Retrospective Study

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Administration of 5% human serum albumin in critically ill small animal patients with hypoalbuminemia: 418 dogs and 170 cats (1994–2008)

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Abstract

Objectives – To describe the administration of 5% human serum albumin (HSA) in 588 critically ill hypoalbuminemic dogs and cats, and report outcome to discharge, changes in albumin concentration, and adverse effects during hospitalization.
Design – Retrospective clinical study.
Setting – Private emergency and general veterinary center.
Animals – Client-owned dogs and cats.
Interventions – None.
Measurements and Main Results – The medical records of 588 critically ill hypoalbuminemic animals (418 dogs and 170 cats) were reviewed. All animals had hypoalbuminemia (serum albumin <20 g/L [2.0 mg/dL]) at admission, received an infusion of 5% HSA, and received no other colloid infusion. The HSA solution was administered through a peripheral vein at 2 mL/kg/h for 10 h/d (total volume 20 mL/kg/d) until albumin reached 20 g/L. The number of days of HSA infusion (median and range) was 4 days (2–11 d) for dogs and 3 days (2–7 d) for cats. Three hundred and sixteen dogs (75.6%) survived to discharge; 56 of 418 (13.4%) died in hospital. One hundred and twenty-three cats (72.3%) survived to discharge; 21 of 170 (12.4%) died in hospital. Severe hypersensitivity reactions such as anaphylaxis, angioedema, and urticaria were not noted. Interruption of albumin infusion and specific treatment of reactions were not required in any animal.
Conclusions – In this study, administration of 5% HSA appeared to be safe in a large group of critically ill, hypoalbuminemic dogs and cats. The results should be interpreted with caution due to the retrospective, descriptive nature of the study, the absence of control groups and the lack of follow-up data, as well as the potentially life-threatening complications of HSA administration.

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Introduction

Albumin is a major blood protein that is responsible for approximately 70% of plasma oncotic pressure.[1–3] Albumin performs many physiological functions, of which maintenance of intravascular volume is one of the most important.[3] At the level of the capillary, hydrostatic pressure alone would create a net loss of fluid out of the intravascular space.[3] Without the counterbalancing effect of oncotic pressure, intravascular volume could not be maintained.[3] The movement of albumin out of the intravascular space is governed by the transcapillary escape rate.[2] This is influenced by albumin concentrations in the intravascular and extravascular fluid compartments, microvascular permeability, movement of solvents and solutes, and transcapillary electrical charge.[2]

Hypoalbuminemia is a common complication of critical illness.[2,4–7] It is often associated with the systemic

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inflammatory response syndrome caused by conditions such as sepsis, peritonitis, pancreatitis, viremia, burns, multiple trauma, and heatstroke.[2,8] Other causes of hypoalbuminemia include neoplasia, liver disease, renal failure, and inflammatory bowel disease.[9,10]

Hypoalbuminemia compromises homeostasis and can result in tissue edema and reduced tissue oxygen delivery.[3,11] The resulting hypoperfusion can be responsible for single or multiple organ dysfunction,[12] endothelial damage, and increased vascular permeability.[13] In critically ill patients, hypoalbuminemia can contribute to other life-threatening complications such as hypotension, hypovolemia, pulmonary edema, and delayed wound healing.[2,4,14,15]

Colloids have been recommended in the human and veterinary literature for restoration of colloid osmotic pressure and blood volume.[16–22] Albumin is a natural colloid and has advantages over synthetic colloids because it transports drugs, ions, hormones, lipids, and metals, and has scavenger activity as a thiol-group donor.[2] Intravenous infusion of human serum albumin (HSA) is a rapid means of correcting hypoalbuminemia and transcapillary escape rate.[14,23] It is a well-documented method of treating hypoalbuminemia in critically ill humans.[14,21,22,24–28] The main indications in humans are: hypovolemia, hypovolemic shock, trauma, burns, peritonitis, pancreatitis, sepsis, ascites, plasmapheresis, and surgical procedures.[9,14,29]

