Human Albumin Therapy in Hypoalbuminemic Dogs

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Albumin is a crucial protein in the body, comprising approximately half of the plasma total protein. Albumin is synthesized exclusively by the liver. Under normal conditions, production occurs at one-third maximum capacity, meaning that in times of need, the liver has reserve capacity to increase albumin production. Stimulus for production is mainly the colloid osmotic pressure (COP) of the blood, but other factors, such as nutritional state, intracellular potassium, and certain hormones, also play a role.

Synthetic substances such as hetastarch and dextrans can also be recognized by the hepatic osmoreceptors and affect albumin synthesis. If these synthetic substances are used to increase COP to or above a normal level (20–40 mm Hg), they can actually turn off the signal to the liver to produce more albumin. Degradation occurs at a rate directly related to concentration, with decreased degradation in times of hypoalbuminemia. Forty percent of the body’s albumin is intravascular; the remaining 60% is interstitial. As albumin levels decrease, the intravascular supply is maintained at the expense of the interstitial supply. However, as hypoalbuminemia begins to correct itself, the interstitial supply is replenished first.

Albumin plays multiple physiologic roles in the body. It exerts 80% of the plasma COP, helping to maintain vascular volume. Albumin also acts to maintain the integrity of the vascular endothelium. Interaction of its negative charge with the endothelial cells helps to decrease microvascular permeability. The coagulation system is influenced by albumin, with attenuation of platelet aggregation as well as a heparin-like acceleration of antithrombin. The result is a trend toward decreased coagulation. The antioxidant effect of albumin is partially attributed to its sacrificial activity in binding free radicals as well as bacterial toxins. It also binds iron to make it less available for certain redox reactions, such as lipid peroxidation. Transport of many endogenous and exogenous substances is mediated by the albumin molecule. The structure of this protein allows it to bind acidic, basic, and neutral substances. Bilirubin, fatty acids, and several drugs (cephalosporin antibiotics, furosemide, digoxin, warfarin, NSAIDs) are all carried to a substantial degree.

Hypoalbuminemia is a fairly common occurrence in many critically ill patients. Production is decreased because of a suboptimal nutritional state and the presence of liver disease and because albumin is a negative acute phase protein. Utilization is increased because these patients are typically in a catabolic state. Loss of albumin is enhanced in certain disease states, including protein-losing nephropathies and enteropathies.
Sequestration occurs in cases such as peritonitis, pyothorax, and significant vasculitis. Hypoalbuminemia has been shown in multiple human and animal studies to be correlated with an increase in morbidity and mortality.

Consequences of hypoalbuminemia are multiple. The coagulation system trends toward hypercoagulability in the absence of albumin. And of course, COP suffers in states of low albumin, leading to edema of the interstitium, gut wall, brain, and pulmonary parenchyma. This edema interferes with oxygen delivery to cells, potentially leading to organ dysfunction or failure. Hypoalbuminemia has been shown in multiple human and veterinary studies to be associated with an increased morbidity and mortality.

Human serum albumin (HSA) as a product is manufactured from pooled human plasma that is ultrafiltrated and heat sterilized. Two concentrations are available: isoncotic 5% at 308 mOsmol/L and hyperoncotic 25% at 1,500 mOsmol/L. The COPs of the 5% and the 25% solutions are 20 and 200 mm Hg, respectively. In comparison, the COP of 6% hetastarch is 30 to 45 mm Hg, and that of dextran 70 is 60 mm Hg (normal plasma COP, 20–40 mm Hg) (Table 1). It is evident that 25% albumin has a significant oncotic advantage over the other synthetic colloids, especially important in edematous states because of the low volume of “water” accompanying the albumin. An infusion of the 25% solution increases intravascular volume by as much as four to five times the infused volume. Additionally, one must consider the many benefits of giving a physiologically active and important molecule such as albumin. Not only does its administration have oncotic and volume expansion properties, but it also helps to maintain vascular endothelial integrity and has effects on coagulation, antioxidant properties, and transport function.

### DIAGNOSTIC CRITERIA

#### Historical Information

Many patients may benefit from the administration of HSA. One of the most important groups is patients with hypoalbuminemia. Hypoalbuminemia may result from a variety of disease processes:

- **Decreased production:** Hepatic failure, inadequate intake, malabsorption, or malnutrition.
- **Increased loss:** Protein-losing enteropathy (PLE), protein-losing nephropathy, exudative cutaneous lesions, or whole blood loss.
- **Sequestration:** Body cavity effusion, pleural, peritoneal, interstitial, or vasculopathy.

