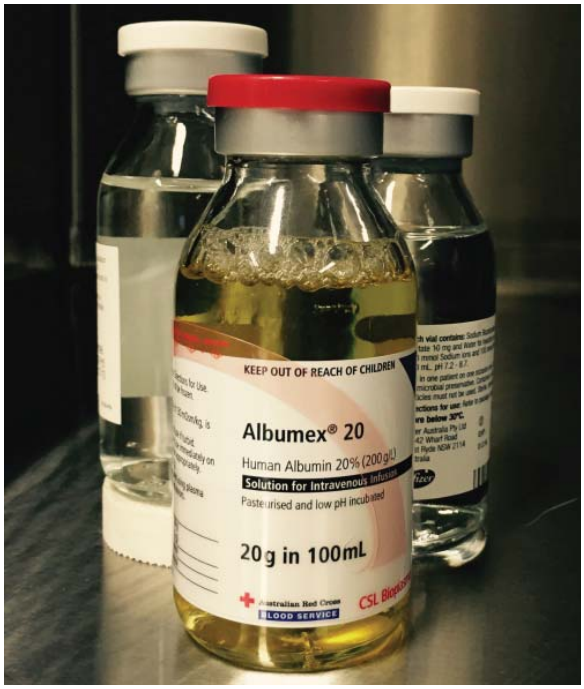

Figure 7.4 Human serum albumin has historically been used for transfusion in veterinary patients, but species-specific albumin products are becoming more widely available (i.e., canine, bovine, and equine albumin).

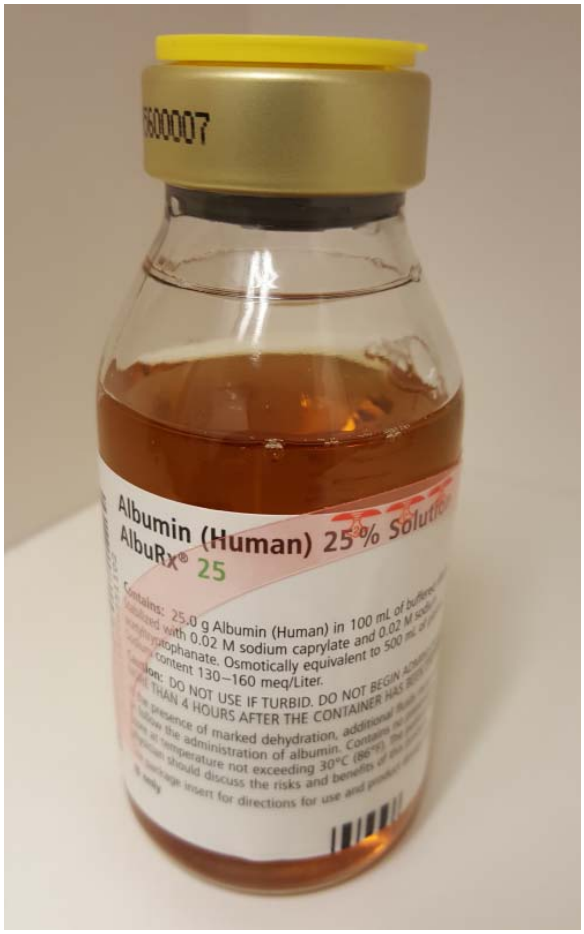

Figure 7.5 A bottle of 25% human serum albumin (AlbuRx®, CSL Behring LLC, Kankakee, IL) can be stored at room temperature. (Image provided by Kenichiro Yagi, BS, RVT, VTS (ECC, SAIM).)

opened, albumin vials should be used or discarded after 24 hours (Mazzaferro *et al*. 2002).

Careful consideration of fluid balance and patient comorbidity is imperative when choosing an appropriate concentration: administration of 25% HSA will increase intravascular volume to four to five times that of the volume infused (Mazzaferro *et al*. 2002). In normovolemic hypoproteinemic patients, an iso-oncotic 5% albumin infusion might be considered to decrease the risks associated with acute intravascular volume expansion. However, there is some evidence that treatment with 5% HSA does not confer the same anti-inflammatory benefits noted after transfusion of 25% HSA. An experimental cell model demonstrates significant differences in neutrophil behavior after incubation in lactated Ringer's solution (LRS), 5% HSA, and 25% HSA: inflammatory cytokine activation and oxidative burst are greater for neutrophils incubated with LRS or 5% HSA compared to those incubated in 25% HSA (Rhee *et al*. 2000).

Table 7.3 Example of a log used for albumin product transfusion.

Transfusion product						
Product volume						
Total volume of transfusion						
Start time						
Time	RR	HR	Temperature	DVM notified if changes	Rate of infusion	Volume infused
Pre-transfusion *Start at ¼ full transfusion rate						
15 minutes after start *If no change in vital signs, increase to ½ full transfusion rate						
30 minutes after start *If no change in vital signs, increase to ¾ full transfusion rate						
45 minutes after start *If no change in vital signs, increase to full transfusion rate						
60 minutes after start						
90 minutes after start						
150 minutes after start						
210 minutes after start						
270 minutes after start						

RR, respiratory rate; HR, heart rate; DVM, veterinarian.

Dosing protocols for veterinary patients

The recommended goal for albumin supplementation in veterinary patients varies, but most clinicians target a serum albumin concentration of 2.0 g/dL (20 g/L) (Rudloff and Kirby 1998; Mazzaferro *et al*. 2002). Several dosing strategies exist and no standard guidelines have been established (Table 7.2). Some clinicians advocate calculating a patient's albumin deficit and replacing it over 6–72 hours (Box 7.3). Unfortunately, the kinetics of HSA in small animals are not well described and the half-life of transfused products is not known at this time.

Alternatively, a recommended dose of 25% HSA has been extrapolated from human studies at 2 mL/kg over 2 hours, followed by 0.1–0.3 mL/kg/hour thereafter. The total dose administered should be 2.5–5 mL/kg of 25% HSA and a daily dose of 2 g/kg should not be exceeded (Powell 2008). A retrospective study documented the administration of 5% HSA to hospitalized dogs at a rate of 2 mL/kg/hour over 10 hours for several days. Daily transfusion was continued until a serum albumin of 2.0 g/dL (20 g/L) was obtained. This dosing regimen was designed to slowly increase albumin concentrations in a more physiologic manner and to decrease the risk of fluid overload. The median number of days required for serum albumin concentrations to reach 2.0 g/dL (20 g/L) was 4. Severe hypersensitivity reactions were not documented in any patient record and all dogs received their entire transfusion without incident (Vigano *et al*. 2010).