Intravenous albumin expands vascular volume, restores oncotic pressure, helps prevent or reverse interstitial edema, protects against ischemia-reperfusion injury, reduces microvascular permeability, and improves microcirculation.[1,30,31] When albumin is administered in human patients with an intact vascular wall, it remains in the vascular compartment for about 24 hours, with a half-life of 16 hours.[2,9] Despite these benefits, the effectiveness of albumin in human medicine is controversial.[6–9,31] Authors have questioned whether the increased cost of albumin can be justified in human patients, in view of the fact that several studies and meta-analyses have found that outcomes were no better for albumin than for saline.[6,8,19,26]

HSA has been used in veterinary patients because of the lack of commercially available animal products. As in human medicine, its use is controversial,[4,17,32,33] but a significant element of the veterinary controversy revolves around safety, because of the potential for severe hypersensitivity reactions to a foreign blood protein.[32] Infusion of 25% HSA provoked a strong IgG antibody response in dogs, peaking several weeks after administration.[34] Severe immediate and delayed adverse reactions[35–37] have been reported in both critically ill[4,5,35] and healthy[36,37] dogs. A retrospective, observational study reported increased albumin concentrations, improved systolic blood pressure and no severe adverse reactions when 25% HSA was used as an adjunctive therapy in 66 critically ill dogs and cats.[5] Current recommendations are that 25% HSA should only be administered to dogs and cats if the potential benefits are likely to exceed the potential risks.[32,35]

The use of iso-oncotic (5%) HSA in veterinary patients has not been reported, and HSA infusion has been reported in only 2 cats.[5] The objectives of this retrospective study were: (1) to describe the administration of 5% HSA as a constant-rate infusion (CRI) in a large group of critically ill, hypoalbuminemic dogs and cats; (2) to report short-term outcomes; (3) to report changes in serum albumin concentrations during infusion; and (4) to report adverse events recorded during hospitalization.

Materials and Methods

The records of patients admitted to a private emergency and general veterinary center that receives both referral and nonreferral type patients were evaluated for inclusion in the study. Patients that received HSA infusions between January 1994 and September 2008 and that: (1) had hypoalbuminemia, defined as serum albumin $<20\,g/L$ (2.0 mg/dL), at admission; (2) were treated with a CRI of 5% HSA; and (3) had not received any other colloid infusion before, during or after the HSA, were included in the study. As part of the hospital's standard operating procedure, owners were required to sign a general consent form agreeing to hospitalization and treatment.

Physical examination records and biochemical data were available for all patients, and blood gas analysis data were available in some cases. Using data from the initial clinical examination, the biochemical profile and records of surgical procedures, the patients were grouped into 5 categories: gastric-dilatation-volvulus complex, peritonitis, nephropathy, liver disease, and protein-losing enteropathy (PLE).

A standard protocol for HSA administration was followed at the authors' clinic during the study period: The albumin solution was made from 25% commercial HSA[a] diluted to 5% in 0.9% saline[b] for patients with alkalosis or hyponatremia, or in lactated Ringer's solution[c] for patients with acidosis. When it was not possible to evaluate the patient's acid-base and electrolyte status, the HSA was diluted in 0.9% saline. Albumin was administered through a peripheral vein either as initial fluid therapy or after resuscitation with a crystalloid solution. The 5% HSA was infused at a constant rate of 2 mL/kg/h over 10 hours (ie, a daily volume of 20 mL/kg/d). Serum albumin was measured before treatment and every 24 hours during the HSA infusion,

until a concentration of 20 g/L was reached. The albumin infusion was discontinued at this point.

