State-of-the-Art Review

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The role of albumin replacement in the critically ill veterinary patient

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Abstract

Objective: To review the human and veterinary literature on the physiological role and effects of therapeutic albumin supplementation.
Data sources: Data from human and veterinary literature was reviewed.
Human data synthesis: Hypoalbuminemia often occurs in a variety of critical illnesses, and contributes to the development of life-threatening complications, including pulmonary edema, delayed wound healing, feeding intolerance, hypercoaguability, and multiple organ dysfunction. Serum albumin concentration has been used as a prognostic indicator in cases of chronic hypoalbuminemia. The use of albumin replacement therapy in humans is sometimes controversial, but may be associated with improved morbidity and decreased mortality.
Veterinary data synthesis: Unlike human literature, there is a paucity of controlled clinical studies in the literature regarding albumin supplementation in veterinary patients. Rather, the majority of published studies were performed in experimental animals or via retrospective analyses. One recent study evaluated the use of plasma to improve albumin concentration in dogs with hypoalbuminemia. Other older studies investigated wound healing in dogs with experimentally induced hypoalbuminemia. As in human medicine, serum albumin concentration may be helpful as a prognostic indicator in critically ill dogs.
Conclusion: Albumin is one of the most important proteins in the body because of its role in maintenance of colloid oncotic pressure, substrate transport, buffering capacity, as a mediator of coagulation and wound healing, and free-radical scavenging. Albumin replacement in veterinary medicine is difficult, but until prospective clinical trials determine the efficacy of albumin replacement are conducted, a suggested clinical guideline would be to maintain albumin concentration at or above 2.0 g/dl utilizing fresh frozen plasma.

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Keywords: colloid therapy, critical illness, oncotic pressure, plasma

Introduction

Albumin is one of the most extensively studied proteins in human medicine because of its multiple roles in maintaining colloid osmotic pressure, carrying endogenous and exogenous substances, mediating coagulation, and inhibiting oxidative damage (Table 1). Hypoalbuminemia is often a consequence of critical illnesses, including sepsis and systemic inflammatory response syndrome (SIRS), burns, end-stage hepatic failure, protein-losing enteropathies, and nephrotic syndrome (Table 2). The resulting hypoalbuminemia can result in life-threatening complications such as systemic organ dysfunction, pulmonary edema,[1,2] enteral feeding intolerance,[3] poor wound healing,[4–6] and hypercoaguability[7–12] (Table 3). Further, hypoalbuminemia has been correlated with increased morbidity and mortality in both humans and in animals.[5,13–17]

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Table 1: Functions of albumin

Maintain colloid oncotic pressure
Important carrier of:
Drugs
Fatty acids
Divalent cations (Ca^{2+}, Zn^{2+})
Hormones
Bilirubin
Platelet function
Normal coagulation
Free radical scavenger in inflammation

Table 2: Diseases commonly associated with hypoalbuminemia

Decreased albumin synthesis
Hepatic disease
Cholangiohepatitis
Cirrhosis
Hepatic lipidosis
Histoplasmosis
Neoplasia
Phenobarbital toxicosis
Portosystemic vascular shunts
Other toxicoses
Endocrinopathies
Hyperadrenocorticism
Hypoadrenocorticism
Albumin loss
Dirofilaria immitis (caval syndrome)
Gastrointestinal disease
Bacterial enteritis
Hemorrhagic gastroenteritis
Histoplasmosis
Inflammatory Bowel disease
Lymphangectasia
Neoplasia
Parasitism
Parvoviral enteritis
Panleukopenia virus
Toxins
Heart disease (right-sided)
Heat-induced illness
Pancreatitis
Peritonitis
Portal hypertension
Pyothorax
Pulmonary edema (non-cardiogenic)
Renal disease
Diabetes mellitus
Ehrlichia canis
Glomerulonephritis
Hereditary nephritis
Renal amyloidosis
Sepsis
Any disease causing systemic inflammatory response syndrome (SIRS)
Vasculitis

Table 3: Consequences of hypoalbuminemia

Gastrointestinal effects
Delayed gastric emptying time
Gastrointestinal ileus
Gastric and intestinal edema
Enteral feeding intolerance
Coagulation effects
Hypercoaguability
Increased platelet aggregation
Decreased AT-3 activity
Oncotic effects
Decreased COP
Increased vascular pore size, leads to increased permeability
Interstitial edema
Pulmonary edema
Cerebral edema
Decreased tissue perfusion
Tissue ischemia
Delayed wound healing
Increased morbidity and mortality

There is little available published information regarding albumin's therapeutic role in veterinary critical care.[18,19] It is important to understand the normal functions and uses of albumin, since supplementation with albumin can become a necessary component of therapy of the critical animal patient. The purpose of this article is first to review the evolution and structure of albumin, then to describe its production, degradation and distribution, as well as its role in normal and abnormal patients, and the pathology associated with hypoalbuminemia, and finally provide recommended guidelines for albumin replacement in critically ill veterinary patients.

