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Original Study

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The use of canine-specific albumin in dogs with septic peritonitis

Elise M. Craft, DVM and Lisa L. Powell, DVM, DACVECC

Abstract

Objective – To assess changes in serum albumin concentration (ALB), colloid osmotic pressure (COP), and Doppler blood pressure (DBP) following transfusion of 5% lyophilized canine-specific albumin (CSA) in hypoalbuminemic dogs following surgical source control for septic peritonitis.
Design – Prospective randomized clinical trial November 2009 – November 2010.
Setting – University teaching hospital.
Animals – Fourteen client-owned dogs with hypoalbuminemia (<27 g/L [2.7 g/dL]) following surgical source control for septic peritonitis.
Interventions – Dogs were randomized to clinician-directed therapy (CDT) and CSA groups. Dogs enrolled in the CSA group received 800 mg/kg of CSA within 24 hours following surgical intervention.
Measurements and Main Results – At enrollment, ALB, COP, and DBP were not different between groups. ALB, COP, and DBP were significantly increased in the CSA group 2 hours following completion of the transfusion compared with the CDT group ($P = 0.0234$, 0.0078, 0.0156, respectively). In comparison to the CDT group, there was a significant change in ALB in the CSA group 24 hours after transfusion ($P = 0.0039$), but no difference in COP ($P = 0.3914$) or DBP ($P = 0.5145$). ALB was significantly higher in the CSA group at 24 hours compared with the CDT group ($P = 0.0367$) At the time of death or discharge, there was no difference between groups regarding ALB, COP, or DBP, but an association between ALB and survival was identified ($P = 0.0273$). One dog experienced tachypnea during transfusion of CSA; this dog died of unknown respiratory causes 120 hours after transfusion.
Conclusions – The administration of CSA in dogs with septic peritonitis results in an increase in ALB, COP, and DBP 2 hours after administration. An increase in ALB persisted at 24 hours compared with a CDT group. Administration of this product was not associated with owner-reported delayed adverse events in this population of dogs.

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Keywords: colloid osmotic pressure, fluid resuscitation, natural colloids, sepsis

Abbreviations

ALB	serum albumin concentration
BP	blood pressure
CDT	clinician-directed therapy
CSA	canine-specific albumin
COP	colloid osmotic pressure
DBP	Doppler blood pressure
HSA	human serum albumin
HES	hydroxyethyl starches
MODS	multiorgan dysfunction syndrome
RER	resting energy requirement
RR	respiratory rate

From the Department of Clinical Sciences, Veterinary Medical Center, University of Minnesota, St. Paul, MN, 55108

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Address correspondence and reprint requests to
Elise M. Craft, DVM, Veterinary Medical Center of Central New York, 5841 Bridge St, Suite 200, East Syracuse, NY 13057, USA.
Email: emcraft111@gmail.com
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Introduction

Septic peritonitis is a complex syndrome commonly encountered in veterinary ICUs. Hypoalbuminemia is frequently present in patients presenting with septic peritonitis.[1,2] Hypoalbuminemia is a result of decreased production of albumin, accelerated loss of albumin, or a combination of these factors. Accelerated albumin loss in the patient with septic peritonitis may occur by leakage through damaged or inflamed endothelial and

peritoneal membranes, dilutional effects from fluid therapy, or denaturation of albumin at sites of inflammation.[2–5] As such, the myriad functions of albumin are lost or diminished in these patients. These functions include maintenance of the colloid osmotic pressure (COP), drug and hormone binding capacity, protection from oxidative damage, and roles in both normal healing ability and coagulation.[2] Because of the loss of these functions, hypoalbuminemia itself has been associated with increased morbidity and mortality in dogs and people hospitalized for treatment of septic peritonitis and other critical illnesses.[6–8]

The survival rate for dogs diagnosed with septic peritonitis is approximately 50%, with a reported range of 27–80%.[1,3,7,9–13] The presence of hypoalbuminemia in patients with septic peritonitis and other critical illnesses is associated with a higher mortality rate in both veterinary and human studies.[6–8,14–18] It is possible that the presence of hypoalbuminemia results in poor outcome secondary to the loss of one or several of albumin's specific functions, but the presence of hypoalbuminemia may simply be a marker of more severe disease.[15]