During hospitalization, the patients had a physical examination completed at least twice daily by a veterinarian; more serious cases were monitored more frequently or continuously as required. The standard examination included at least rectal temperature, heart rate, mucous membrane color, pulse quality, respiratory rate, and lung auscultation. All findings were routinely recorded. Because of the clinicians' awareness of the potential for adverse reactions to HSA, particular attention was paid to these. The catheter sites were checked regularly for signs of perivascular inflammation (swelling and pain around the catheter site). For infusions extending beyond 3 days, the catheters were removed every third day and replaced with new catheters in substitute peripheral veins.

The patient records were scrutinized for reports of adverse reactions to HSA, which were considered severe (anaphylaxis, angioedema, urticaria) or minor (diarrhea, hyperthermia, and tremor not associated with fever [temperature $\geq$ 39.5°C {103.1°F}]).

Normally distributed data are reported as mean (standard deviation) and nonnormally distributed data are reported as median (range).

Results

The records of 588 patients were reviewed. There were 418 dogs and 170 cats. The mean age for dogs was 7.11 years (2.19 y). The mean age for cats was 7.70 years (3.26 y). Two hundred and eighty-four of 418 (67.9%) dogs were male and 134 of 418 (32.1%) were female. Eighty-nine of 170 (52.4%) cats were male and 81 of 170 (47.6%) were female.

The frequency of various disease classifications for dogs was: gastric-dilatation-volvulus complex (n = 255), peritonitis (n = 62), nephropathy (n = 37), liver disease (n = 18), and protein-losing enteropathy (n = 46) (Table 1). The causes of peritonitis were pancreatitis (n = 17), diffuse neoplasia (n = 12), intestinal perforation (n = 9), postoperative diaphragmatic hernia (n = 9), uterine perforation (n = 4), bladder rupture (n = 4), gastric perforation (n = 3), bile duct rupture (n = 2), postoperative duodenal or jejunal dehiscence (n = 1), and urethral rupture (n = 1).

Of the cats, 62 had peritonitis, 95 had nephropathy, and 13 had liver disease (Table 2). The causes of peritonitis were feline infectious peritonitis (n = 14), postoperative diaphragmatic hernia (n = 14), bladder rupture (n = 9), intestinal perforation (n = 8), urethral rupture (n = 5), pancreatitis (n = 4), diffuse neoplasia (n = 3), uterine perforation (n = 2), postoperative duodenal or jejunal dehiscence (n = 2), and bile duct rupture (n = 1).

Three hundred and sixteen of the 418 (75.6%) dogs survived to discharge and 56 (13.4%) died in hospital. Seventeen of 418 (4.1%) were euthanized due to cost considerations or a poor to hopeless prognosis, and in 29 of 418 (6.9%) the outcome was unknown. These 29 dogs were discharged early at the owners' request, usually due to financial considerations. All had albumin of at least 20 g/L at the time of early discharge. No follow-up data were available for this group.

One hundred and twenty-three of 170 (72.3%) cats survived to discharge, 21 of 170 (12.4%) died in hospital, 11 of 170 (6.5%) were euthanized, and outcome was unknown in 15 of 170 (8.8%), due to early discharge at the owners' request. Outcomes for the different disease groupings are shown in Tables 1 and 2.

The median number of days of HSA infusion required for serum albumin to reach 20 g/L was 4 days (2–11 d) for dogs and 3 days (2–7 d) for cats.

Severe hypersensitivity reactions such as anaphylaxis, angioedema, and urticaria were not noted in any patient record. In no case was it necessary to discontinue or interrupt the albumin infusion due to adverse effects. Diarrhea, hyperthermia, or tremors were noted in 182 of 418 (43.5%) dogs and 62 of 170 (36.5%) cats. A combination of adverse reactions was recorded in 58 of

Table 1: Outcomes for 418 critically ill hypoalbuminemic dogs treated with 5% human serum albumin infusion

		Disease groups				
Outcome	**All (n = 418)**	**GDV (n = 255)**	**Peritonitis (n = 62)**	**Nephropathy (n = 37)**	**Liver disease (n = 18)**	**PLE (n = 46)**
Survived	316 (75.6)	209 (82.0)	38 (61.3)	25 (67.6)	10 (55.5)	34 (73.9)
Died	56 (13.4)	28 (11.0)	15 (24.2)	5 (13.5)	3 (16.7)	5 (10.9)
Euthanized	17 (4.1)	7 (2.7)	2 (3.2)	3 (8.1)	3 (16.7)	2 (4.3)
Outcome unknown*	29 (6.9)	11 (4.3)	7 (11.3)	4 (10.8)	2 (11.1)	5 (10.9)

Data are shown as frequency counts (%).

