# Update on Albumin Therapy in Critical Illness

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**KEYWORDS**

• Albumin • Colloid osmotic pressure • Endothelial glycocalyx
• Type III hypersensitivity reaction • Transfusion

**KEY POINTS**

- Albumin is among most important proteins in the body and plays a significant role in maintenance of colloid osmotic pressure, wound healing, decreasing oxidative damage, carrying drugs and endogenous substances, and coagulation.
- Hypoalbuminemia is common in a variety of acute and chronic illnesses. An albumin concentration of less than 2.0 g/dL is a negative prognostic indicator in veterinary patients.
- Replenishment of albumin can be in the form of fresh frozen, frozen, or cryopoor plasma or in the form of human or canine albumin concentrates.
- Infusion of human albumin concentrate to healthy and critically ill dogs can induce acute and delayed hypersensitivity reactions that range in signs from fever, urticaria, vomiting, peripheral edema, joint effusion, and renal failure. Death has been reported.

## INTRODUCTION

Albumin is one of the most important proteins in the body. The functions of albumin are numerous and include maintenance of colloid osmotic pressure (COP) within the intravascular and extravascular body compartments and carrier of endogenous hormones and ions, as well as exogenous drugs, scavenger of oxygen-derived free radical species in sites of inflammation, participation in the acid–base balance within the body, contributor to waste product elimination, and mediator of coagulation.[1,2]

During states of health, albumin is synthesized exclusively in the liver in response to local COP and the presence of available amino acid nutrients.[3] During states of critical illness, however, hypoalbuminemia, which is defined as a serum albumin of less than 3.0 g/dL,[4] is common, and has a prevalence that ranges from 9.8%[5] to 25.2%.[6] The causes of hypoalbuminemia are numerous, and result from a lack of production with

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preferential synthesis of acute phase proteins,[1,7,8] as well as a lack of available nutrient stores for hepatic albumin synthesis. Increased loss into body cavities or from wound exudates, renal glomerular dysfunction, or gastrointestinal disease, as well as dilution caused by infusion of natural and synthetic colloids also contribute to hypoalbuminemia (**Box 1**). In both human and veterinary patients, hypoalbuminemia has been associated with impaired wound healing,[9] decreased binding of drugs,[10] increased risk of gastrointestinal surgical site dehiscence,[11] and increased patient morbidity and mortality.[12–18] In 1 study of human patients, the relative risk of mortality increased by 25% to 50% for each 0.25 g/dL decrease in serum albumin.[19] In another meta-analysis of hypoalbuminemia in acute illness in people, for each 10 g/L decrease in albumin, there was a 137% increase in odds of death, a 71% increase in length of hospital stay and an 89% increase in overall morbidity.[20]

Because of the negative consequences of hypoalbuminemia, restoration of total body albumin is encouraged. However, this can be challenging and controversial in both human and veterinary medicine. A Cochrane meta-analysis evaluated outcome in a heterogeneous population of critically ill human patients who received 4% or 5% human serum albumin (HSA) as a resuscitative fluid.[21] The resultant analyses determined that the use of HSA did not improve clinical outcome and may increase the relative risk of death in some patient populations. This study had a profound effect on the use of albumin in practice and it is estimated that subsequent to the publication of the Cochrane review, use of albumin decreased by more than 40% in the UK.[22] A later study, the Saline versus Albumin Fluid Evaluation (SAFE) trial, compared the use of 5% HSA with 0.9% saline for fluid resuscitation in human patients in the intensive care unit, and not only found lack of evidence to support detrimental effects of HSA, but found that its use may improve survival in human patients with sepsis.[23] Subsequent to the SAFE trial, a large meta-analysis of septic human patients found a decreased mortality for those patient who received albumin (odds ratio, 0.82; 95% confidence interval, 0.67–1.0).[24] This study and others have led the human health care community to recommend the use of HSA in conjunction with crystalloids for initial resuscitation in septic patients.[25] Veterinary advocates of albumin supplementation, therefore, have continued to support the supplementation and replenishment of albumin in critically ill small animal patients, provided that possible risks outweigh the perceived benefits.