Evolution and Structure of Albumin

Myoglobin, hemoglobin and albumin all share areas of structural homology, and are thought to have evolved from a single common ancestral molecule consisting of 77 amino acid residues approximately 100–530 million years ago.[20,21] Amino acid sequence analysis has demonstrated an evolutionary relationship between albumin in different animal species.[20]

The exquisite design of albumin allows it to take on many important physiologic roles in the body. Albumin is a highly flexible, symmetrical protein consisting of a single amino acid chain whose structure is based primarily on 17 disulfide bonds in repeating double loop domains. The disulfide bridges result in an ellipsoid 'spherocolloid' shape, consisting of a polar outer face and a non-polar inner central channel containing both hydrophilic and hydrophobic moieties.[20–22] The

hydrophilic nature of the outer alpha-helix structure causes it to be highly soluble in plasma water.[23,24]

Albumin contains many charged amino acid residues, resulting in a net charge of (–)19 at normal physiologic pH.[23–26] The vascular endothelium throughout most of the body has capillary pores measuring 6–7 nanometers in width, a size slightly smaller than the albumin molecule.[27] The negative charge, along with its large molecular size of 69,000 Daltons, favors albumin retention within the vascular space under normal conditions. Albumin can bind reversibly to both cations and anions,[25] allowing it to be an important carrier molecule of both endogenous and exogenous substances within the body.

Production, Degradation and Distribution of Albumin

Albumin synthesis: Albumin synthesis occurs exclusively in the liver, accounting for approximately 50% of the substances synthesized by the liver at any one time.[21,28] Many factors influence albumin synthesis, including nutrition, intracellular potassium concentration, plasma colloid oncotic pressure (COP), and hormones.[29] However, synthesis is primarily regulated by the nutritional state and the COP at or near the hepatic interstitial space.[2,26,28]

Osmoreceptors within the hepatic interstitial matrix can sense changes in plasma oncotic pressure.[25] The hepatic vascular beds differ from those located elsewhere in the body by having larger capillary pore sizes and a protein reflection coefficient of zero, rendering them permeable to molecules whose size is less than 620,000 Daltons. Molecules such as albumin and globulins, and synthetic colloids such as hydroxyethyl starch (HES) and dextrans, can accumulate within the hepatic interstitial matrix to mediate COP.[26,28] Changes in COP within the hepatic interstitium have been shown to result in inverse changes in albumin synthesis. For example, supranormal increases in COP following exogenous administration of natural and synthetic colloids can result in suppression of albumin synthesis.[25] Conversely, states of hypoalbuminemia decrease hepatic interstitial oncotic pressure, stimulating albumin synthesis when adequate nutrients are available[2] (Figure 1).

Nutrition and adequate nitrogen intake are essential for normal albumin synthesis. During times of adequate nutrition, albumin synthesis consumes approximately 6% of the daily nitrogen intake.[21] In normal individuals, the rate of albumin synthesis is not constant; rather, the liver works at only one-third of its capacity to produce albumin, preventing a state of hyperalbuminemia. This serves as a conservation mechanism, utilizing available amino acids for other purposes.

The hormonal environment further affects albumin synthesis. The effects of cortisol, thyroxine, sex hormones, and growth hormone are all additive.[30] *In vitro*, the addition of cortisone, thyroxine, and testosterone to hepatocytes will stimulate albumin synthesis.[23,26] The increase in these hormones also appears to cause increased albumin synthesis *in vivo*, however, increased albumin concentrations are not seen clinically. Although albumin synthesis is increased in patients with hyperadrenocorticism and hyperthyroidism, circulating albumin concentration does not become elevated due to concurrent increases in the rate of albumin degradation and loss.[25,26,29]

Degradation: The degradative mechanism of albumin is less well understood than its synthesis. Approximately 4% of total body albumin is degraded daily at