Patient history may vary depending on the underlying disorder.

#### Age Predisposition

- **Causes of hypoalbuminemia in young animals:**
  - Liver failure associated with toxin exposure or congenital portosystemic shunts.
  - PLE seen with parvoviral enteritis, intestinal parasites, and pythiosis.
  - Protein-losing nephropathy caused by amyloidosis in shar-peis.
- **Causes of hypoalbuminemia in middle-aged to older animals:**
  - Liver failure caused by neoplasia or cirrhosis.
  - PLE associated with inflammatory bowel disease, lymphangiectasia, or neoplasia.
  - Protein-losing nephropathy caused by amyloidosis in older beagles.
- **Causes of hypoalbuminemia in animals of any age:**
  - Glomerulonephritis causing protein-losing nephropathy, pyothorax, peritonitis, vasculitis or capillary leak, or other acute illnesses.

#### Breed Predisposition

- **Varies depending on underlying disease process.**
  - **Liver failure:**
    - **Chronic hepatitis:** Bedlington terriers, cocker spaniels, standard poodles, Doberman pinschers, West Highland white terriers.
    - **Congenital portosystemic shunt:** Yorkshire terriers, miniature schnauzers, Maltese, golden retrievers, Labrador retrievers.
    - **Toxicity:** Labrador retrievers for carprofen toxicity.
  - **Protein-losing enteropathy:**
    - Soft-coated wheaten terriers.
  - **Lymphangiectasia:** Yorkshire terriers, Lundehunds.
  - **Parovirus:** Rottweilers, pit bull terriers, Doberman pinschers.
  - **Inflammatory bowel disease:** Shar-peis, Basenjis.
Protein-losing nephropathy:

— **Glomerulonephritis**: Doberman pinschers, Samoyeds, Rottweilers, Bernese mountain dogs, soft-coated wheaten terriers.

— **Amyloidosis**: Beagles, shar-peis.

**Owner Observations**

Vary depending on the underlying disease process, but general signs such as lethargy, inappetence, vomiting or diarrhea, polyuria and polydipsia, tissue edema, a distended abdomen caused by ascites, and increased respiratory rate or effort are commonly seen.

**Physical Examination Findings**

• Tissue edema, usually in dependent areas (ventrum, legs, mandible).

• Distended abdomen (peritoneal effusion).

• Fast, shallow breathing (pleural effusion).

• Tachycardia.

• Poor pulse quality.

• Pale mucous membranes with prolonged capillary refill time.

• Hypothermia.

• Cachexia if chronic illness is present.

**Laboratory Findings**

• Hypoalbuminemia (reference range, 2.5–4.0 g/dl):
  — **Mild**: 2.0–2.4 g/dl
  — **Moderate**: 1.5–1.9 g/dl
  — **Severe**: <1.5 g/dl

• Hypoglobulinemia (reference range, 2.6–5.0 g/dl) may be present, especially in patients with PLE. However, hyperglobulinemia may be present in those with chronic inflammatory conditions (e.g., inflammatory bowel disease, rickettsial infections).

• Hyoproteinemia (reference range, 5.1–7.3 g/dl).

• Decreased COP (reference range, 20–40 mm Hg).

• If the patient is in liver failure, decreased blood urea nitrogen (BUN; reference range, 10–25 mg/dl), cholesterol (reference range, 68–224 mg/dl), or glucose (reference range, 80–100 mg/dl) levels can be seen in addition to increased bilirubin (reference range, 0.1–0.3 mg/dl) and fasting ammonia (reference range, <100 µg/dl) levels. Liver enzymes may be normal to increased (alanine aminotransferase [ALT]: reference range, 26–200 U/L; alkaline phosphatase [ALP]: reference range, 4–95 U/L; aspartate aminotransferase [AST]: reference range, 15–50 U/L) depending on the stage of disease. Coagulopathy, as evidenced by an increased prothrombin time (PT; reference range, 6.1–10.1 seconds) and activated partial thromboplastin time (aPTT; reference range, 8–14.4 seconds), may also be seen.

• Patients with protein-losing nephropathy show proteinuria (reference range, none to trace with inactive sediment), isosthenuria (urine-specific gravity, 1.008–1.012), and increased urine protein:creatinine ratio (reference range, <1) with inactive sediment. BUN and creatinine (reference range, 0–1.3 mg/dl) may be normal to increased. Hypercholesterolemia (reference range, 68–224 mg/dl) is often seen with nephrotic syndrome.