### *Immunogenicity*

Albumin shares 83% to 88% structural homology across animal species.[26–28] Canine albumin is approximately 79.3% structurally homologous to human albumin.[29] Species differences in the genetic amino acid sequence, molecular weight, net charge, and isoelectric set point of albumin are thought to contribute to antigenicity with the potential to develop adverse immediate and delayed hypersensitivity reactions in some dogs.[26,30] Even among different dog breeds, there seem to be small variations in the genetic sequencing of albumin,[31] which can result in variations in drug-binding capacity. It is unknown whether the small differences in amino acid sequencing in dog albumin can potentially contribute to its antigenicity at this time. Type I hypersensitivity reactions occur within minutes to hours of exposure to an antigen and requires prior exposure with subsequent sensitivity.[32] Type III or Arthus reactions are delayed and occur after soluble immune complexes adhere to the endothelium of vessels and other organs that then lead to the activation of the complement, with subsequent activation of the inflammatory cascade.[32] Type III hypersensitivity reactions are typically observed 1 to 3 weeks after antigenic exposure. The resultant widespread vasculitis with clinical signs

**Box 1**
**Conditions associated with hypoalbuminemia**

- Albumin loss
  - Renal loss
    - Sepsis
    - Diabetes mellitus
    - Glomerulonephritis
    - Amyloidosis
    - *Ehrlichia canis*
  - Gastrointestinal loss
    - Inflammatory bowel disease
    - Lymphangectasia
    - Infectious
      - Bacterial enteritis
      - Parvoviral enteritis
      - Histoplasmosis
      - Parasitism
        - Whipworm (*Trichuris vulpis*)
        - Roundworms (*Toxocara canis*, *Toxocara cati*)
        - Hookworms (*Ancylostoma caninum*, *Ancylostoma braziliense*)
        - Giardia (*Giardia intestinalis*, *Giardia duodenalis*, *Giardia lamblia*)
        - Coccidia (*Isospora* spp.)
      - Panleukopenia virus
  - Neoplasia
  - Toxins
  - Heat-induced illness/hyperthermia
  - Pancreatitis
  - Peritonitis
  - Pleural space/pulmonary loss
    - Pyothorax
    - Noncardiogenic pulmonary edema
    - Acute respiratory distress syndrome
- Endocrinopathy
  - Hypoadrenocorticism
  - Hyperadrenocorticism
- Decreased synthesis
  - Malnutrition
  - Hepatic disease
    - Cholangiohepatitis
    - Cirrhosis
    - Lipidosis
    - Phenobarbital toxicosis
    - Portosystemic shunt
  - Histoplasmosis
  - Neoplasia
- Increased hydrostatic pressure
  - Heartworm caval syndrome (*D immitis*)
  - Right sided cardiac disease
  - Portal hypertension

*Data from* Mazzaferro EM, Rudloff E, Kirby R. The role of albumin replacement in the critically ill veterinary patient. J Vet Emerg Crit Care 2002; 12(2):113-124.

of fever, lethargy, joint effusion, polyarthralgia, lymphadenopathy, and urticaric skin lesions can be self-limiting or can lead to significant morbidity or mortality.

From the onset of considering using more concentrated forms of albumin for supplementation therapy in hypoalbuminemic patients, concern has been raised about

the possible immunogenicity of xenotransfusions of non–species-specific albumin to veterinary patients.[33,34] Because canine-specific albumin was only sporadically available until recently, researchers initially investigated the use of bovine and human albumin concentrates to healthy and critically ill dogs. An early study that investigated the use of 500 mg/kg IV bovine albumin to healthy dogs,[19] 2 dogs demonstrated immediate adverse reactions that ranged from mild urticaria and pruritus to severe anaphylaxis during administration of a second dose 14 days after the initial administration. Five of the remaining 8 dogs that received only 1 initial infusion of bovine serum albumin developed clinical signs of mild to severe type III hypersensitivity reactions 15 to 18 days after bovine serum albumin administration.