In 1998, the Cochrane Injuries Group concluded that critically ill people receiving albumin-containing fluids had a 6% increase in mortality compared to those that did not.[19] Potential mechanisms by which albumin could worsen outcome included induction or worsening of a coagulopathy via inhibition of platelet aggregation or worsening of edematous states via movement across the capillary membrane.[19] However, a second meta-analysis[20] in addition to a randomized clinical trial evaluating a 4% albumin solution versus normal saline (ie, the SAFE study)[21] concluded that the use of albumin-containing solutions in a heterogenous population of critically ill people had no effect on mortality.[20,21] Interestingly, a planned subgroup analysis of this trial did identify a potential benefit of the treatment of patients with severe sepsis with albumin-containing fluids.[21] Additionally, the Surviving Sepsis Campaign recommends the use of either crystalloid or colloid fluids (including albumin-based fluids) for use in patients with sepsis.[22] This was further supported by a meta-analysis in which the use of albumin-containing fluids for resuscitation in severe sepsis was associated with a decrease in mortality.[23]

Sepsis and septic shock results in an increased microvascular permeability secondary to the pro-inflammatory effects of cytokines released from leukocytes and the endothelium itself.[24,25] Increased microvascular permeability combined with decreased systemic vascular resistance may result in an inadequate oxygen delivery to tissues and the subsequent production of reactive oxygen species.[26] The development of third spacing of fluid and hypotension require intensive fluid therapy throughout the initial resuscitation and recovery periods.[27] The infusion of an albumin-containing solution will result in additional intravascular expansion as opposed to a crystalloid solution administered in equal volumes.[28] Aside from the obvious benefit of a resultant increase in COP, the delivery of a decreased amount of fluid volume may decrease secondary complications, such as peripheral edema and the acute respiratory distress syndrome.[29–33] In addition, albumin helps mediate the inflammatory response itself via alteration of endothelial cell reactivity as well as providing anti-oxidant effects.[32,34–37]

In critically ill veterinary patients, the use of synthetic colloids, species-specific plasma, and human serum albumin (HSA) infusions have been utilized as albumin or albumin-related function replacement therapies.[38,39] The use of synthetic colloids, such as hydroxyethyl starches (HES), results in an increase in COP but does not provide the other more specific functions of albumin.[40] 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 and the resultant cost.[39] Previous publications evaluating the use of HSA in critically ill animals have demonstrated an increase in ALB, and increases in blood pressure (BP), total protein concentrations, and COP.[40–42] Potential side effects of HSA used in clinical animals were difficult to elucidate as these studies were retrospective, and it was impossible to know if adverse events were secondary to the underlying disease or to the administration of HSA. The administration of HSA to healthy animals has resulted in both anaphylactoid and delayed hypersensitivity reactions and the development of anti-HSA antibodies.[43] In addition, complications secondary to delayed hypersensitivity reactions experienced after the administration of HSA to healthy dogs resulted in the death of 2 dogs described in a case series.[44] As a result of these findings, recommendations against repeated infusions of HSA in critically ill animals and the administration of HSA to healthy animals have been reported.[43,45]

The advent of a commercially available canine lyophilized albumin (CSA [canine-specific albumin]) product[a] has provided an avenue for species-specific albumin replacement in dogs. The purpose of this study was to prospectively evaluate the safety and efficacy of a CSA product in hypoalbuminemic dogs with septic peritonitis, and to determine if its use following source-control surgery resulted in an increase in ALB, COP, or Doppler blood pressure (DBP).

Materials and Methods

Study design

This study was a prospective, randomized clinical trial of the safety and efficacy of a transfusion of a lyophilized

CSA product in dogs following source control for septic peritonitis. Client-owned dogs diagnosed with septic peritonitis were recruited for inclusion in the study from November 2009–2010. Inclusion criteria included dogs >4 months of age that were diagnosed with septic peritonitis and concurrent hypoalbuminemia (<27 g/L [2.7 g/dL]). Septic peritonitis was diagnosed via cytologic demonstration of intracellular bacterial organisms in peritoneal fluid, intra-operative identification of a perforated gastrointestinal organ, or identification of a ruptured intra-abdominal abscess (cytologically confirmed via visualization of bacterial organisms). Informed client consent was obtained from all owners or agents before enrollment in the study. The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee. Following enrollment in the study, dogs were assigned randomly to either the CSA or clinician-directed therapy (CDT) group. Group assignment was performed by opening a sealed, numbered envelope containing assignment to 1 of the 2 groups. Group assignment was uncovered to the investigators at the time of enrollment. All dogs were enrolled following definitive surgical intervention performed at the enrolling institution for septic peritonitis. Dogs in the CDT group received CDT postoperatively. Dogs in the CSA group received CDT and a single transfusion of CSA postoperatively.