Box 7.3 CALCULATION OF ALBUMIN DEFICIT

$$\text{Albumin deficit (g)} = 10 \times (\text{serum albumin concentration desired} - \text{current serum albumin}) \times \text{body weight (kg)}$$

Human serum albumin administration in feline patients

There is limited information regarding the use of albumin transfusion in cats. An early retrospective study included two cats in a population of 66 critically ill animals receiving 25% HSA, with

one cat dying within 18 hours of transfusion (Mathews and Barry 2005). More recently, another retrospective study documented HSA use in 170 hypoalbuminemic cats. A 5% HSA infusion was administered at a rate of 2 mL/kg/hour for 10 hours daily until serum albumin concentrations reached 2.0 g/dL (20 g/L). The cats received HSA transfusions for a median of 4 days and 123 cats survived to discharge. Adverse effects of HSA transfusion were reportedly mild, with diarrhea, tremors, or hyperthermia occurring in 36% of cats (Vigano *et al*. 2010). Although these results are encouraging, albumin transfusion in feline patients should be considered cautiously until further studies are conducted. No feline-specific albumin products are available at this time.

Canine-specific albumin

Commercially produced CSA has recently become available and has created a new option for albumin supplementation in canine patients. Theoretically, this product is non-antigenic in dogs, so repeat transfusions should not be problematic. CSA is labelled for the treatment of hypovolemic shock or hypoalbuminemia regardless of the etiology, but little data exist evaluating its efficacy. A prospective, randomized study included 14 dogs with septic peritonitis that received 5% CSA within 24 hours of surgical intervention. CSA transfusion resulted in an increase in serum albumin, COP, and blood pressure within 2 hours of administration. One dog experienced tachypnea during the transfusion, but it could not be determined if this was secondary to a transfusion reaction, aspiration pneumonia, or multiple organ dysfunction syndrome. No other dogs exhibited adverse effects associated with CSA administration. Follow-up occurred by phone 6 weeks post transfusion and no evidence of delayed hypersensitivity was reported (Craft and Powell 2012). Although this group of dogs tolerated CSA well, it is again unclear whether CSA therapy resulted in decreased morbidity or mortality. Furthermore, serum albumin concentrations were only measured for 24 hours after the transfusion, so the long-term impact of CSA transfusion remains unknown.

Available products

CSA is manufactured from plasma collected via plasmapheresis, but is only marketed in a lyophilized form. Each vial of CSA contains 5 grams of albumin, which is roughly equivalent to the amount present in 250 mL of canine plasma (Animal Blood Resources International, Stockbridge, MI; Equitech-Bio Inc., Kerrville, TX). Lyophilized CSA should be reconstituted with 0.9% saline or 5% dextrose in water and gently swirled until all powder is rehydrated. The vial can be warmed in a 37°C water bath to speed rehydration, but should not be shaken. CSA can be stored for up to 24 months prior to reconstitution, but once it is rehydrated it should be used or discarded within 24 hours. Recommendations differ by manufacturer, with the most conservative recommendations advising use of CSA within 6 hours of reconstitution. CSA should be refrigerated to decrease the risk of bacterial growth (Barton 2005). Once rehydrated, CSA can be administered as a 5%, 10%, or 16% solution; a 5% concentration solution is iso-oncotic, similar to 5% HSA. Because administration of hyper-oncotic solutions carries a risk of volume overload in certain patients, careful monitoring and judicious patient selection are vital for successful and safe CSA therapy.

Dosing recommendations

According to one manufacturer of CSA, a 450 mg/kg dose is required to raise the serum albumin concentration by 0.5 g/dL (5 g/L) (Animal Blood Resources International 2011). A maximum dosage of canine albumin per day has not been determined. Elimination of exogenously administered canine albumin is estimated to occur within 20–24 days and the half-life is 8–10 days (Animal Blood Resources International 2011).

Bovine and equine serum albumin

Bovine and equine serum albumin (25%) products are also available (Animal Blood Resources International, Stockbridge, MI; Equitech-Bio Inc., Kerrville, TX), but are highly immunogenic to dogs. Because administration results in immediate and/or delayed hypersensitivity reactions, use in small animals is not recommended (Mazzaferro *et al*. 2002).

General guidelines for albumin administration

Albumin products (canine and human) can be administered through a peripheral or central catheter. Recommendations for filter usage vary with the product, but aseptic technique is imperative. If the solution is contained in a bottle, venting of the delivery set is recommended for ease of administration. Hypodermic needles are not appropriate for this purpose and can predispose to contamination. Albumin solutions should not be administered if they appear turbid or if sediment is present. Albumin solutions can be administered alone or in conjunction with other parenteral products such as whole blood, plasma, saline, glucose, or crystalloid solutions with standard electrolyte additives. Albumin transfusions should not be mixed with protein hydrolysates, amino acid solutions, or solutions containing alcohol (Mathews 2008). Because specific recommendations for administration vary by product, manufacturer guidelines should always be consulted prior to transfusion.

Regardless of the dose or product chosen, albumin transfusions should be administered slowly and recipients monitored carefully. Although transfusing with species-specific albumin reduces risks of immunologic complication, vascular overload can still occur if a hyper-oncotic solution is rapidly administered. Standard transfusion guidelines should be followed. The transfusion should start slowly at a rate of 0.25 mL/kg/hour for 15 minutes. Heart rate, respiratory rate, blood pressure, and temperature should be continually monitored throughout the transfusion (Table 7.3). If the transfusion is well tolerated, the administration rate can be gradually increased every 30–60 minutes until a predetermined maximum rate is reached. If any signs of allergic reaction develop (Table 7.4), the transfusion should be discontinued immediately and diphenhydramine 2 mg/kg IM should be administered (Mathews 2008). In cases of anaphylaxis secondary to the transfusion, standard therapy with epinephrine might be required.

Table 7.4 Clinical manifestations of hypersensitivity reactions secondary to albumin product administration.