In 2007, 2 separate groups of researchers performed prospective studies that investigated the use of 25% concentrated HSA in healthy dogs.[32,35] In the first study,[35] 6 healthy dogs received a single dose of 25% HSA (2 mL/kg IV over 1 hour) as a part of an investigation that compared the effects of various natural and synthetic colloids with crystalloids on coagulation, COP, and packed cell volume and total solids. One dog developed vomiting and facial edema within 15 minutes of the onset of HSA infusion. The remaining 5 dogs developed no immediate signs of adverse reaction; however, all 6 dogs developed delayed clinical signs that were consistent with a type III hypersensitivity reaction 5 to 37 days after HSA administration. Four dogs had mild clinical signs that did not require hospitalization, whereas, in 2 dogs, clinical signs progressed in severity and included protein-losing nephropathy, generalized severe vasculitis, and subsequent death. In both animals that died, the histopathology of the skin and kidneys demonstrated leukocytoclastic vasculitis and membranoproliferative glomerulonephritis, consistent with type III sensitivity reactions. An enzyme-linked immunosorbent assay test was developed to document anti-human albumin antibodies and found that all 6 dogs had developed antibodies directed against human albumin after initial exposure.

The second study[32] administered 50 g of 25% HSA to 9 healthy purpose-bred dogs at incremental doses of 0.5 mL/kg/h to a maximum of 4 mL/kg/h. One dog developed an acute anaphylactic reaction after receiving less than 1.5 mL/kg of 25% HSA and later developed facial edema and urticaria after HSA administration. A second dog developed urticaria and facial edema 7 days after HSA infusion. Two dogs received a second infusion of 25% HSA 14 days after the first and developed almost immediate signs of a hypersensitivity reaction. Although HSA infusion statistically increased serum albumin concentration and COP above baseline values, it also resulted in the production of IgG antibodies and positive skin testing supportive of IgE antibodies.[32]

A third study[29] measured anti-human albumin antibodies in 2 healthy dogs and 14 critically ill dogs that received 25% HSA as a part of therapy. The healthy dogs received 2 mL/kg 25% HSA over 2 hours, then a second infusion of 1 mL/kg over 1 hour 10 days later. One of the dogs developed facial edema and decreased appetite 8 days after the first infusion. Both dogs developed erythema, vomiting, and diarrhea during the second infusion. Serum IgG anti-human albumin antibodies were detected with 10 days of HSA administration and peaked at 3 weeks after administration.

The median dose of 25% HSA administered to critically ill dogs was 5.2 mL/kg (range, 1.8–47.1 mL/kg) over a median time of 0.8 mL/kg/h (range, 0.2–1.8 mL/kg/h). No acute or delayed hypersensitivity reactions were observed in the critically ill dogs. Critically ill dogs had no significant increase in anti-human antibodies at the time of hospital discharge but did develop increased anti-human albumin antibodies 4 and 6 weeks later. The duration of antibody response was prolonged through 6 months in both healthy and critically ill dogs tested. Five of 68 negative control dogs who did not receive HSA also tested positive for anti-human albumin antibodies.

The authors proposed a potential mechanism of cross-reactivity with bovine albumin when dogs are exposed to bovine albumin during the ingestion of food products or vaccination. Others have documented leukocytoclastic vasculitis and type III sensitivity reactions in critically ill dogs who received 25% HSA diluted to 5% and infused over 3 to 4 hours.[36] A case series of 2 critically ill dogs who received 25% HSA as part of therapy for septic peritonitis documented type III hypersensitivity reactions that progressed to acute glomerulonephritis, proteinuria, oligoanuria, and death.[37] This final article is the first to document death secondary to type III hypersensitivity reactions in critically ill dogs that had received 25% HSA.

Despite immune stimulation to HSA in critically ill dogs and cats, the majority of studies that have prospectively and retrospectively evaluated its use have demonstrated significant increases in serum albumin concentration, COP, and blood pressure in critically ill dogs without severe adverse sequelae.[34,38–42] Mathews and Barry[38] first reported the use of 25% serum albumin in 64 critically ill dogs and 2 cats in combination with fresh frozen and stored plasma, pentastarch and whole blood or packed red blood cells. Infusions were administered as a slow constant rate infusion (0.1–1.7 mL/kg/h) or more rapidly (2–4 mL/kg) for the treatment of hypoalbuminemia and hypotension, respectively. Facial edema was reported in 2 dogs during the 25% HSA infusion. Serum albumin, systolic blood pressure, and total solids significantly increased in treated patients, with a 71% survival to discharge.