*These animals were discharged early at the owners' request.

GDV, gastric dilatation volvulus; PLE, protein-losing enteropathy.

Table 2: Outcomes for 170 critically ill hypoalbuminemic cats treated with 5% human serum albumin infusion

		Disease groups		
Outcome	**All ($n = 170$)**	**Peritonitis ($n = 62$)**	**Nephropathy ($n = 95$)**	**Liver disease ($n = 13$)**
Survived	123 (72.3)	47 (75.8)	73 (76.8)	3 (23.1)
Died	21 (12.4)	8 (12.9)	7 (7.4)	6 (46.1)
Euthanized	11 (6.5)	3 (4.8)	6 (6.3)	2 (15.4)
Outcome unknown*	15 (8.8)	4 (6.4)	9 (9.5)	2 (15.4)

Data are shown as frequency counts (%).
*These animals were discharged early at the owners' request.

182 (31.9%) dogs and 21 of 62 (33.9%) cats (Tables 3 and 4). One hundred and sixteen of 418 (27.8%) dogs and 18 of 170 (10.6%) cats showed reactions on >1 day. Reactions were not noted beyond Day 3. Specific treatment for minor adverse effects was not required in any patient. Perivascular inflammation at catheter sites following HSA infusion was noted in 71 of 418 (17.0%) dogs and 58 of 170 (34.1%) cats.

Discussion

To the authors' knowledge, this is the first study to document the administration of iso-oncotic (5%) HSA as a CRI over several days in critically ill, hypoalbuminemic animals. The standardized protocol for HSA infusion at the authors' clinic provided a study group with uniform criteria for albumin administration, a clear end-point and serial measurements of serum albumin. The group included a large number of dogs and, importantly, 170 cats. To date, the use of HSA has been reported in only 2 cats.[5]

The major limitations of this study were its retrospective nature, the lack of control groups, the lack of a defined method for identifying adverse reactions and the unavailability of follow-up data to assess delayed reactions. Prospective controlled trials are required to properly assess the safety and efficacy of 5% HSA infusion in critical veterinary patients.

In most previous studies, HSA was administered as a hyperoncotic (25%) bolus.[5,34,36,37] In the current study, 5% HSA, which is iso-oncotic,[4,38] was infused as a CRI of 2 mL/kg/h for 10 h/d. This rate and concentration are commonly used for colloid infusions in patients with acute decreases in colloid osmotic pressure.[18,25,26,30,39,40] The use of an iso-oncotic solution to slowly increase plasma albumin concentration represents a physiologic approach to hypoalbuminemia. Administering a hyperoncotic solution can alter the transcapillary fluid dynamic and may result in edema due to fluid overload.[16,41,42] It has also been suggested that supraphysiologic infusions of albumin could increase the risk of hypersensitivity reactions to albumin.[36] The slow, incremental nature of CRI allows immediate discontinuation of administration should severe reactions occur, compared with a bolus, where the entire volume might have been administered before a reaction is detected.

Trow et al[35] diluted HSA to 10% in saline and administered it as a CRI for 12 hours in dogs. In that study, 50.7% of dogs survived to discharge, while 71% of small animal patients survived to discharge in a study that used 25% HSA,[5] a rate similar to the current study. The retrospective nature of all 3 studies makes it difficult to interpret these findings.