Immediate (type I) (minutes)	Delayed (type III) (days to weeks)
Tachycardia	Vasculitis
Pyrexia	Polyarthritis
Tachypnea	Dermatitis/cutaneous lesions
Hypotension	Glomerulonephritis/kidney failure
Coagulopathy	Thrombocytopenia
Cardiac or respiratory arrest	Hemolysis
Cardiac arrhythmias	Coagulopathy
Urticaria	
Pruritus	
Conjunctival injection	
Peripheral edema	
Pulmonary edema	
Laryngeal edema or stridor	
Bronchospasm	
Seizures	
Vomiting	
Diarrhea	
Tremors	
Syncope/collapse	

Alternatives to albumin transfusions

Nutritional support

The importance of early and reliable nutritional support in critically ill patients cannot be overemphasized. Without question, the most important factor in enabling albumin synthesis is adequate nutrition (Figure 7.6). Experimental studies show that an 18–24 hour fast can decrease albumin synthesis by 50%. Conversely, infusion of a complete amino acid solution stimulates albumin synthesis within minutes. Once nutrient supply is adequate, protein concentrations gradually increase after 16–18 hours (Mazzaferro *et al*. 2002). Although albumin transfusion might be beneficial in certain patient populations, it does not take the place of appropriate nutritional support.

Plasma transfusion

Plasma products such as fresh frozen plasma (FFP), frozen plasma, cryopoor plasma, or liquid (refrigerated) plasma contain albumin, but transfusion is not generally considered reasonable for albumin replacement because large plasma volumes are required to be effective. For medium or large-breed dogs, FFP transfusion can be prohibitive due to cost and resources. However, plasma transfusion might be reasonable in small dogs or cats as a means of albumin supplementation. A dose of 22.5 mL/kg will increase serum albumin by 0.5 g/dL (5 g/L), depending on concurrent albumin losses (Doweiko and Nompleggi 1991). Although feasible, note that large volume plasma transfusion has an added risk of circulatory (volume) overload and immunologic complications (Rudloff and Kirby 1998). More information regarding plasma products can be found elsewhere in this textbook (see Chapter 4).

Figure 7.6 A dog with septic peritonitis has a nasogastric feeding tube in place to provide enteral nutrition, an important adjuvant therapy in hypoproteinemic patients. (Image courtesy of Marie K. Holowaychuk, DVM, DACVECC).

Human intravenous immunoglobulin

Human intravenous immunoglobulin (hIVIG) possesses many immunomodulating properties and has been used for the management of immune-mediated conditions in humans for decades (Scott-Moncreiff *et al*. 1995; Scott-Moncreiff and Regan 1997; Emmi and Chiarini 2002). Immunoglobulin for intravenous administration is prepared from fastidiously purified immunoglobulin collected from pooled human plasma. Donors are screened for infectious disease and preparations are filtered to ensure no aggregates, kinins, plasmin, or kalikrein activators are present in the finished product. Human immunoglobulin formulations contain over 90% biologically active IgG, as well as trace amounts of IgA, IgM, CD4, CD8, and leukocyte antigen molecules. Some commercially available products have low pH ranges to decrease risk of bacterial colonization and prevent aggregation (Mackay *et al*. 2001).

Immunomodulation

Transfusion of hIVIG has been used to confer passive immunity to deficient humans since the 1940s. Over time, hIVIG therapy has shown value beyond antibody replacement, as a mediator of various inflammatory processes. Although not well established, it is widely postulated that hIVIG exerts immunomodulatory

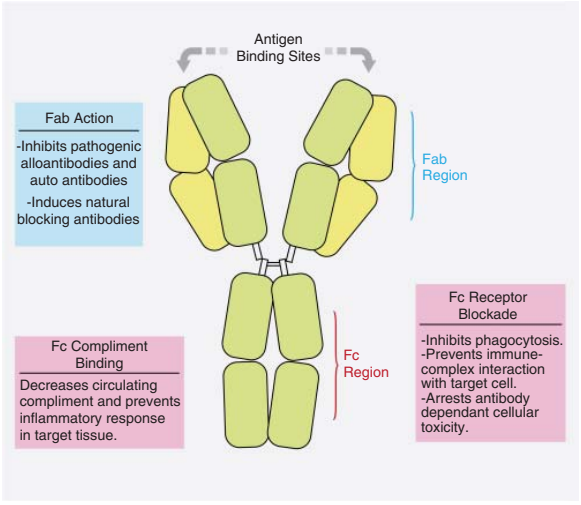

Figure 7.7 Anti-inflammatory and immunomodulatory functions of human intravenous immunoglobulin. (Illustration courtesy of Brandon Mugar.)

action via blockage of Fc receptors, elimination of pathogenic autoantibodies, modulation of cytokine synthesis, inhibition of complement, and mediation of Fas–Fas ligand (FasL) interactions (Knezevic-Maramica and Kruskall 2003; Vaccaro *et al*. 2005). Additionally, hIVIG mediates the immune system by elimination of pathogenic autoantibodies (Figure 7.7). Donor antibody present in hIVIG is postulated to bind directly to abnormal host antibodies and stimulate their removal (Vaccaro *et al*. 2005; Boros *et al*. 2005).

Fc membrane receptors are proteins found on the cell membranes of macrophages, neutrophils, natural killer cells, B cells, eosinophils, platelets, and mast cells (Emmi and Chiarini 2002). In humans, Fc receptors bind to antibody-antigen complexes and stimulate antibody-mediated phagocytosis (Figure 7.8). Transfused hIVIG also binds inflammatory cells; once bound, hIVIG blocks macrophage Fc receptors, inhibits phagocytosis, and truncates tissue damage (Regan *et al*. 1998).

Inflammatory cytokines are also affected by hIVIG infusion. Research shows that stimulated T cells produce significantly fewer cytokines (IL2, IFN-γ, TNFα) in the presence of hIVIG