Another retrospective case series[39] described the administration of 25% human albumin diluted to 10% in 73 critically ill dogs (1.4 g/kg median dose) that resulted in significantly higher serum albumin, total protein, and COP after infusion, with a 50.3% survival to hospital discharge. The serum albumin concentration was found to be higher in survivors versus nonsurvivors. Although some dogs experienced clinical signs of tachypnea, fever, peripheral edema, and tachycardia with ventricular dysrhythmias during or soon after administration of the HSA, the nature of their critical illness also could explain the same clinical signs. Three dogs did develop signs of a type III hypersensitivity reaction 5 to 14 days after the administration of the HSA.

A retrospective analysis of administration of HSA to dogs with septic peritonitis demonstrated statistically significant increases in serum albumin concentration, COP and total protein after albumin administration.[43] The postinfusion serum albumin concentrations were significantly higher in survivors versus nonsurvivors, with an overall survival rate of 46%. Despite these findings, the administration of HSA was not correlated with survival. No adverse reactions were reported, although the retrospective nature of the case series may have precluded follow-up.

The retrospective case series discussed administered concentrated human albumin as 25% or diluted to 10% solutions. Curiously, 2 studies[34,40] by the same veterinary researchers in Italy have documented no adverse reactions to HSA infusions diluted to 5% in a retrospective study of 418 dogs and 170 cats and in a prospective study of 40 critically ill cats. In both studies, 25% HSA was diluted to 5% then administered as a constant rate infusion of 2 mL/kg/h for 10 h/d until the patient's serum albumin reached 2.0 g/dL. In this study, 75.6% of dogs and 72.3% of cats survived to discharge. Similarly, the prospective study by the same group documented the apparent safety of 10 to 20 mL/kg 5% human albumin to 40 critically ill cats to significantly increase serum albumin, with no evidence of immediate or delayed hypersensitivity reactions through 28 days after the infusion.

The exact cause of immediate and delayed hypersensitivity reactions remains unknown. Despite lack of anti-human antibodies in healthy dogs that received 25% HSA, immediate reactions occurred after administration of a very small amount of infusion, suggesting previous sensitivity.[29] Further healthy animals naïve to HSA infusion

also showed that some cross-reactivity, suggesting possible exposure to other species albumin (bovine, equine, other) in food products or vaccinations may sensitize the immune system to xenotransfusions with albumin. The majority of critically ill dogs in the United States and Canada received 25% HSA undiluted or diluted to 10% as a rapid infusion or as a slower constant rate infusion, but still had immediate and delayed hypersensitivity reactions.[29,32,35,36,38,39,44] Two large-scale studies from the researchers in Italy, who diluted 25% HSA to 5% and administered the product as a slow infusion over 10 hours each day, documented no adverse effects. Only 1 study in the United States that diluted 25% HSA to 5% documented type III hypersensitivity reactions. It is possible that the total dose of HSA administered, and rate of administration could potentially stimulate immune stimulation compared with smaller doses over a longer period of time. It is also possible that food and vaccine products in the United States and Canada differ from those in Italy, or that the albumin product pooled from human plasma differs, making animals in geographic locations more or less susceptible to immune stimulation. Because many critically ill patients have compromised immune systems and are hypoalbuminemic at the time of albumin replenishment therapies, the antigenic effects of infusion of non–species-specific albumin may be blunted or delayed, but still occur in a small population of patients. Clearly, more research must be performed to determine the cause of antigenicity and subsequent reactions using HSA before its use is advocated in our veterinary patients. When no other sources of albumin are available, clients must be informed of the potential adverse reactions including death before the infusion of HSA to critically ill dogs and cats.