Transfusion protocol

Dogs randomized to the CSA group received 800 mg/kg of CSA reconstituted in 0.9% NaCl[b] to yield a 5% CSA solution administered intravenously over 6 hours as instructed by the manufacturer. The mean time from the beginning of surgical procedure to CSA administration was 10 hours (range 5–17 h). Only study investigators were permitted to prepare and administer the CSA product. Simultaneous fluid administration with CSA was at the discretion of the clinician. However, all dogs' crystalloid infusions were continued, and HES[c] infusions, if utilized, were halted during CSA administration. Standard transfusion monitoring, including heart rate, respiratory rate (RR), and temperature were measured at baseline, 15 min, 30 min, 1 hour, 2 hours, 4 hours, and at the conclusion of the transfusion. At each time point, dogs were examined by either a certified veterinary technician or the attending clinician for evidence of facial swelling, urticaria, or pruritis. Evidence of regurgitation, vomiting, or diarrhea were noted, and the attending clinician was to be notified if they occurred.

Monitoring/data acquisition

Baseline heart rate, RR, temperature, and DBP were recorded for each dog at enrollment and once daily thereafter until release from the hospital or death. Laboratory values, including ALB and COP were measured at enrollment and once daily thereafter until release from the hospital or death. In addition, dogs randomized to the CSA group had ALB, COP, and DBP measured 2 hours following the completion of the transfusion. Serum was utilized to measure albumin concentrations via a benchtop chemistry analyzer.[d] Whole blood was utilized to measure COP via a colloid osmometer.[e] In addition, the COP of the administered CSA product was measured via the same colloid osmometer.

Attempts were made to provide all enrolled dogs with 100% of their resting energy requirement (RER) within 24 hours following surgical intervention. RER was calculated as (Body Weight [kg] $\times$ 30) + 70 = kcal required per day or (70 $\times$ Body Weight [kg])$^{0.75}$ = kcal required per day dependent on animal size.[46] The use of nutritional support was clinician directed, and the amount, type, and method of delivery was recorded for each dog.

Fluid therapy for enrolled dogs was clinician directed. No limits were placed regarding the use of artificial colloids or blood products. However, the use of CSA was restricted to dogs enrolled in the CSA group during the study period; HSA was not available for use in dogs enrolled in the study. The amount of crystalloid fluid, synthetic colloid, or blood product that each dog received was recorded daily.

Assessment for multiorgan dysfunction syndrome (MODS)

The records of enrolled dogs were retrospectively reviewed to evaluate for the presence of MODS as described by Kenney et al.[47] Dogs that had an increase in serum creatinine $\geq$38 μmol/L (0.5 mg/dL) between any 2 time points in hospitalization were considered to have kidney dysfunction, provided that there was no evidence of pre- or postrenal azotemia. Any dog that received vasopressor therapy was considered to have cardiovascular dysfunction. Dogs that received supplemental oxygen therapy during their hospitalization were considered to have pulmonary dysfunction. Hepatic dysfunction was diagnosed if the total bilirubin concentration exceeded 8.5 μmol/L (0.5 mg/dL) at any time during hospitalization, and coagulation dysfunction was diagnosed if the prothrombin time or the activated partial thromboplastin time exceeded the upper limit of the normal range by 25% or if the platelet count was $\leq$100,000/uL, or both. MODS was diagnosed if there was dysfunction of $\geq$2 organ systems.

Assessment for delayed reaction

Clients whose dogs were randomized to the CSA group received a follow-up phone call 6 weeks following

Table 1: Comparison of baseline characteristics in dogs that received a canine-specific albumin transfusion (CSA) versus those that received clinician-directed therapy (CDT) following surgical source control for septic peritonitis

Variable—median	CDT	CSA	*P* value
Age (years)	6.0	8.0	0.4408
Weight (kg)	23.1	24.5	0.9491
Sex (males)	5	4	1.000

release from the hospital. They were questioned as to their dog's general health, and direct questions were asked regarding facial swelling, limping, or urticaria.