Administering species-specific albumin to cats currently requires the use of species-specific fresh or frozen

Table 3: Number of adverse reactions in 182 of 418 critically ill hypoalbuminemic dogs treated with 5% human serum albumin infusion

Reactions	**Day 1**	**Day 2**	**Day 3**
Diarrhea (D)	32	17	0
Hyperthermia (H)	44	12	8
Tremors (T)	8	3	0
D+T	1	0	0
D+H	32	14	0
H+T	3	1	0
D+H+T	4	3	0
Perivascular inflammation	0	7	64

Table 4: Number of adverse reactions in 62 of 170 critically ill hypoalbuminemic cats treated with 5% human serum albumin infusion

Reaction(s)	**Day 1**	**Day 2**	**Day 3**
Diarrhea (D)	5	3	2
Hyperthermia (H)	13	5	3
Tremors (T)	5	3	2
D+T	5	4	0
D+H	3	2	2
H+T	0	0	0
D+H+T	2	1	2
Perivascular inflammation	0	2	56

plasma.[10,20,41] Canine serum albumin is now commercially available in the US market, but canine and feline albumin and plasma were not commercially available during the study period. For these reasons, over the past 14 years the authors have administered HSA when colloid therapy was indicated, particularly in hypoalbuminemic patients with continuous albumin loss. Only 1 brand of HSA was used, to reduce the potential risk of administration of different alloalbumins. In addition, only 1 type of colloidal fluid was administered. It would be of interest to establish whether either of these precautions might have helped to reduce the incidence of serious immune reactions.

The safety and efficacy of HSA in veterinary medicine are controversial.[4,17,32] The current study is noteworthy because it suggests that the risk: benefit ratio of HSA in critically ill dogs and cats might be more favorable than has been supposed.[34,36,37] Within the limitations of the study, albumin infusion was found to be safe in this patient group within the study period. No animal required interruption of the albumin infusion or administration of any drug to control allergic reactions. No severe adverse reactions were observed during HSA infusions.

Immediate hypersensitivity reactions to albumin can range from precipitous life-threatening events such as anaphylactic shock, cardiac arrest, ventricular arrhythmias, and pulmonary edema, to acute renal failure, urticaria, pruritus, peripheral edema, hyperthermia, diarrhea, vomiting, tremors, and hypotension.[7,10,34–37,43–46] Immediate reactions may occur within 15–30 minutes of initiating an infusion containing albumin.[35,43,44] In the current study, no life-threatening events or severe immediate reactions were noted; this is consistent with human and animal studies indicating that their incidence is low.[5,35,46] Considering the critical condition of these patients and the retrospective nature of the study, it is possible that some of the deaths attributed to the underlying disease could have been caused by reactions to HSA. The difficulty in accurately diagnosing adverse reactions has been acknowledged in the human literature, where subgroups of possible, probable, and unknown reactions have been reported.[46]

In 1 previous study, 6.8% of dogs had severe complications (coagulopathy, cardiac arrest) during or soon after 10% HSA infusion, while 27% overall had reactions that could have been due to the infusion.[35] In another study, 3.1% of dogs developed facial edema.[5] Anaphylaxis was not observed in either study.[5,35] Two dogs given repeat 25% HSA infusions after an interval of several months did not exhibit adverse reactions within 48 hours.[5]

In critical patients, nonspecific events such as diarrhea, tachycardia, hyperpnea, dyspnea, and hyperthermia could represent adverse reactions to HSA but these might also be attributable to the underlying disease process. Thus, minor reactions could have been over- or underdiagnosed in this study. Prospective, controlled clinical studies are required to assess the true incidence of adverse reactions during or after HSA infusion.