## CLINICAL SIGNS OF TYPE I AND TYPE III HYPERSENSITIVITY REACTIONS AND TREATMENT

Clinical manifestations of type I and type III hypersensitivity reactions have been documented in several articles following infusion of HSA to healthy and critically ill dogs. Although the manifestation of new-onset facial edema, anaphylaxis, and collapse during infusion seems to be directly associated with an immediate hypersensitivity reaction, other possible signs of infusion reactions are not as clear-cut, but have been described as tachypnea, vomiting, hypotension, fever, shaking, weakness, or tachycardia during or shortly after infusion. Cats may also manifest with bradycardia and hypothermia when experiencing an infusion reaction. Because many of the animals who receive albumin were not responding to more traditional therapies, one could argue that some of the reported signs of reaction could possibly be associated with the critical illness, and not a hypersensitivity reaction at all. More compelling evidence of type III hypersensitivity reactions 6 to 18 days after infusion include the clinical signs of lethargy, inappetence, facial and peripheral edema, urticaria, and skin lesions consistent with vasculitis, joint effusion, lameness, scleral hemorrhage, and the more serious developments of acute kidney injury and proteinuria that can progress to oligoanuria and death.

The early recognition of clinical signs of a hypersensitivity reaction is important for aggressive therapy. If clinical signs of an immediate anaphylactic reaction develop, dexamethasone-SP (0.15 mg/kg IV) or diphenhydramine (1–2 mg/kg IM, IV) should be administered. If collapse and hypotension develop, epinephrine (0.01 mg/kg IV) should also be administered. The treatment of more delayed hypersensitivity reactions includes administration of a glucocorticoid (predniso[lo]ne 1 mg/kg/d $\times$ 5 days, then 0.5 mg/kg/d $\times$ 7 days, then 0.5 mg/kg/d every other day for 1 week) along with diphenhydramine (1–2 mg/kg by mouth every 8 hours) should be administered, along with

supportive care in the form of antiemetics, gastroprotectants, analgesia, and appetite stimulants as indicated.

## ALBUMIN PRODUCTS

Until roughly the past decade, albumin replacement in small animals was largely in the form of large volumes of fresh frozen plasma or with concentrated human albumin products.[34] A 2001 study demonstrated that the replacement of albumin was the primary cause for administration of fresh frozen plasma in 63% of cases.[45] Another retrospective study that evaluated trends in use of fresh frozen plasma over 2 decades reported the primary reason for administration of fresh frozen plasma was to treat coagulopathies.[46] Curiously, that same study demonstrated that, when fresh frozen plasma was administered to treat hypoalbuminemia, the mean serum albumin concentration significantly decreased (17.4 g/L after the administration of fresh frozen plasma vs 21.5 g/L before infusion) after fresh frozen plasma administration.[46]

A recent study that solicited on-line feedback from more than 1000 veterinary practitioners in 42 countries found that the use of crystalloids and natural or synthetic colloids for intravascular volume replacement and maintenance of COP varies, possibly owing to clinician preference, geographic location, and the availability of the product.[47] More than 75% of practitioners use synthetic colloids such as hydroxyethyl starch for oncotic support despite recent concerns about the potential for contributing to acute kidney injury.[47–49] The same study found that 46% of respondents still used fresh frozen plasma for oncotic support, and 23% to 28% of respondents used some form of human or canine albumin concentrate, when available. Similarly, another Internet survey of transfusion practices in veterinary teaching hospitals and private referral hospitals showed that approximately 30% to 45% of these practices kept some form of lyophilized albumin product on hand. Unfortunately, the proportions of human versus canine albumin was not reported nor was the frequency that these products were used.[50]