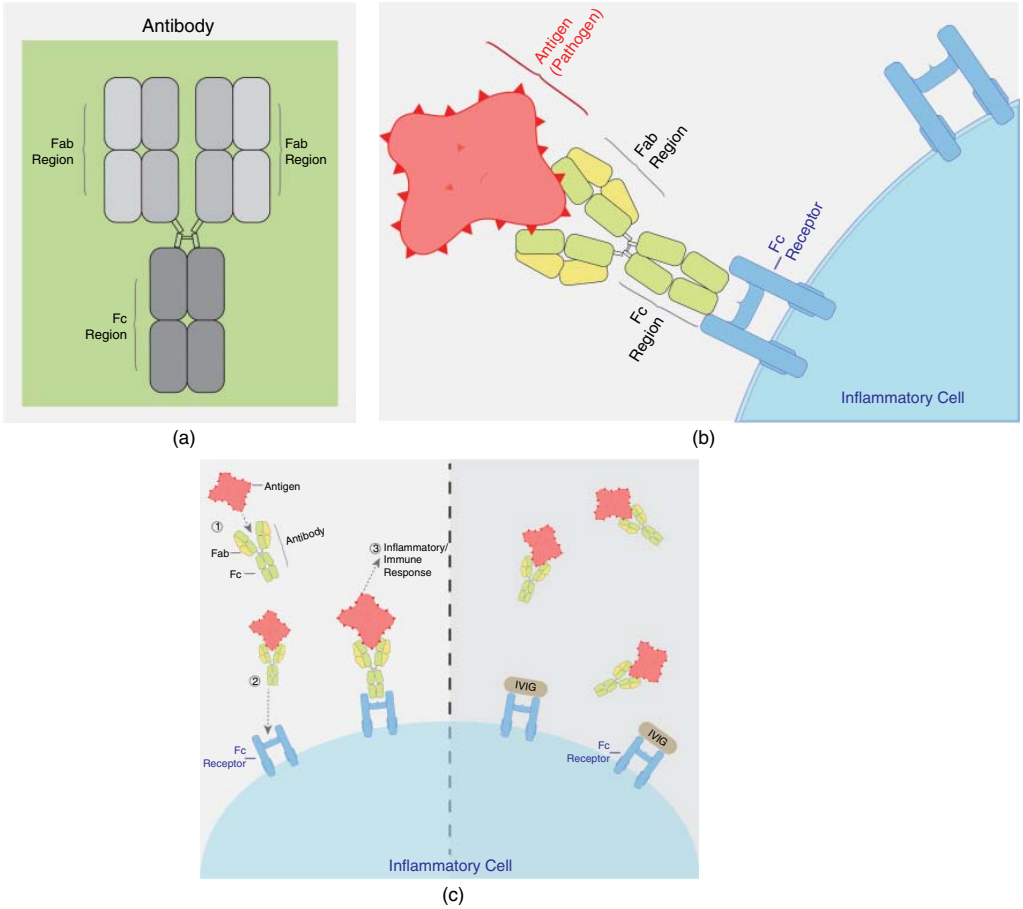

Figure 7.8 a. Each antibody is made up of antigen binding fragment regions (Fab) and crystallizable fragment regions (Fc). b. Antigens bind to Fab regions of antibodies and form antibody–antigen complexes. Antibody Fc regions bind to Fc receptors located on macrophages, neutrophils, platelets, mast cells, natural killer cells, and B cells. Once formed, antibody–antigen complexes bind to Fc receptors and stimulate an immune response. c. Intravenous immunoglobulin saturates Fc receptors on inflammatory cells and blocks receptor mediated immune response. (Illustrations courtesy of Brandon Mugar.)

(Emmi and Chiarini 2002). Down-regulation of cytokine activity decreases inflammation and resulting cellular damage. Intravenous immunoglobulin further moderates immune response via inhibition of complement. Generally speaking, complement proteins mediate antibody response to antigenic stimulation. More specifically, IgG-antigen complexes form, then bind to circulating complement and initiate pathways that ultimately end in cell death. Human immunoglobulin inhibits complement dependent injury by blocking active complement fragments (Emmi and Chiarini 2002).

Finally, hIVIG infusion is believed to moderate the cell surface receptor Fas and Fas ligand (FasL) interaction. The FasL precipitates cellular death via transduction of apoptotic signals to epidermal cells (keratinocytes). When present, hIVIG molecules block Fas–FasL complex formation and support keratinocyte viability. Fas–FasL complex blockage is considered the major mechanism behind successful therapy with hIVIG in dermatologic conditions, as it breaks the cycle of ongoing keratinocyte apoptosis (Knezevic-Maramica and Kruskall 2003; Trotman *et al*. 2006).

Use in human medicine

There are few US Federal Drug Administration (USFDA) approved uses for hIVIG. Currently, hIVIG is labeled for the treatment of Kawasaki disease, allogenic bone marrow transplantation, chronic lymphocytic leukemia, common variable immunodeficiency, pediatric human immunodeficiency virus (HIV), and symptomatic primary immunodeficiency (Foster *et al*. 2010). Despite USFDA limitations, hIVIG therapy is used for an expanding list of conditions including dilated cardiomyopathy, peripheral neuropathy, sepsis, and autoimmune hemolytic anemia (Stella *et al*. 2001; Alejandria *et al*. 2002; Foster *et al*. 2010). More than half of all prescribed hIVIG is used to manage the off-label conditions of toxic epidermal necrolysis (TEN), Guillain–Barre syndrome, and necrotizing fasciitis (De Albuquerque *et al*. 2000; Prins *et al*. 2003; Foster *et al*. 2010). A multicenter study compared efficacy and risk associated with labeled and off-label administration of hIVIG to humans and found no significant differences in positive outcome or adverse effects between populations (Chen *et al*. 2000). The use of hIVIG for human patients is rapidly growing and expanding into exciting new directions. The newest studies focus on therapy for ischemic brain injury and Alzheimer's disease, and might offer new options for the treatment of many other serious diseases (Counts and Lahiri 2014; Widiapradja *et al*. 2014).

Uses in veterinary medicine

Anecdotal accounts of successful hIVIG therapy in companion animals have been circulating for decades. Efficacy in human medicine makes hIVIG an attractive choice for the management of immune-mediated disease in veterinary patients, but no consensus exists regarding the indications, dose, or safety of hIVIG infusion in companion animals. At this time, data regarding hIVIG use in veterinary patients is limited to patients with immune-mediated hemolytic anemia (IMHA), immune-mediated thrombocytopenia (ITP), Evans syndrome (ES), cutaneous drug reactions, pemphigus foliaceus (PF), sudden acquired retinal degeneration syndrome (SARDS), and myasthenia gravis (MG) (Table 7.5).

Immune-mediated hemolytic anemia

Application of hIVIG use in veterinary patients was first demonstrated in dogs with IMHA (Kellerman and Bruyette 1997; Scott-Moncrieff and Regan 1997). Classically, glucocorticoid therapy is the mainstay of treatment for IMHA and can be successful as a monotherapy. However, in many cases, additional immunosuppressive medications are necessary for disease control. Cyclosporine, cyclophosphamide, and azathioprine are often successful adjuncts to glucocorticoid therapy, but can take days to weeks to become effective (Rozanski *et al*. 2002; Whelan *et al*. 2009). In some IMHA patients, this time lag allows for a precipitous decline and contributes significantly to mortality. Because circulating hIVIG immediately blocks Fc receptors, an infusion is thought to result in rapid immunosuppression. Temporary control of autoimmune dysfunction by hIVIG might stabilize critical IMHA patients and allow appropriate time for long-term immunosuppressive therapy to become effective (Gerber *et al*. 2002; Whelan *et al*. 2009).