Statistical analysis

Given the small sample size, nonparametric statistical tests were chosen. Continuous result variables were summarized as median (minimum, maximum). The Wilcoxon rank sum test was used to test for differences between the medians. Categorical result variables were described using percentages and Fisher's exact test was used to test for differences between groups. For all comparisons, *P* values less than 0.05 were considered significant. All statistical analyses were performed using a standard statistical analysis software.[f]

Results

Fourteen dogs were eligible for enrollment in the study: 7 dogs were randomized to the CDT group and 7 dogs were enrolled in the CSA group. Breeds represented included Labrador retrievers (2), standard poodles (2), dachshunds (2), and mixed breed dogs (3). A variety of other purebreds represented the remaining dogs: American Staffordshire terrier, Siberian husky, Brittany spaniel, German shepherd, and Doberman pinscher. The median age of all dogs was 6.4 years (range 0.3–12 years). The median weight of all dogs was 22.3 kg (range 2.6–35 kg). There was no significant difference between groups in the baseline characteristics of age, sex, or weight (Table 1). No patient had a history of a diagnosed protein-losing disease at the time of enrollment.

Causes of septic peritonitis were varied. In the CDT group causes included dehiscence following intestinal resection and anastomosis for foreign body obstruction in 2 dogs, and 1 each of the following: intestinal perforation secondary to foreign body ingestion, gastric dilatation and volvulus with subsequent gastric rupture, dehiscence of gastrectomy incision, traumatic rupture of intestine secondary to motor vehicular trauma, and hepatic abscess. Causes of septic peritonitis in the CSA group included dehiscence following resection and anastomosis for foreign body obstruction in 2 dogs, and 1 each of the following: intestinal perforation secondary to foreign body ingestion, dehiscence following a previous gastrectomy for gastric dilatation and volvulus, perforation of the duodenum secondary to gastrointestinal lymphoma, mesenteric abscess, and pancreatic abscess. Thirteen dogs had positive bacterial or fungal cultures from abdominal samples; the dog with a negative bacterial culture had intracellular rod bacteria noted on abdominal fluid cytology reviewed by a board-certified veterinary clinical pathologist. Bacteria isolated included *Escherichia coli* (3), *Enterococcus sp.* (3), *Enterococcus faecium* (1), *Streptococcus viridans* (1), *Clostridium sp.* (1), and *Staphylococcus sp.* (1). Three dogs had culture results reported as numerous mixed bowel flora with no further speciation performed. Two dogs had cultures positive for *Candida glabrata*. Both of these dogs also had positive bacterial cultures (*Enterococcus sp.*; mixed bowel flora).

All dogs in the CSA group completed the transfusion of lyophilized CSA. One dog experienced an increased RR 3 hours into the transfusion. The tachypnea resolved after the transfusion rate was decreased and a 2 μg/kg bolus of fentanyl citrate was administered. Central venous pressure at the time of the tachypneic episode was 2.5 cm H_2O. This dog completed the transfusion in approximately 7 hours and survived to discharge. At the time of discharge, the patient had severe, unresolved regurgitation, and was released from the hospital against medical advice. The dog returned for evaluation 48 hours after discharge in a moribund condition with acute respiratory distress, and euthanasia was performed at the request of the owner. Physical examination findings at that time revealed tachycardia (180/min), tachypnea (70/min), and pyrexia (41°C). Dehydration was estimated at 10%. Crackles were ausculted in all lung fields, and the dog regurgitated during examination. A diagnosis of aspiration pneumonia was suspected; however, acute respiratory distress syndrome or complications secondary to CSA transfusion cannot be ruled out as further diagnostic testing including necropsy were declined. The death of this dog occurred 120 hours after CSA transfusion. No dog was noted to have regurgitation, vomiting, or diarrhea during the transfusion of CSA. Follow-up calls were completed in the remaining 6 dogs enrolled in the CSA group after a period of 6–8 weeks posthospital discharge. No owner reported signs consistent with delayed immunologic reaction (eg, facial swelling, dermatologic lesions, lameness, anorexia).