## ALLOGENIC ALBUMIN ADMINISTRATION

Canine fresh frozen and stored plasma contains 25 to 30 g of albumin per liter.[38] Plasma may be beneficial because it contains coagulation factors, alpha-2 macroglobulin, antithrombin, and fibrinogen in addition to albumin30, however, up to 25 mL/kg of plasma may be required to increase serum albumin by 0.5 g/dL.[51] Because of the dilutional effects of such as large volume of plasma required, hospital resource availability, and cost limitations for some clients, the administration of plasma is not an efficient means of albumin supplementation for many patients. Lyophilized canine specific concentrated albumin pooled from healthy donors available for use in the United States and Canada from multiple manufacturers. The product can be stored at room temperature and is stable for 36 months. The manufacturers recommend reconstitution to 5% to 25% solution using 0.9% NaCl or 5% dextrose in water, then administered within 6 hours or stored refrigerated for up to 24 hours. The manufacturers' indications for this product are for hypoproteinemia and shock or hypovolemia. Safety studies performed by Animal Blood Resources International administered the canine albumin product to healthy beagle dogs once weekly for 4 consecutive weeks without any immediate or delayed signs of hypersensitivity reaction. A prospective study that evaluated the use of canine-specific albumin in dogs with septic peritonitis documented a significant increase in serum albumin concentration, COP, and systolic blood pressure after administration.[52] A higher serum albumin concentration was positively associated with survival. The study documented no

immediate or delayed adverse reactions in patients who received the canine albumin product. Similarly, the administration of canine-specific albumin to healthy dogs, with repeat infusions on days 2 and 14, had no immediate or delayed reactions, and significantly increased both COP and serum albumin concentration.[53] A list of veterinary studies using human serum and canine-specific albumin is provided in **Table 1**.

Given the cost and potential lack of availability of canine-specific albumin products in some countries, other resources have also been investigated for the replenishment of albumin in critically ill animals. A prospective study that evaluated albumin concentration, COP, and coagulation factors in fresh frozen plasma with cryoprecipitate and cryopoor plasma from healthy greyhound donor dogs found that cryopoor plasma had significantly higher albumin and COP compared with FFP,[54] suggesting that cryopoor plasma may be a viable alternative to FFP or species-specific albumin concentrates, depending on availability. The same researchers have successfully used cryopoor plasma to increase serum albumin concentrations in critically ill hypoalbuminemic dogs.[54,55] Despite its successful use, the volume of cryopoor plasma required (median 31 mL/kg) to increase serum albumin and replace whole body albumin deficit is still large compared with albumin concentrate.[54]

An alternative method has been reported to purify canine albumin from FFP or surplus stored plasma.[56] Briefly, this method, which was adapted from a similar method used to convert human plasma to albumin,[57] involves adding a stabilizing agent to the plasma, heating the plasma in a water bath to denature all but the stabilized albumin, and then acidifying the plasma to precipitate the denatured proteins. The purified albumin can then be expressed into a satellite bag and pH neutralized. Through this process, a roughly 5% canine albumin solution with a purity of greater than 91% can be obtained. At this point, in vivo research is still needed to determine the effects of this product on severely ill dogs.

### *Treatment Recommendations*

Albumin can be replenished in hypoalbuminemic animals with infusion of fresh frozen or stored plasma, cryopoor plasma, concentrated HSA, or canine-specific albumin. Although a number of studies have documented that serum albumin, total solids, and COP can be successfully increased with use of HSA in critically ill dogs, there is a real risk of inciting both immediate and delayed hypersensitivity reactions in dogs. The serum albumin concentration in some studies was higher in survivors versus nonsurvivors; however, this finding was not necessarily associated with HSA infusion. Whenever possible, treatment of the primary critical illness and provision of early enteral nutrition is an important component of therapy. In many patients, however, clinicians reach for an albumin concentrate when the more traditional methods of replenishment of total protein, albumin, and oncotic support with natural and synthetic colloids is failing. It seems that critical illness results in a delayed immune response after HSA infusion compared with healthy dogs; however, all critically ill dogs who received HSA developed IgG and IgE antibodies after exposure, which can lead to immediate or delayed hypersensitivity reactions. The administration of glucocorticoids at the time of HSA infusion does not seem to blunt or prevent the occurrence of a hypersensitivity reaction.[44] The severity of documented acute and delayed hypersensitivity reactions to HSA range from self-limiting with administration of glucocorticoids and diphenhydramine, to progressive leading to death in some patients. For this reason, if alternate specific-specific albumin sources are available, their use is preferable and recommended.