Several retrospective studies have been conducted over the past 20 years, but no definitive evidence exists to support the benefit of hIVIG administration in veterinary patients with IMHA. Furthermore, few prospective studies exist evaluating the use of hIVIG in animals with IMHA. The use of hIVIG infusion in dogs not responsive to conventional IMHA therapy was first described in the 1990s (Scott-Moncrieff *et al*. 1995). Rapid improvement was initially noted after administration of hIVIG, but all dogs quickly relapsed. The authors concluded that hIVIG might be useful as a temporary immunosuppressive agent and allow time for traditional therapies to become effective. Unfortunately, the immunosuppressive effects of the hIVIG and other concurrently administered agents could not be separated and hIVIG therapy could not be recommended without further investigation.

More recently, a prospective, blinded, randomized clinical trial was performed in 28 dogs with IMHA (Whelan *et al*. 2009). Subjects were randomly assigned to receive multiple doses of hIVIG or placebo for 3 consecutive days; after the first 3 days, all dogs received glucocorticoid therapy for 2 weeks and no additional immunosuppressive agents were administered during treatment. Upon completion of the study, no significant difference was noted in length of hospitalization, survival time, or number of blood transfusions required for patient stabilization. Investigators conceded that it was difficult to draw meaningful conclusion from such a small study group and were unsure if hIVIG therapy would result in significantly different outcomes in a larger patient population. Regardless, the authors surmised that if a true difference was present, it was not significant enough to justify the additional cost of hIVIG therapy in IMHA patients. Certainly, larger clinical trials are required to determine if hIVIG has a place in the routine management of canine IMHA.

Immune-mediated thrombocytopenia

As with IMHA, immunosuppressive therapy is the cornerstone of ITP management in veterinary patients. Once glucocorticoid

Table 7.5 Human intravenous immunoglobulin use in veterinary patients.

Condition	Study design	Animals	Adverse effects	Dose
IMHA	Blinded, randomized, controlled clinical trial (Whelan *et al*. 2009)	28 dogs	Swelling at catheter site (7%) Volume overload (3.5%)	0.5 g/kg over 6 hours for 3 consecutive days
ITP	Case series (Bianco *et al*. 2007, 2009)	5 dogs	None (followed over 6 months)	0.28–0.76 g/kg of a 5% solution over 6 hours once 0.5 g/kg of a 6% solution over 6 hours once
Evans syndrome	Case report (Bianco and Hardy 2009)	1 dog	None	1.3 g/kg of a 5% solution over 8 hours once
Cutaneous drug reactions	Cases reports (Trotman *et al*. 2006; Byrne and Giger 2002)	2 dogs 1 kitten	None	1 g/kg of a 6% solution over 4 hours for 2 consecutive days
SJS	Case report (Nutall and Malham 2004)	1 dog	None	0.5 g/kg of a 5% solution over 7 hours once
PF	Case report (Rahilly *et al*. 2006)	1 dog	None	0.5 g/kg of a 10% solution over 4 hours for 4 days, followed by the same dose 3 weeks after discharge Two subsequent doses 9 weeks post discharge, additional doses every 7 days on weeks 12, 22, 26, and 31
SARDS	Case series (Grozdanic *et al*. 2008)	8 dogs	None	0.5 g/kg of a 5% solution over 7 hours once
MG	Case series (Abelson *et al*. 2009)	3 dogs	None Erythema and anxiety during third transfusion; anaphylaxis during fourth transfusion	0.5 g/kg over 6 hours once 0.5 g/kg over 6 hours for 2 consecutive days Two additional does administered 12 and 17 days after discharge

IMHA, immune-mediated hemolytic anemia; ITP, immune-mediated thrombocytopenia; SJS, Steven–Johnson syndrome; PF, pemphigus foliaceous; SARDS, sudden acute retinal degeneration syndrome; MG, myasthenia gravis.

therapy is initiated, severe thrombocytopenia usually resolves within 1 week. If vincristine is added to the treatment protocol, improvement might occur within 5 days (Bianco and Hardy 2009). Unfortunately, before these agents become effective, it is common for hemorrhagic events to occur and impact mortality, especially if they occur in the central nervous system or lungs. Many clinicians advocate the use of hIVIG to rapidly and effectively increase platelet counts before traditional agents become effective. In human medicine, infusion of hIVIG maximizes patient recovery by decreasing the number of blood transfusions required for stabilization. Therefore, reduced time in hospital and fewer allocated resources should offset the cost of hIVIG transfusion (Darabi *et al*. 2006).

With the hope that similar successes could extend to veterinary patients, several canine studies were performed. A retrospective case series assessed outcome in five dogs with ITP administered one hIVIG infusion in conjunction with standard glucocorticoid therapy (Bianco *et al*. 2007). All dogs had severe ITP and were experiencing uncontrollable hemorrhage. Four of five dogs rapidly and significantly improved after hIVIG transfusion, with mean platelet counts increasing from 2.5×10^9/L (2.5×10^3/uL) to 62.7×10^9/L (62.7×10^3/uL) within 24 hours of hIVIG therapy. Responders to hIVIG did not require additional packed red blood cell (PRBC) transfusions after hIVIG infusion and no adverse effects of hIVIG transfusion were documented. Responders in this study were also discharged an average of 46 hours earlier compared to dogs in another report that were managed with vincristine and prednisone alone (Rozanski *et al*. 2002). Researchers determined that hIVIG infusion was well-tolerated, rapidly increased platelet counts, and led to resolution of clinical signs in most dogs presenting with ITP (Bianco *et al*. 2007). However, while preliminary results were promising, the retrospective design, lack of controls, and small study population limited broad recommendations for hIVIG administration in dogs with ITP.