The median COP of administered CSA was 22 mm Hg (range 21–25 mm Hg). The median ALB of all dogs upon enrollment in the study was 15 g/L (1.5 g/dL) ([range 10–24 g/L] 1.0 – 2.4 g/dL). The median COP of all dogs upon enrollment in the study was 9.3 mm Hg (range 7.9–11.7 mm Hg; reference interval 18–24 mm Hg). The median DBP of all dogs upon enrollment to the

Table 2: Comparison of serum albumin concentrations (ALB), colloid osmotic pressure (COP), and Doppler blood pressure (DBP) at the time of enrollment in dogs that received a transfusion of canine-specific albumin (CSA) versus those that received clinician-directed therapy (CDT) following surgical source control for septic peritonitis

Variable—median	CDT	CSA	*P* value
ALB g/L (g/dL)	15 (1.5)	15 (1.5)	1.0000
COP (mm Hg)	9.3	10.1	0.6089
BP (mm Hg)	129	133	0.7009

study was 120 mm Hg (range 90–152 mm Hg; reference interval 90–140 mm Hg). There were no significant differences between groups regarding enrollment ALB, COP, or DBP (Table 2). The dogs enrolled in the CSA group experienced a significant increase compared to baseline in ALB, COP, and DBP 2 hours after transfusion (Table 3). In addition, there was a significant difference in the median ALB at 24 hours between groups ($P = 0.0039$), but at no other time point during the study period. The median ALB was significantly higher in the CSA group at 24 hours, but at no other time point during the study period ($P = 0.0367$). The change in ALB between enrollment and the date of discharge from the hospital or death was not statistically significant between groups ($P = 1.00$). There were no differences between the 2 groups in regards to COP or DBP at 24 hours following CSA administration or at the date of death or discharge (Table 4).

There was no difference in the median crystalloid or synthetic colloid rates between the groups throughout the period of hospitalization. No dog received boluses of crystalloids or synthetic colloids during the transfusion of CSA. Three dogs received plasma transfusions during the pre-enrollment period (anesthesia). Two of these dogs were in the CDT group; 1 dog was in the CSA group. The mean dose of fresh frozen plasma (FFP) administered was 7.6 mL/kg. One dog received a FFP transfusion during the study period (8.6 mL/kg), and 1 dog received a packed red blood cell transfusion during the study period (12 mL/kg). Median percentage RER consumed was not statistically different between the groups. Four dogs received parenteral nutrition during the study period. Eight dogs received enteral nutrition through either a nasoesophageal tube or a jejunostomy tube (Table 5).

Twelve dogs survived to discharge, 1 dog died, and 2 were euthanized. The overall mortality rate was 21%. Five dogs (35.7%) met the criteria for diagnosis of MODS, including all 3 nonsurvivors. The mortality rate among dogs with MODS was 60%. One dog was euthanized following histopathologic diagnosis of gastrointestinal lymphoma, and 1 dog was euthanized due to a third dehiscence of a resection and anastamosis site. Two nonsurvivors were enrolled in the CSA group, and 1 nonsurvivor was enrolled in the CDT group. There was no statistical association between survival and ALB at enrollment ($P = 0.9899$), but there was a statistical association between survival and the last ALB on the date of death or discharge, regardless of group assignment ($P = 0.0352$). There was no statistical association between administration of CSA transfusion and survival ($P = 1.00$).

Discussion

This study revealed an increase in ALB, COP, and DBP 2 hours following a transfusion of 5% lyophilized CSA. In addition, the ALB was higher in the CSA group in comparison to a CDT group at 24 hours posttransfusion. There were minimal adverse events that were potentially attributed to administration of CSA product in this population of dogs.