The incidence of complications associated with HSA appears to be higher in healthy dogs[36,37] than in sick ones.[5,34,35] It is possible that the immune dysfunction present in critically ill patients might have a protective effect by reducing antibody production.[35,47–50]

No follow-up data were available for the current study. The authors did not receive any reports of adverse events from owners or referring veterinarians, but this cannot be taken to mean that none occurred. Delayed reactions to HSA in dogs[35,37] are attributed to the antibody response to human albumin, which peaks 4–6 weeks after administration.[34] Delayed reactions include pulmonary edema, increased respiratory effort, lameness, joint effusions, ecchymoses, renal failure, peripheral edema, lethargy, inappetance, cutaneous lesions indicative of vasculitis, fever, and pain.[10,34–37] Three of 73 (4%) dogs in a recent study had suspected delayed complications.[35] Reactions have been reported from 5 days to 2 weeks following treatment.[35–37] Weekly follow-up after HSA infusion is recommended, and owners and referring veterinarians must be informed about the risk and nature of delayed reactions.[32]

In the current study, mean serum albumin concentrations increased during administration of 5% HSA. Several days were required to reach 20 g/L in most animals, with a maximum of 11 days for dogs and 7 days for cats. Other studies reported significant increases in albumin after HSA infusions;[5,35] serum albumin was significantly higher in survivors than nonsurvivors, as was the amount of albumin infused.[35,51] Controlled clinical trials in critical patients are required to define the precise contribution of 5% HSA to increased serum albumin concentrations.

Conclusions

The results of this study suggested that administration of 5% HSA appeared to be safe in a large group of critically ill, hypoalbuminemic dogs and cats, and that severe adverse reactions were uncommon. However, these results must be interpreted with caution, due to the retrospective, descriptive nature of the study, the absence of controls and the lack of follow-up data, as well as the potentially life-threatening complications of HSA administration. The same caveat applies to the short-term outcome data, which are difficult to interpret in the absence of controls or follow-up data.

Current recommendations, that HSA only be administered if the potential benefits outweigh the potential risks, should continue to be followed. Randomized, prospective, controlled trials are warranted to investigate the safety and efficacy of 5% HSA in critically ill dogs and cats.

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Footnotes

[a] Albital, Hardis S.P.A., Naples, Italy.
[b] Sodium Chloride 0.9 g/100 mL, Pierrel, Potenza, Italy.
[c] Ringer Lactate, Pierrel.