Subsequently, a prospective, randomized, blinded, placebo-controlled study was conducted to analyze the use of hIVIG as a fast-acting intervention for the acute stages of primary ITP (Bianco *et al*. 2009). The use of standard corticosteroid therapy alone was compared to corticosteroid therapy in addition to one dose of hIVIG; no additional immunotherapeutics were allowed

until day 7, after which any immunosuppressive drug could be added at the attending clinician's discretion. Differences in platelet count recovery, transfusion requirements, hospitalization time, cost of patient care, and mortality were evaluated and results were compelling. Dogs receiving hIVIG exhibited recovery from thrombocytopenia ($>40\times10^9$/L [40×10^3/uL]) a median of 4 days before those in the placebo group. Additionally, the hIVIG dogs reached "complete resolution" platelet count $>160\times10^9$/L [160×10^3/uL]) a median of 5 days before the placebo group. Most significantly, dogs receiving hIVIG were discharged an average of 4 days earlier than those treated with steroids alone and there was no difference in overall cost between the groups. No adverse effects of hIVIG infusion were recorded in any dogs and although platelet function was not specifically analyzed, no evidence of bleeding occurred once platelet counts reached 40×10^9/L (40×10^3/uL). Ultimately, these authors concluded that a single infusion of hIVIG administered within 24 hours of institution of steroid therapy is associated with significant reduction in time to resolution of thrombocytopenia and did not increase the cost of therapy in dogs with primary ITP (Bianco *et al*. 2009). Although further research should be conducted to fully define the role of hIVIG for the treatment of ITP, existing evidence suggests that hIVIG is valuable for the initial stabilization of ITP, especially in cases complicated by active hemorrhage.

Evans syndrome

ES is an autoimmune disorder involving concurrent IMHA and ITP. Given that hIVIG therapy appears valuable for the treatment of ITP, but equivocal for the management of IMHA, application for hIVIG therapy in ES remains questionable. A case report described the use of leflunomide and a single dose of hIVIG for management of ES in a dog with pre-existing diabetes mellitus. After administration of the hIVIG infusion, the platelet count increased to normal within 24 hours, but the PCV remained low and three PRBC transfusions were required prior to discharge (Bianco and Hardy 2009). The findings in this report parallel previous observation that benefits of hIVIG for managing IMHA are questionable and transient at best, but can be advantageous for the treatment of thrombocytopenia in immune-mediated disease.

Cutaneous disease

Conditions such as erythema multiforme (EM), TEN, and Stevens-Johnson syndrome (SJS) cause full thickness epidermal detachment, as well as systemic compromise and are associated with high mortality. Standard immunosuppressive therapy is not effective for the management of these syndromes in human or veterinary patients (Jolles *et al*. 1998; Trotman *et al*. 2006). Although not a USFDA approved use for hIVIG, transfusion is widely employed for the management of cutaneous immune disease in people. A retrospective study documents an 83% decrease in patient mortality when hIVIG infusion is added to standard treatment (Trent and Kerdel 2003). Likewise, a consensus statement recommends hIVIG transfusion for human patients with refractory autoimmune blistering cutaneous disease (Jolles *et al*. 1998). Currently, no controlled randomized trials have been performed evaluating hIVIG for dermatologic immunopathy, but success in human medicine has generated great interest in the use of hIVIG for cutaneous dysfunction in animals.

Canine Stevens-Johnson syndrome

A case report describes complete resolution of SJS after a single infusion of hIVIG in a dog (Nuttall and Malham 2004). This dog developed SJS after exposure to trimethoprim-potentiated sulfadiazine (TMS) and steadily declined despite standard therapy. Within 12 hours of hIVIG infusion, visible improvement in dermal lesions was seen and within 7 days all dermal lesions were fully healed. No adverse effects were noted secondary to the hIVIG transfusion.

Canine toxic epidermal necrolysis

Another case report describes hIVIG transfusion in two dogs with life-threatening necrotic dermatitis (Trotman *et al*. 2006). Each dog was treated with two infusions of hIVIG given 24 hours apart. Each dog received a total hIVIG dose of 2 g/kg in combination with broad-spectrum antimicrobials, analgesics, and IV fluid therapy. Both dogs experienced significant improvement in dermal and systemic symptoms within 72 hours of transfusion and no adverse effects of hIVIG transfusion were reported. The dogs were followed for 3 years after discharge and no evidence of relapse or delayed transfusion reactions was recorded.

Feline erythema multiforme

Almost no information exists regarding hIVIG use in cats, but a case report describes the successful treatment of EM in a recently vaccinated kitten with lesions refractory to steroids (Byrne and Giger 2002). The kitten received two hIVIG transfusions 24 hours apart; improvement in general health and dermal lesions occurred within 4 days of hIVIG infusion and the lesions mostly resolved within 8 days. Adverse reaction to hIVIG therapy was not noted and no signs of relapse were present upon recheck 8 weeks later.

Canine pemphigus foliaceus

Human IVIG therapy might also have benefit in management of dermal disease unrelated to drug reactions. PF is the most common canine immune-mediated cutaneous disease and has a high morbidity and mortality rate. Dogs with pemphigus have destruction of keratinocyte adhesions (desmosomes) and resultant blister and pustule formation (Mackay *et al*. 2001).

There is little research regarding the efficacy of hIVIG in the treatment of PF. A case report documents the successful use of hIVIG infusion to treat PF in a dog, initially in lieu of steroid therapy (Rahilly *et al*. 2006). Infusions of hIVIG were administered daily for 5 days and an additional hIVIG transfusion was prescribed 3 weeks later. Marked improvement was noted during and after the 5-day course of hIVIG, after which time, treatment with standard immunosuppressive steroids was started. The dog had a mild relapse 9 weeks after discharge when two additional hIVIG transfusions were given 24 hours apart. The dog was subsequently scheduled for maintenance therapy with hIVIG infusions delivered on weeks 12, 22, 26, and 31. The dog remained asymptomatic for at least 4 months after his final infusion, but was then lost to follow-up. No adverse effects related to the hIVIG infusions were noted, even after multiple infusions.

Sudden acquired retinal degeneration syndrome

SARDS is poorly defined in veterinary medicine but describes acute, painless blindness in dogs. Tissue analysis has demonstrated the presence of Ig-producing plasma cells in the retinas of SARDS patients, which ultimately cause immune-mediated blindness (Bellhorn *et al*. 1988; Keller *et al*. 2006). Canine SARDS has long been considered irreversible and does not respond to anti-inflammatory, antimicrobial, or immunosuppressive therapy. Immune-mediated retinopathy is similarly difficult to treat in humans, but blindness is partially responsive to treatment with hIVIG (Guy 1999).

The potential benefit of hIVIG therapy for canine SARDS patients was investigated in eight dogs that received two hIVIG infusions over 6 hours, 48 hours apart (Grozdanic *et al*. 2008). Although significant recovery in visual maze behavior and photoreceptor-mediated pupil response was noted, general vision was considered crude at best and likely absent in dim light. Although no adverse reactions were recorded, given the equivocal results and high cost of therapy, it is difficult to recommend hIVIG for the routine management of canine SARDS.