As a general guideline, the authors consider colloid support when a patient's albumin approaches 2.0 g/dL or less, and albumin supplementation when serum albumin

**Table 1**
**List of current retrospective and prospective studies using various concentrations of concentrated human and canine albumin, effects, and adverse reactions**

| Author | Type of Study | Animals | Albumin Product | Dose | Administration Rate | Concentration | Outcome | Adverse Reactions |
|---|---|---|---|---|---|---|---|---|
| Cohn et al,[32] 2007 | Prospective | 9 healthy dogs | ZLB Bioplasma | 50 g | 0.5–4 mL/kg/h | 25% | Increased [albumin] at 7, 14, and 21 d | 1 dog anaphylaxis immediately, facial edema and urticaria 6 d later<br>1 dog urticaria, edema 7 d after first infusion<br>8/9 dogs positive intradermal skin test |
| Craft & Powell,[52] 2012 | Prospective | 7 critically ill dogs, septic peritonitis | Canine albumin | 800 mg/kg | | 5% | Increased [albumin], COP and BP, no effect on survival<br>79% survival | No adverse reactions |
| Francis et al,[35] 2007 | Prospective | 6 healthy dogs | Plasbumin | 500 mg/kg | 1 h | 25% | | 1 dog facial edema, vomiting within 15 min<br>2 dogs died |
| Vigano et al,[40] 2019 | Prospective | 40 critically ill cats | Uman human albumin | 10–20 mL/kg | 2 mL/kg/h × 10 h/d | 5% | Increased [albumin] | No reactions through 28 d after infusion |
| Powell et al,[36] 2013 | Retrospective | 2 critically ill dogs | Plasbumin | 1300 mg/kg | 4 h | 25% diluted to 5% | | Lymphocytoclastic biopsies |

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**Table 1**
**(*continued*)**

| Author | Type of Study | Animals | Albumin Product | Dose | Administration Rate | Concentration | Outcome | Adverse Reactions |
|---|---|---|---|---|---|---|---|---|
| Mosley & Mathews,[19] 2005 | Prospective | 8 healthy dogs<br>2 dogs second infusion | Bovine albumin | 500 mg/kg<br><br><br><br><br><br>500 mg/kg | | | | 5/8 mild to generalized signs type III hypersensitivity 15 d after infusion<br>Immediate urticaria and pruritus in 1 dog, anaphylaxis in second dog |
| Martin et al,[29] 2008 | Prospective | 2 healthy dogs<br>14 critically ill dogs | Plasbumin | 500 mg/kg<br>250 mg/kg<br>1300 mg/kg | 2 h<br>1 h<br>0.8 mL/kg/h | 25%<br>25%<br>25% | | Decreased appetite, facial edema 8 d after albumin<br>Increased anti-albumin IgG at 10 d after albumin, peak at 3–9 wk after infusion<br>No acute or delayed reactions<br>Increased anti-albumin IgG antibodies 4–6 wk after infusion |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Trow et al,[39] 2008 | Retrospective | 73 critically ill dogs | Baxter product | 1400 mg/kg | | | Increased [albumin], TP | Increased [albumin] and TP |
| Vigano et al,[34] 2010 | Retrospective | Critically ill dogs (418) and cats (170) | Albital | | 2 mL/kg/h × 10 h/d | 5% | 75.6% survival (dogs, 72.3% survival) (cats) | No hypersensitivity reactions observed or reported<br>3 dogs lethargy, edema, urticaria, lameness, vomiting and inappetence 6–18 d after discharge |
| Mathews & Barry,[38] 2005 | Retrospective | Critically ill dogs (n = 64) and cats (n = 2) | Plasbumin | | 2–4 mL/kg bolus or 0.1–1.7 mL/kg/h | 25% | Increased [albumin], TS and BP<br>71% survival | 2 dogs facial edema during infusion |
| Horowitz et al,[43] 2015 | Retrospective | 22 dogs septic peritonitis | Human | | 2550 mg/kg | 25% | Increased [albumin], TP | No association between albumin administration and survival |
| Loyd et al,[44] 2016 | Retrospective | 21 dogs protein losing enteropathy | Human, Octapharma | | 500 mg/kg | 20–30 min | 1 dog with acute reaction euthanized<br>1 dog with delayed reaction euthanized | 9.5% developed signs associated with acute reaction (vomiting or labored breathing). 9.5% developed signs of delayed reaction. Corticosteroids had no effect on occurrence of signs |