CSA was administered at a dose of 800 mg/kg and infused as a 5% solution in this study. The dose of CSA was determined from the package insert as recommended for dogs suffering from hypoalbuminemia or hypoproteinemia. CSA can be administered as a 16%, 10%, (both hyperosmotic), or 5% (iso-osmotic) solution per the manufacturer. Five percent was selected for the current population of patients due to the potent osmotic pull of albumin-containing solutions.[48] While patients suffering from sepsis frequently require large volumes of crystalloid and colloid solutions, enrollment of these dogs took place following diagnosis of septic peritonitis, initial resuscitation, and definitive surgical intervention. Dogs returning to the ICU for enrollment were often diagnosed as volume replete or having increased intravascular

Table 3: Comparison of median serum albumin concentration (ALB), colloid osmotic pressure (COP), and Doppler blood pressure (DBP) at enrollment versus 2 hours following transfusion of 800 mg/kg of canine-specific albumin

Variable	Enrollment	2 hours posttransfusion	Median change from enrollment to 2 hours	*P* value
ALB g/L (g/dL)	15 (1.5)	22 (2.2)	8 (0.8)	0.0234*
COP (mm Hg)	10.1	13.8	3.3	0.0078*
BP (mm Hg)	133	144	15	0.0156*

*A statistically significant value ($P < 0.05$).

Table 4: Comparison of serum albumin concentrations (ALB), colloid osmotic pressure (COP), and Doppler blood pressure (DBP) at various time points in dogs that received a transfusion of canine-specific albumin (CSA) versus those that received clinician-directed therapy (CDT) following surgical source control for septic peritonitis

Variable—median	CDT	CSA	*P* value
Albumin g/L (g/dL) 24 hour posttransfusion	14 (1.4)	20.5 (2.05)	0.0367*
Albumin g/L change in 24 hours posttransfusion	0	5.5 (0.55)	0.0039*
Albumin g/L date of death or discharge	19 (1.9)	19 (1.9)	1.0000
Albumin g/L change from enrollment to date of death or discharge	4 (0.4)	5 (0.5)	0.7478
COP mm Hg 24 hour posttransfusion	13.9	14.0	0.6682
COP mm Hg change in 24 hours posttransfusion	4.0	4.35	0.3914
COP mm Hg date of death or discharge	15.7	13.3	0.2248
COP mm Hg change from enrollment to date of death or discharge	5.3	4.8	0.7981
BP mm Hg 24 hour posttransfusion	137	140	0.7206
BP mm Hg change in 24 hours posttransfusion	16	24	0.5145
BP mm Hg date of death or discharge	140	144	1.0000
BP mm Hg change from enrollment to date of death/discharge	13	12	0.9491

*A statistically significant value ($P < 0.05$).

Table 5: Comparison of median fluid rates and percentage of resting energy requirement ingested throughout the study period in dogs receiving a transfusion of canine-specific albumin (CSA) versus dogs that received clinician-directed therapy (CDT) following surgical source control for septic peritonitis

Variable—median	CSA	CDT	*P* value
Crystalloids (mL/kg/h)	2.2	1.6	0.5649
Synthetic colloids (mL/kg/h)	0.58	0.48	0.8982
Resting energy requirement (%)	54	55	0.8478

volume based on central venous pressure measurements, plasma lactate measurements, and physical examinations. Concerns for the development of intravascular volume overload following use of a hyperosmotic solution was a factor in selection of a 5% CSA solution.

There were minimal adverse events that were potentially attributed to administration of CSA product in this population of dogs. This is consistent with a safety study performed by the manufacturer in adult, purpose-bred beagles.[49] One dog in our study did experience an increased RR during the transfusion. Potential causes of tachypnea in this dog include acute transfusion reaction, pain, anxiety, volume overload, aspiration pneumonia, or acute respiratory distress syndrome. The tachypnea resolved following a slowing of the CSA transfusion and an IV injection of an opioid. Other diagnostics that could have excluded other causes may have included thoracic radiography or arterial blood gas analysis. These were not performed as the dog improved immediately following the above interventions. This same dog was euthanized in a terminal condition due to unknown respiratory complications 120 hours following CSA administration. Francis et al[44] described the adverse reactions of 6 dogs given HSA. One dog experienced an acute reaction, characterized by vomiting and facial edema. All 6 dogs in that report experienced clinical signs consistent with a Type III hypersensitivity reaction. These included peripheral edema, vasculitis, lameness, vomiting, diarrhea, pruritis, lethargy, and inappetance. Two dogs ultimately succumbed to complications secondary to Type III hypersensitivity reactions. These 2 dogs were also the only dogs to experience respiratory signs; these occurred late in the course of each dog's hospitalization. The first dog was suspected to have respiratory signs secondary to pulmonary hemorrhage as sequelae of disseminated intravascular coagulation. The second dog's respiratory signs were suspected to be secondary to acute respiratory distress syndrome with septic shock as an underlying cause. The dog that experienced an acute reaction recovered with supportive care. The dog described in our study did not have any evidence of peripheral edema, vasculitis, pruritus, or lameness preceding its respiratory signs. Regurgitation had been reported in this dog prior to CSA transfusion and persisted through its hospitalization. However, due to the dog's underlying disease, the clinical signs associated with any reaction may be altered. Therefore, delayed hypersensitivity reaction secondary to CSA administration cannot be dismissed as a cause of death in this dog. In all other surviving dogs that received CSA, no symptoms of a delayed reaction were reported by the owners.