References

1. McGrotty Y, Tennant K. Alterazioni delle proteine plasmatiche, In: Villiers E, Blackwood I. eds. Gli Esami di Laboratorio. Torino: UTET; 2006, pp. 107–121.
2. Quinlan GJ, Martin GS, Evans TW. Albumin: biochemical properties and therapeutic potential. Hepatology 2005; 41(6):1211–1219.
3. Haller C. Hypoalbuminemia in renal failure: pathogenesis and therapeutic considerations. Kidney Blood Press Res 2005; 28:307–310.
4. 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.
5. Mathews KA, Barry M. The use of 25% human serum albumin: outcome and efficacy in raising serum albumin and systemic blood pressure in critically ill dogs and cats. J Vet Emerg Crit Care 2005; 15(2):110–118.
6. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomized controlled trials. Br Med J 1998; 317:235–240.
7. Dubois MJ, Orellana-Jimenez C, Melot C, et al. Albumin administration improves organ function in critically ill hypoalbuminemic patients: a prospective, randomized, controlled, pilot study. Crit Care Med 2006; 34:2536–2540.
8. SAFE Study Investigators, Finfer S, Bellomo R, et al. Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study. Br Med J 2006; 333(7577):1044, doi:10.1136/bmj.38985.398704.7C.
9. Goldwasser P, Feldman J. Association of serum albumin and mortality risk. J Clin Epidemiol 1997; 50:693–703.
10. Abrams-Ogg A. Practical Blood Transfusion, In: Day MJ, Mackin A, Littlewood JD. eds. BSAVA Manual of Canine and Feline Hematology and Transfusion Medicine. Gloucester, UK: British Small Animal Veterinary Association; 2000, pp. 263–303.
11. Martin GS, Mangialardi RJ, Wheeler AP, et al. Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury. Crit Care Med 2002; 30:2175–2182.
12. Vincent JL. Issues in contemporary fluid management. Crit Care 2000; 4(2):S1–S2.
13. Wang H, Ma S. The cytokine storm and factors determining the sequence and severity of organ dysfunction in multiple organ dysfunction syndrome. Am J Emerg Med 2008; 26(6):711–715.
14. Hedin A, Hahan RG. Volume expansion and plasma protein clearance during intravenous infusion of 5% albumin and autologous plasma. Clin Sci 2005; 108:217–224.
15. Zhang S, Li H, Ma L, et al. Polynitroxyl-albumin (PNA) plus tempol attenuate lung capillary leak elicited by prolonged intestinal ischemia and reperfusion. Free Radic Biol Med 2000; 29(1):42–50.
16. Mathews KM. Various types of parenteral fluids and their indications. Vet Clin North Am Small Anim Pract 1998; 28(3):498–504.
17. Hughes D, Boag AK. Fluid therapy with macromolecular plasma volume expanders, In: Di Bartola SP. ed. Fluid Therapy in Small Animal Practice, 3rd ed. Philadelphia: Elsevier; 2006, pp. 621–634.
18. Smiley LE. The use of hetastarch for plasma expansion. Probl Vet Med 1992; 4(4):652–667.
19. Schierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solution in critically ill patients: a systematic review of randomised trials. Br Med J 1998; 316:361–364.
20. Mishler JM. Synthetic plasma volume expanders: their pharmacology, safety and clinical efficacy. Clin Haematol 1984; 13:75–92.
21. Vercueil A, Grocott MP, Mythen MG. Physiology, pharmacology, and rationale for colloid administration for the maintenance of effective hemodynamic stability in critically ill patients. Transfus Med Rev 2005; 19(2):93–109.
22. Kuper M, Gunning MP, Halder S, et al. The short-term effect of hyperoncotic albumin, given alone or with furosemide, on oxygenation in sepsis-induced acute respiratory distress syndrome. Anaesthesia 2007; 62(3):259–263.
23. Greissman A, Silver P, Nimkoff L, et al. Albumin bolus administration versus continuous infusion in critically ill hypoalbuminemic pediatric patients. Intensive Care Med 1996; 22(5):495–499.
24. Martin GS, Moss M, Wheeler AP, et al. A randomized controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. Crit Care Med 2005; 33(8):1681–1687.
25. Runyon BA. Management of adult patients with ascites caused by cirrhosis. Hepatology 1998; 27:264–272.
26. Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2007; (4):1–65.
27. Péron JM, Bureau C, Gonzales L, et al. Treatment of hepatorenal syndrome as defined by the international ascites club by albumin and furosemide infusion according to the central venous pressure: a prospective pilot study. Am J Gastroenterol 2005; 100(12):2702–2707.
28. Vincent JL, Navicks R, Wilkes M. Morbidity in hospitalized patients receiving human albumin: a meta-analysis of randomized, controlled trials. Crit Care Med 2004; 32(10):2029–2038.
29. Qiao R, Siflinger-Birnboim A, Tiruppathi C, et al. Albumin and *Ricinus communis* agglutinin decrease endothelial permeability via interactions with matrix. Am J Physiol Cell Physiol 1993; 265:C439–C446.
30. Ramirez-Vick J, Vargas FF. Albumin modulation of paracellular permeability of pig vena caval endothelium shows specificity for pig albumin. Am J Physiol Heart Circ Physiol 1993; 264:H1382–H1387.
31. Soni N. Lessons from meta-analysis: the case of albumin. Transfus Altern Transfus Med 2001; 3(4):6–13.
32. Mathews KA. Monitoring fluid therapy and complications of fluid therapy, In: Di Bartola SP. ed. Fluid Therapy in Small Animal Practice, 3rd ed. Philadelphia: Elsevier Inc; 2006, pp. 377–390.
33. Kheirabadi BS, Crissey JM, Deguzman R, et al. Effects of synthetic versus natural colloid resuscitation on inducing dilutional coagulopathy and increasing hemorrhage in rabbits. J Trauma 2008; 64(5):1218–1229.
34. Martin LG, Luther TY, Alperin DC, et al. Serum antibodies against human albumin in critically ill and healthy dogs. J Am Vet Med Assoc 2008; 232(7):1004–1009.
35. Trow AV, Rozanski EA, deLaforcade A, et al. Evaluation of human albumin in critically ill dogs: 73 cases (2003–2006). J Am Vet Med Assoc 2008; 233(4):607–612.