(*continued on next page*)

**Table 1**
**(*continued*)**

| Author | Type of Study | Animals | Albumin Product | Dose | Administration Rate | Concentration | Outcome | Adverse Reactions |
|---|---|---|---|---|---|---|---|---|
| Klainbart & Aroch,[41] 2005 | Retrospective | 8 dogs, 3 cats | Human | | 2 mL/kg, then 0.2–0.7 mL/kg/h | 25% | Increase albumin in 3 dogs; 3 dogs survived, 5 dogs and 8 cats died | |
| Bell et al,[42] 2004 | Retrospective | 4 dogs, 1 cat | 20% human, ALBA 20% | | 0.14–0.25 mL/kg/h, 5 mL/kg/h 1 dog hypovolemic shock | 20% | Increased [albumin] from baseline, 3 dogs survived to discharge | |
| Enders et al,[53] 2018 | Prospective | 6 healthy dogs | Hemosolutions, canine albumin | | 1 g/kg over 2 h on days 0, 2, and 14 | 16% | Increased [albumin] and COP | |

*Abbreviation:* BP, blood pressure.
*Data from* Refs. [19,29,32,34-36,38-44,52,53].

is less than 1.5 g/dL. Albumin should be supplemented up to a goal of 2.0 g/dL, with additional colloidal support in the form of other natural or synthetic colloids. Any albumin administered will first replenish the interstitial albumin pool before serum albumin concentrations increase, making arbitrary administration of products challenging to meet goals and to alleviate clinical signs of peripheral edema, cavitary effusions and enteral feeding intolerance. As a general guideline, the following formula can be used to calculate an albumin deficit[4]:

Dose albumin (g) = 10 × (2.0 g/dL – patient albumin g/dL) × body weight in kg × 0.3.

As a general goal, a dose of 450 mg/kg canine albumin will increase the serum albumin by 0.5 g/dL.

If plasma products, rather than albumin concentrate are to be used, a clinician can use the following formula to help increase total solids, taking into consideration that albumin contributes roughly 50% of total solids:

mL of plasma to increase recipient TS (total solids) = desired recipient TS g/dL – recipient TS g/dL × weight (kg) × 50/donor TS g/dL.

Like other transfusions, the infusion of albumin products should be started slowly with careful monitoring for clinical signs of reaction. The canine albumin product should be reconstituted to a dilution of 5% according to manufacturer's recommendations, then initially administered at a rate of 1 to 2 mL/kg. If after 20 to 30 minutes no clinical signs of adverse reaction occur, the volume can be increased to administer a total dose over 3 to 4 hours. If volume expansion in addition to correction of hypoalbuminemia is needed, then the canine albumin product can be reconstituted with sterile water to a dilution of 10% to 16% according to manufacturer's recommendations. Then the reconstituted product can be administered through a dedicated central venous catheter initially at 0.5 to 1 mL/kg. If after 20 to 30 minutes no clinical signs of adverse reaction occur, the volume can be increased to administer the total dose over 3 to 4 hours.

## SUMMARY

Albumin's functions are numerous and important for a wide variety of normal body functions. In critically ill small animal patients, hypoalbuminemia is associated with adverse consequences, including increased patient morbidity and mortality. Replenishment of albumin is recommended in hypoalbuminemic animals; however, cases must be selected carefully. The availability of albumin product, cost, volume required for infusion, and potential risk of immediate and delayed hypersensitivity reactions should be considered when choosing the method of albumin supplementation. The evidence to date indicates that species specific albumin should be considered the product of choice for correction of hypoalbuminemic patients. If plasma products or species specific albumin is not available, HSA can be considered if the risk to benefit ratio is low and provided that clients are informed of potential adverse sequelae that could occur after administration.

## DISCLOSURE

The views expressed in this article are those of the authors and do not reflect the official policy or position of the US Army Medical Department, Departments of the Army, the Department of Defense, or the US Government.

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