Myasthenia gravis

Acquired MG is an immune-mediated neuromuscular disorder caused by antibody-induced destruction of postsynaptic acetylcholine (Ach) receptors. Anticholinesterase inhibition is the mainstay of therapy, but efficacy depends on the number of receptors available for salvaged Ach to bind. This is problematic for patients suffering from MG, as circulating antibodies competitively bind to these same receptors. Immunosuppressive therapy is utilized in human patients with severe or refractory MG to decrease the cost of therapy and reduce mortality (Zinman *et al*. 2007; Abelson *et al*. 2009). Although hIVIG is not labeled for MG, infusion is anecdotally purported to be an effective treatment with rapid onset of action in humans (Zinman *et al*. 2007).

Standard treatment strategies for veterinary patients with MG include prednisone, cyclosporine, azathioprine, and mycophenolate mofetil (Abelson *et al*. 2009). Many of these agents take weeks to months to become effective and have significant side effects associated with administration. No prospective, randomized trials have been performed evaluating benefit of immunosuppressive therapy for companion animals with MG. However, a case series describes the use of hIVIG in two dogs with MG (Abelson *et al*. 2009). One dog received a single hIVIG transfusion without incident and the other dog received four hIVIG transfusions over several weeks and experienced an anaphylactic reaction during the final transfusion. The reaction resolved upon cessation of the transfusion and treatment with antihistamines and corticosteroids. Although both dogs exhibited improvement in muscle strength within 48 hours, both dogs suffered relapses within days to weeks. Clearly, the benefit of hIVIG administration in dogs with MG is debatable and cannot be recommended until larger, more definitive research is completed.

Adverse effects

Human IVIG is well tolerated in people, with less than 5% of patients experiencing adverse effects of transfusion (Kazatchkine and Kaveri 2001). The most common complication of hIVIG infusion is acute hypersensitivity, but other reported sequelae include thromboembolism, kidney failure, hypotension, aseptic meningitis, fluid overload, and type III hypersensitivity reactions (Duhem *et al*. 1994; Nydegge and Sturzennegger 1999; Orbach *et al*. 2005). Veterinary patients treated with hIVIG have these same risks, but are more likely to suffer from transfusion reactions because hIVIG therapy involves introduction of xenoproteins.

Hypersensitivity and anaphylaxis

In general, reactions are thought to occur secondary to IgG aggregation and complement activation. Reactions can manifest in a multitude of ways, but classic signs include fever, dyspnea, urticaria, convulsions, diarrhea, vomiting, tachycardia, hypotension, and facial swelling (Table 7.4). Type I (immediate) hypersensitivity reactions are usually mild and transient, but can rapidly progress to anaphylactic shock. In an effort to maximize the safety profile of hIVIG, commercially available preparations remove aggregates prior to distribution. Appropriate transfusion protocols also decrease the risk of allergic reaction (Duhem *et al*. 1994).

Hypercoagulation

Thromboembolic events, including pulmonary embolism, myocardial infarction, deep venous thrombosis, cerebrovascular events, and hepatic vein occlusion, have been reported in humans after transfusion with hIVIG (Marie *et al*. 2006; Tsuchiya *et al*. 2009). Research in beagles transfused with hIVIG has documented increased circulation of fibrin and fibrinogen degradation products (FDP) and heightened thrombin-antithrombin (TAT) aggregation (Tsuchiya *et al*. 2009). Because FDP and TAT complexes are important biomarkers for hypercoagulability, investigators surmised that hIVIG infusion promotes a hypercoagulable state in dogs. Since hIVIG infusion is often utilized to increase platelet number and activation, although hIVIG might not result in thrombocytosis, an increase in platelet activation could also contribute to a hypercoagulable state. Additionally, some preparations contain factor Xa, which is pro-thrombotic and plays a major role in clot formation (Knezevic-Maramica and Kruskall 2003). Many preparations are also hyperosmolar, which is thought to increase the risk of thrombosis.

Development of hyperviscosity post-transfusion might also contribute to the development of a hypercoagulable state. Rapid infusion of hyperosmotic protein preparations like hIVIG can disrupt capillary flow and encourage microthrombi formation (Nydegge and Sturzenegger 1999). To prevent abrupt increases in viscosity, slow infusion of hIVIG is recommended in humans at a rate of <400 g/kg over 8 hours (Tsuchiay *et al*. 2009). Rates used in veterinary medicine are largely extrapolated from human guidelines, but rarely exceed rates of 2.2 g/kg. However, duration of infusion varies widely in veterinary medicine.

Patients with critical illness have many factors contributing to an increased risk of thromboembolic events, even when not exposed to hIVIG. As many conditions treated with hIVIG are intrinsically hypercoagulable, infusion of hIVIG might exacerbate the risk of thromboembolic complications. As such, some

clinicians advocate the use of prophylactic anticoagulant therapy in tandem with hIVIG infusion for patients with known hypercoagulable disease (Orbach *et al*. 2005).

Kidney failure

Kidney failure has been associated with hIVIG therapy in geriatric humans and those with diabetes or chronic kidney disease. Acute kidney injury (AKI) occurs secondary to osmotic nephrosis caused by the sucrose used as a stabilizing agent in some hIVIG preparations (Foster *et al*. 2010). Azotemia is noted within 2–5 days of therapy and is usually transient (Cayao *et al*. 1997). Immunoglobulin products without sucrose are preferred for administration, but sucrose-containing solutions are sometimes used in diabetic patients to avoid disruption of euglycemia. Although much less frequent, tubular damage sometimes occurs when preparations do not contain sucrose and is likely secondary to high solute loads encountered with the hIVIG infusion (Cayco *et al*. 1997; Orbach *et al*. 2005). Type III (delayed) hypersensitivity reactions can also result in kidney failure. Glomerulonephritis develops when antigen-antibody (IgG) complexes form and are deposited in the basement membrane (Duhem *et al*. 1994).

Miscellaneous risks

Hypotensive events occur rarely during hIVIG transfusion. Frequency of hypotensive complications is directly related to the size of the donor pool and is likely due to a mixed population of immunogenic proteins. As such, larger donor pools increase the risk of hypotension in hIVIG recipients (Kroez *et al*. 2003). Separately, hypotension can also result from an anaphylactic reaction. Acidic products (pH 4.7) and those containing lower levels of IgA reduce the risk of anaphylaxis and hypotension (Kroez *et al*. 2003).

Aseptic meningitis is another rare complication of hIVIG infusion and is dose-dependent. The pathophysiology is poorly understood, but signs generally occur within 48 hours of infusion and are more common in people with a history of migraine headaches (Sekul 1994).