36. Francis AH, Martin LG, Haldorson GJ, et al. Adverse reactions suggestive of type III hypersensitivity in six healthy dogs given human albumin. J Am Vet Med Assoc 2007; 230(6):873–879.
37. Cohn LA, Kerl ME, Lenox CE, et al. Response of healthy dogs to infusion of human serum albumin. Am J Vet Res 2007; 68(6):657–663.
38. Falk JL, Rackow EC, Weil MH. Colloid and Crystalloid Fluid Resuscitation, In: Shoemaker WC, Ayres S, Grenvick A, Holbrook PR, Thompson WL. eds. Textbook of Critical Care, 2nd ed. Philadelphia: WB Saunders Co; 1989, pp. 1055–1073.
39. Hiltebrand LB, Kimberger O, Arnberger M, et al. Crystalloids versus colloid for goal-directed fluid therapy in major surgery. Crit Care 2009; 13(2):1–13.
40. Rudloff E, Kirby R. The critical need for colloids: administering colloids effectively. Comp Cont Ed Pract Vet 1998; 20(1):27–43.
41. Logan JC, Callan MB, Drew K, et al. Clinical indications for use of fresh frozen plasma in dogs: 74 dogs (October through December 1999). J Am Vet Med Assoc 2001; 218:1449–1455.
42. Hughes D. Fluid therapy with artificial colloids: complications and controversies. Vet Anaesth Analg 2001; 28:111–118.
43. Green MT. Transfusion medicine, In: Wingfield WE, Raffe MR. eds. The Veterinary ICU Book. USA: Teton New Media; 2002, pp. 189–201.
44. Brooks M. Transfusion of plasma and plasma derivates, In: Feldman BF, Zinkl JG, Jain NC. eds. Schalm's Veterinary Hematology, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2000, pp. 838–843.
45. Yamaya Y, Niizeki K, Kim J, et al. Anaphylactoid response to optison® and its effects on pulmonary function in two dogs. J Vet Med Sci 2004; 66(11):1429–1432.
46. Vincent JL, Wilkes MM, Navickis RJ. Safety of human albumin—serious adverse events reported worldwide in 1998–2000. Br J Anaesth 2003; 91(5):625–630.
47. Modiano JF. Immunoglobulins, In: Feldman BF, Zinkl JG, Jain NC. eds. Schalm's Veterinary Hematology, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2000, pp. 904–909.
48. Zoran D. Immunodeficiency disorders, In: Feldman BF, Zinkl JG, Jain NC. eds. Schalm's Veterinary Hematology, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2000, pp. 941–946.
49. Azoulay E, Delclaux C. Is there a place for granulocyte colony-stimulating factor in non-neutropenic critically ill patients? Intensive Care Med 2004; 30(1):10–17.
50. Schmitz D, Wilsenack K, Lendemanns S, et al. β–adrenergic blockade during systemic inflammation: impact on cellular immune functions and survival in a murine model of sepsis. Resuscitation 2007; 72(2):286–294.
51. Siegel JH, Fabian M, Smith JA, et al. Oxygen debt criteria quantify the effectiveness of early partial resuscitation after hypovolemic hemorrhagic shock. J Trauma 2003; 54(5):862–880.