This study focuses on a novel canine-specific lyophilized albumin product in a population of critically ill dogs following source control for septic peritonitis. Our results revealed an increase in ALB 2 hours following transfusion and an increased ALB in comparison to a CDT group at 24 hours. However, this difference in ALB between groups was no longer present at the date of death or discharge. This may be attributable to several reasons. It is unlikely that albumin production in this population of animals was normal. Albumin production, in health, is dependent mostly upon COP and adequate nutritional intake.[48] Although these dogs did uniformly exhibit abnormally low COP readings, our results indicate that most animals did not receive their calculated RER despite aggressive nutritional support. However, the amount of nutrition provided between the CSA and CDT groups was not significantly different. Additionally, albumin synthesis is downregulated during times of acute illness, regardless of nutritional status.[2,50]

Continued microvascular dysfunction and persistent third space fluid loss may have contributed to ongoing albumin loss.[11,51] The amount of intravenous crystalloid and synthetic colloid that each dog received during hospitalization may also have contributed to differences in albumin concentration. However, there was no difference in the amount of crystalloid or synthetic colloid administration between the study groups.

There was an association between a higher ALB at the date of death or discharge and survival in this study. This is consistent with previous veterinary studies in which hypoalbuminemia is associated with an increased risk of morbidity and mortality in populations of animals with septic peritonitis.[6,7,14,52] However, these studies report on preoperative ALB concentrations, not postoperative ALB. Nonetheless, Dominguez de Villota et al described a group of critically ill human patients classified by the lowest recorded ALB in which lower ALB were associated with increased risk of infection and mortality.[53] In addition, 2 meta-analyses identified hypoalbuminemia at any point during illness or a declining albumin concentration within the normal range as independent risk factors for poor outcome.[8,15] It is likely that an association between preoperative ALB was not noted in this group of dogs due to its small size and homogenous population of dogs with septic peritonitis.

Dogs that received CSA did show a significant increase in COP value 2 hours after the transfusion. However, no difference was seen between the CSA and CDT groups at 24 hours or at the date of death or discharge. The mean increase in COP (4.36 mm Hg) seen in the CSA group was consistent with the mean increase in COP reported by Trow et al[41] when using 10% HSA in a population of critically ill dogs.[41] Twenty-seven percent of those dogs had been diagnosed with septic peritonitis.[41] However, the use of synthetic colloids was not evaluated in that retrospective study. In this population of dogs treated prospectively and followed over a longer period of time, this lack of difference in COP between CSA and CDT groups is likely secondary to the administration of HES. All dogs enrolled in the study received continuous rate infusions of HES. HES has a reported COP of 32.7 mm Hg, while 5% human albumin and 12.5% human albumin have a reported COP of 23.2 mm Hg and 95.3 mm Hg, respectively.[54] Given that the CSA utilized in this study had a COP of 21–25 mm Hg, it is likely that any changes in COP that may have been the result of CSA administration would have been masked by HES administration over subsequent hospitalization.

Similarly, an increase in DBP was noted in dogs in the CSA group 2 hours following CSA administration, but no difference between the CSA or CDT group was ever noted. This is similar to what was reported by Mathews and Barry,[40] in which patients receiving a 25% solution of HSA did have a significant increase in SBP following IV bolus, slow push, or continuous rate infusion.[40] It was unclear as to what time period these BPs were obtained due to the retrospective nature of the study. Mean increase in SBP in dogs diagnosed with peritonitis (not necessarily septic peritonitis) was similar to that reported in this study (19 mm Hg in study by Mathews, versus 17.6 mm Hg in present study), despite the difference in concentration of infused product (25% versus 5%).[40] BP may be affected by numerous factors, including intravascular volume status, systemic vascular resistance, cardiac output, pain, anxiety, and pharmaceuticals.[27] It is likely that these dogs may have had contributions of any of these factors in determining BP, making it difficult to ascertain changes secondary to the administration of CSA itself.