Circulatory (volume) overload has been documented in people secondary to hIVIG transfusion and is most commonly seen in patients with underlying cardiac disease or after massive transfusion (Orbach *et al*. 2005). As with any transfusion, it is important to consider the total volume and rate, as well as individual patient limitations. Preparations of hIVIG are available in concentrations of 3–16% and transfusions administered at a higher concentration can reduce the total volume required. Because globulins contribute less to plasma COP compared to albumin, administration of higher concentration hIVIG solutions is generally well tolerated.

Administration recommendations for veterinary patients

Human IVIG preparations are available in lyophilized and liquid forms (Table 7.6). Liquid preparations are convenient, but should be refrigerated to discourage bacterial growth. Refrigerated products should reach room temperature prior to infusion to decrease patient discomfort and shivering (Kirmse 2009). Lyophilized products are reconstituted over 15–20 minutes; a variety of diluents can be used depending on the product, which allows flexibility in determination of the final concentration and osmolality (Duhem *et al*. 1994).

Human IVIG can be administered through a peripheral catheter, but should be given via a dedicated line (i.e., without concurrently administered fluids). During infusion, the catheter site should be closely monitored for extravasation and swelling (Murphy *et al*. 2005; Kirmse 2009). Most manufacturers recommend using an in-line filter during infusion and have varying guidelines for filter size. Some clinicians recommend discontinuation of medications, feedings, and other fluid therapy during hIVIG infusion to decrease the risk of complications, but no consensus opinion exists on this practice. Ultimately, it is best to consult with the manufacturer regarding their specific recommendations.

Monitoring

As there are currently no established guidelines for appropriate monitoring during hIVIG transfusion in veterinary patients, comprehensive supervision is imperative. In human patients, IVIG transfusions are typically administered over 6–12 hours to decrease the risk of anaphylaxis, fluid overload, and hyperviscosity. Temperature, pulse rate, respiratory rate, and character, as well as blood pressure should be measured at the start of therapy and frequently during transfusion (Table 7.3). Signs of transfusion reactions warrant prompt cessation of the infusion and antihistamine administration; some patients might tolerate completion of the transfusion at a slower rate. In cases of anaphylaxis, therapy with epinephrine might also be required. Vital parameters should be monitored frequently for 24 hours after the transfusion. Some clinicians recommend patient follow-up for 6 months after therapy to monitor for type III hypersensitivity reactions.

Dose and rate of administration

The use of hIVIG in companion animals is still in its infancy and veterinary protocols are largely extrapolated from human medicine. Early veterinary investigations utilized doses ranging from 0.5 to 1.5 g/kg, but more recent work has documented doses up to 2.2 g/kg (Table 7.6). Veterinary studies have utilized infusion times of 4–8 hours. In all situations, the infusion should be initiated slowly and gradually increased every 30–60 minutes to a maintenance rate not exceeding 0.8 mL/kg/min (Murphy *et al*. 2005; Kirmse 2009).

Safety of repeated administration

There is also a question regarding the safety of multiple transfusions of hIVIG in small animals. Serial transfusion is employed in people for the management of several immune mediated disorders, but it is unclear if repeated infusion is safe for veterinary patients. While several veterinary reports describe repeated infusions without incident, others report anaphylactic events after serial hIVIG infusions. As hIVIG infusion involves introduction of foreign protein to veterinary patients, repeat infusion should be performed cautiously due to risk of severe immediate or delayed hypersensitivity reactions. Without question, more research

Table 7.6 Human intravenous immunoglobulin products used in veterinary studies.

	Carimmune NF	Flebogama 5% DIF	Gammaguard liquid	Gammaguard SD	Polygam S/D	Sandoglobulin
Product concentration (%)	3, 6, 9, 12	5	10	5 and 10	10	3, 6, 9, 12
Form	Lyophilized	Liquid	Liquid	Liquid	Lyophilized	Liquid
pH	6.6	5–6	4.6–5.1	6.8	6.4–7.2	3%, 6.5 6%, 6.61 9%, 6.64 12%, 6.8
IgA content (mcg/mL)	720	<50	37	2.2	<2.2	Trace
Donor pool size	>16,000	>1000	Unlisted	>10,000	>1500	>16,000
Diluent	5% dextrose Sterile water 0.9% NaCl	NA	NA	Sterile water	Sterile water	5% dextrose Sterile water 0.9% NaCl
Osmolality (mOsm/L)	Varies with concentration and diluent	240–370	240–300	5%: 636 10%: 1,250	1250	Varies with concentration and diluent
Fluid compatibility	5% dextrose 0.9% NaCl Sterile water? (listed above)	NA	5% dextrose *incompatible with 0.9% NaCl*	0.9% NaCl 5% dextrose	Sterile water	5% dextrose 0.9% NaCl
Sugar content	1.67 g sucrose per gram of protein	5% D-sorbitol	0	2% glucose	2% glucose	1.67 g sucrose per gram of protein
Filter size (um)	15	15–20	15	15	15	Not required
Storage requirements	24 months 36–77°F (2–25°C)	24 months 36–77°F (2–25°C)	36 months 36–46°F (2–8°C) 9 months 77°F (25°C)	24 months <77°F (<25°C)	24 months <77°F (<25°C)	24 months <77°F (<25°C)
Website	www.cslbehring-us.com	www.grifols.com	www.gammagard.com	www.gammagard.com	www.baxter.com	www.cslbehring-us.com; www.novartis.com

mOsm, milliosmole; NA, information not available.

needs to be completed to determine optimal practice guidelines for hIVIG administration.

Conclusions

Although albumin transfusion remains controversial, an expanding body of evidence suggests that albumin supplementation might be beneficial in specific populations of canine patients. Several products are available for transfusion, each with differing risk profiles. Treatment of the underlying disease process precipitating the hypoalbuminemic state is paramount for a successful outcome, but support in the form of canine or human albumin transfusions might assist recovery in patients with sepsis, ALI, or ARDS. Ongoing research is vital to fully illuminate the role of albumin supplementation in critically ill patients.

Although common in specialty practice, hIVIG therapy can be cost prohibitive for many veterinary clients. Proponents of hIVIG use in veterinary patients argue that administration can induce rapid remission of immune disease and significantly decrease the

length of hospitalization and associated costs. Currently, hIVIG therapy has not proven to decrease transfusion requirements in patients with IMHA, but shows great promise for management of ITP and some dermatologic diseases. However, adequate data is not currently available to fully elucidate the role of hIVIG for veterinary patients. Further research is required to determine appropriate indications, dosing, and transfusion practices for small animals.

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