• Pyothorax or peritonitis is evidenced by an exudative effusion with either an increased or decreased peripheral white blood cell count (reference range, 6,000–17,000/µl).

• Patients with vasculitis typically show a transudative cavitary effusion with decreased circulating platelets (reference range, 150,000–500,000).

**Other Diagnostic Findings**

• Ultrasonographic examination

  — **Liver**: Nonspecific echogenic changes, microhepatica, hepatic nodules, ascites.

  — **Intestinal**: Thickened walls with loss of normal layering in infiltrative diseases; often decreased peristalsis; increased size of mesenteric lymph nodes.

  — **Renal**: Normal, decreased, or increased size of kidneys; decreased corticomedullary differentiation; increased echogenicity of cortex.

**Summary of Diagnostic Criteria**

• Hypoalbuminemia.

• Decreased COP.

• Interstitial edema.

• Other results depending on underlying disease process.

**Diagnostic Differentials**

• **Liver failure**:
  — Decreased BUN, cholesterol, glucose.
  — Variable changes in ALT, ALP, AST.
  — Increased bile acids or ammonia.
  — Prolonged aPTT or PT.

• **Protein-losing enteropathy**:
  — Low globulins.
  — Often diarrhea but not always.

• **Protein-losing nephropathy**:
  — Proteinuria.
  — Increased urine protein:creatinine ratio.
  — Globulins usually normal to increased.

• **Pyothorax**:
  — Exudative effusion.
  — Positive bacterial or fungal culture of fluid.
  — Intracellular organisms on cytology of fluid.

• **Peritonitis**:
  — Septic: Exudative effusion; positive bacterial culture of fluid; intracellular organisms on cytology of fluid.
  — Uroabdomen: Modified transudate effusion; creatinine in fluid > creatinine in blood.
  — Bile: Icteric or green-colored abdominal fluid; nonseptic exudative fluid but can become septic if biliary tract becomes infected or secondary infection is left untreated.
TREATMENT RECOMMENDATIONS

Initial Treatment
• Because albumin contributes 80% of the plasma COP, increasing this value usually helps resolve some of the clinical signs, regardless of the underlying problem. These clinical signs include subcutaneous edema, vomiting, or diarrhea associated with gastrointestinal wall edema, ascites, and tachypnea or respiratory distress caused by pleural effusion or pulmonary edema in states in which the vascular integrity is compromised.
• Synthetic colloids have historically been used to augment plasma COP. However, use of these products carries the risk of allergic reactions and hypocoagulation as well as leakage of the smaller molecules into the interstitium, thereby potentiating edema formation. Synthetic colloids also have the limitation of acting as an osmotic particle only and do not carry the physiologic benefits of the albumin molecule, as previously discussed. $— Hetastarch 6%: 10–20 ml/kg/day IV is the standard dose, although doses up to 50 ml/kg/day have been used to achieve results. The risk of side effects increases as the dose increases.
— Dextran 70: 10–20 ml/kg/day IV; can also be increased, as with hetastarch, but the side effect risk is also greater.
• HSA 25% is a natural colloid that, in addition to augmenting plasma COP, has the physiologic benefits of the albumin molecule. Human albumin is stored at room temperature and has a shelf life of 3 years. Administration does not require a crossmatch or blood typing, nor does it need to be given and has a shelf life of 3 years. Administration does not require
• Dosage for euvoletic humans is 1 to 2 g/kg/day IV.
• Dosage for canine patients is still under investigation and is patient dependent. Current recommendations to supplement COP are to administer as a constant-rate infusion (CRI). Based on patient requirements, 0.7 to 1.7 ml/kg/hr of the 25% solution, to a maximum volume of 25 ml/kg administered continuously for 72 hours, has been reported; however, mean volumes are approximately 5 ml/kg. It is important to monitor albumin concentrations so as to not make the patient hyperalbuminemic and to monitor for signs of fluid overload (tachycardia, serous nasal discharge, pulmonary crackles), which may be associated with the rate of administration if given to the appropriate patient population with severe hypoalbuminemia.
— The maximum bolus given as a slow push or bolus to treat refractory hypotension is reported to be 4 ml/kg, with a mean of 2 ml/kg.
— The 25% solution has also been diluted out to a 10% solution (50 ml of the 25% added to 75 ml 0.9% NaCl) or as a 5% solution (50 ml of the 25% added to 200 ml 0.9% NaCl) and run as a continuous IV infusion over a variable period (anywhere from 2 to 12 hours). It should be noted that the 5% solution is isoncotic and has no colloidal benefits over plasma but is significantly less expensive.