Survival to discharge in this population of dogs was 80%, which is higher than previously reported survival rates of 27–62% in populations of dogs with septic peritonitis.[1,3,7,9,11] The most likely reason for this difference is the small sample size. This study was not adequately powered to evaluate for a difference in mortality between groups, as sample size was limited by the amount of CSA product that was donated by the company. A sample size calculation was not performed as part of the design of the study, but post hoc analysis revealed that 46 dogs would be required in each group to give the study a power of 80% at a significance level of 5% to detect an increase in survival rate from a baseline of 50% to a treatment result of 75%. Therefore, the high survival rate associated with this group of dogs may simply be due to chance. A second reason for the increased survival rate in this population could be secondary to a decreased severity of illness; however, injury severity scoring was not performed. Evidence of MODS was present in just over one-third (35.7%) of enrolled dogs, and almost two-thirds (60%) of these dogs died. This is consistent with a previous multicenter retrospective study demonstrating higher mortality in dogs with MODS secondary to septic peritonitis, than in those without.[47] It could also be argued that the dog that was discharged from the hospital against medical advice and was subsequently euthanized 48 hours later should not be included in the survival to discharge group. If instead this dog is included in the group that did not survive to discharge, the survival rate associated with this population of dogs is 71%.

Administration of species-specific plasma is also a source of albumin. Only 1 dog received FFP during the study period (8.6 mL/kg). Three dogs received FFP transfusions during the pre-enrollment period (eg, during general anesthesia). These dogs received a mean of 7.6 mL/kg of FFP. It is unlikely that this amount of plasma would result in a clinically relevant increase in

ALB. A recent retrospective study evaluating the use of FFP found no statistically significant increase in albumin concentrations at median doses of FFP of 15 and 18 mL/kg.[39]

Other limitations to this study exist aside from small sample size and lack of illness severity scoring. Due to financial constraints, evaluation of ALB, COP, and DBP were not performed in the CDT group at the 2-hour post-transfusion time point. This prevented statistical analysis of data between groups at that time point, necessitating the CSA group to act as its own control for that data point. Additionally, only a single transfusion of CSA was administered. It would have been ideal to administer multiple transfusions to a specific endpoint to truly eliminate the hypoalbuminemic state. This would be similar to the pilot data published by Dubois et al,[31] in which a group of hypoalbuminemic, critically ill people were administered 60 g of 20% albumin at randomization, and then 40 g of 20% albumin each day until ALB was >31 g/L (3.1 g/dL). Patients randomized to receive albumin did show improvement in ALB and illness severity scores, as well as a less positive fluid balance.[31]

Although group assignments were randomized, this study was not blinded, and there was no placebo controlled cohort, raising the possibility that clinician decisions may have been influenced by CSA therapy. In addition, dogs were not reexamined by a veterinarian following discharge from the hospital. Untrained animal owners were thus responsible for recognizing potential problems secondary to CSA transfusion, which may have resulted in the inability to identify some possible adverse reactions.

This study is the first description of the use of a lyophilized CSA product in a population of dogs following surgical source control for septic peritonitis. The use of a 5% solution of CSA resulted in an increase in ALB, COP, and DBP 2 hours after administration. An increase in ALB persisted 24 hours after administration in comparison to a CDT group. Minimal adverse events were observed in this small population of dogs; however, further evaluation of this product in larger populations of critically ill dogs is recommended to further assess other outcome parameters.

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Footnotes

[a] Lyophilized canine albumin, Animal Blood Resources International, Dixon, CA.
[b] 0.9% Sodium chloride injection USP, Baxter Healthcare Corp, Deerfield, IL.
[c] Hespan, B Braun Medical, Inc., Irvine, CA.
[d] AU 400e, Beckman Coulter, Inc., Brea, CA.
[e] 4420 Colloid osmometer, Wescor, Princeton, NJ.
[f] JMP version 8.0.2, SAS Institute, Inc., Cary, NC.

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