CHECKPOINTS
— Appropriate dosage and rate of administration are points of contention among various experts. At this time, only one published article examining the use of HSA in dogs is available. This article used the dosages recommended above (0.7–1.7 ml/kg/hr of the 25% solution) in order to support COP and found it to work well in their patient population.
— HSA is not appropriate for all patient populations. HSA is currently the most economical way to provide colloidal support for large-breed dogs with hypoalbuminemia associated with clinical signs and ongoing losses. To support low albumin and oncotic pull, its use should be reserved for patients with severe hypoalbuminemia (especially before surgery with intestinal biopsies), refractory decreased COP, ongoing losses (PLE, septic peritonitis with open abdomen), or reversible liver failure. HSA is used to improve perfusion and promote healing through reduction in edema until the animal is able to begin eating and maintain a positive nitrogen balance.
— HSA is intended for animals with reversible conditions that are unlikely to require long-term colloidal support. Remember that HSA should only be given within a 3- to 5-day period before the immune system has a chance to respond to the foreign molecule. Continued administration after this runs the significant risk of adverse immune response and should not be attempted until further safety studies are completed.
— Rare delayed immunologic effects, such as polyarthritis or vasculitis, may be seen. These problems may be associated with the original disease; however, owners should be warned of the possibility of immunologic effects. Again, further safety studies are needed to fully evaluate the risk of these effects.

• Vasculitis:
  — Thrombocytopenia.
  — Increased serum titer for rickettsial disease, leptospirosis infection.
  — Positive bacterial blood culture.
  — Transudative cavitary effusion.
— Animals with ascites and peripheral edema should receive the 25% solution as a CRI to provide maximum oncotic pull from the interstitium. Animals that are dehydrated and hypovolemic should either receive the 25% solution along with crystalloids at a lower rate or the diluted 10% or 5% solution to provide rehydration as well as oncotic support.

— Because of the potential for immune response to the human albumin molecule, it is advised that doses be administered within a 3- to 5-day window. Repeated administration after that period has elapsed carries the potential for an unknown immunologic response and is not recommended until further long-term safety studies are completed.

• Species-specific plasma is available. In addition to albumin, fresh-frozen plasma contains coagulation factors, antithrombin, antiproteases, fibronectin, and macroglobulins that may be beneficial (e.g., liver failure). However, plasma is generally not an effective albumin substitute except in small patients. It takes 22 ml/kg of plasma to make a 0.5-g/dl difference in serum albumin concentration, translating into 440 ml for a 20-kg dog. $–$$

— Dose: 10–20 ml/kg IV.

• Additional treatments should be based on the underlying disease process. Specific options are considered outside of the scope of this article.

Supportive Treatment

• Supportive therapy is also somewhat dictated by the underlying disorder. General principles include IV therapy to maintain hydration, oxygen support as needed for respiratory distress, thermal support to help maintain body temperature, and other procedures to keep the patient clean and comfortable.

• Specific attention should be paid to nutritional support in order to supply the body with the nutrients needed to manufacture endogenous albumin. This may include syringe feedings, placement of various feeding tubes, or use of total or partial parenteral nutrition. Parenteral nutrition should not be used concomitantly with HSA because of the hyperosmolarity of these solutions.

Patient Monitoring

• Serum albumin or total protein: Avoid hyperaluminaemia and hyperproteinaemia.

• COP: Avoid raising COP too high into the normal range (typically aim for 15–17 mm Hg) in order to maintain the stimulus to the liver to produce more albumin.

• Blood pressure: 25% HSA is also used to support blood pressure in cases of refractory hypotension. Monitor blood pressure (systolic reference range, 100–160 mm Hg) to avoid making the patient hypertensive.

• Interstitial edema should resolve with increased COP.

• Heart rate should return to normal as intravascular volume is replenished.

• Urine production should return to normal (1–2 ml/kg/hr) as intravascular volume is replenished and renal perfusion improved.

Treatment Contraindications

• Other oncotic solutions should not be used simultaneously with HSA.

• HSA use should be avoided in cats until further safety studies have been conducted.

• HSA should be used with extreme caution in patients with cardiac disease.

PROGNOSIS

Favorable Criteria

• Patients should show some response within 24 hours of continuous administration. Plasma COP and protein levels should improve; heart rate, blood pressure, and urine output should normalize; and interstitial edema and cavitary effusions should show some improvement.

Unfavorable Criteria

• No improvement or worsening of clinical signs or laboratory values within 24 hours of continuous administration.

RECOMMENDED READING