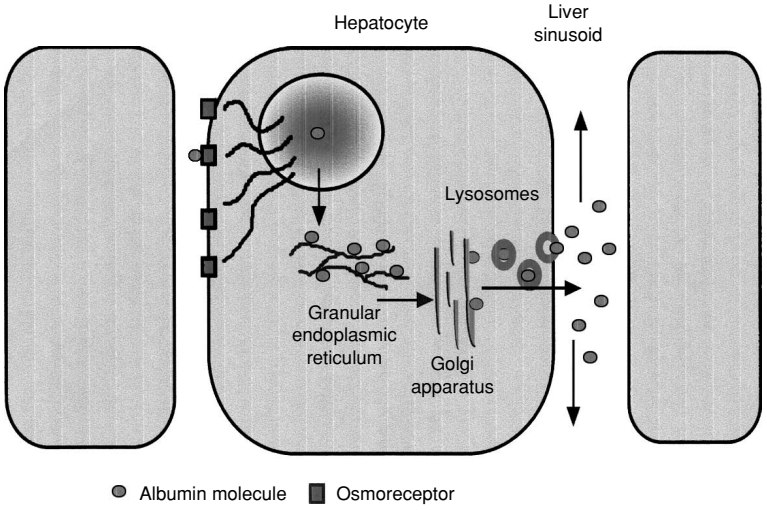

Figure 1: Albumin production. Osmoreceptors within the hepatocellular matrix respond to decreased plasma oncotic pressure by signaling hepatocyte production and release of albumin.

a rate directly related to albumin concentration.[2] However, the sites of albumin degradation are largely unknown.[29,31] The prevailing opinion is that albumin catabolism takes place all over the body in states of health. The half-life of albumin in normal dogs is approximately 8.2 days.[32] In states of hypoalbuminemia, the rate of degradation decreases in an attempt to conserve albumin.[3]

Distribution: In addition to albumin synthesis and degradation, serum albumin concentration is affected by loss from the body, exchange between intra- and extravascular compartments, and the volume in which albumin is dispersed.[28] Serum albumin concentration represents approximately 30–40% of total body stores.[28,29,33] A total of 60 to 70% albumin is contained in the interstitial space of the skin, muscle, liver, lung, heart, kidneys, and spleen.[28,30]

Following synthesis, albumin distribution to the extravascular pool reaches equilibrium within 7–14 days in normal individuals.[2,26,30] Approximately 75–85% of the intravascular albumin exchanges with the interstitial (extravascular) pool every 2–3 days[30] (Figure 2). The extravascular albumin pool serves as a source to replenish the intravascular pool during times of stress and acute loss.[28,34] During times of acute albumin loss or decreased synthesis, there is rapid equilibration of extravascular albumin to the intravascular space until the extravascular supply is depleted. Some albumin remains tissue-bound and is therefore unavailable to replenish the intravascular pool.[28] Acute intravascular loss of albumin can occur when capillary integrity is compromised, such as with inflammation or renal glomerular dysfunction, resulting in abnormal fluid shifts and significant organ dysfunction.

Functions of Albumin: Colloid Osmotic Pressure

Albumin functions as a major contributor to plasma COP, as a carrier molecule, and a scavenger of toxic substances generated during inflammatory states. Plasma oncotic pressure is maintained by the presence of protein molecules within the vascular space. One of albumin's primary functions is the maintenance of intravascular oncotic pressure. Of the serum proteins, albumin contributes approximately 80% of the plasma COP.[26,28,29,35] Fibrinogen (molecular weight 624,000 Daltons) and globulins (molecular weight range 53,000–160,000 Daltons) contribute relatively little to plasma COP.[33] Colloid osmotic pressure is the principal force regulating transvascular fluid flow and is one of the forces opposing fluid exit from the vascular space.[36] Together, the Gibbs–Donnan Effect and albumin's net negative charge govern albumin's water attraction.

Another factor to consider in the water-holding properties of albumin within the vascular space is termed the Gibbs–Donnan Effect.[33] Albumin molecules are numerous in circulation, and have a large net negative charge. The negative charge of albumin causes sodium ions (Na^+) and other cations to accumulate around its core structure. The accumulation of ions causes water to follow across a semipermeable capillary endothelial membrane, contributing to the water-holding property of albumin within the vascular space[33] (Figure 3).

A 5% solution of human albumin has a COP of approximately 20 mmHg.[37] Each gram of albumin is capable of holding 18 ml of water within the intravascular space.[28] Albumin therefore increases serum COP and facilitates the translocation of water from the extravascular to the intravascular space.[38] There is

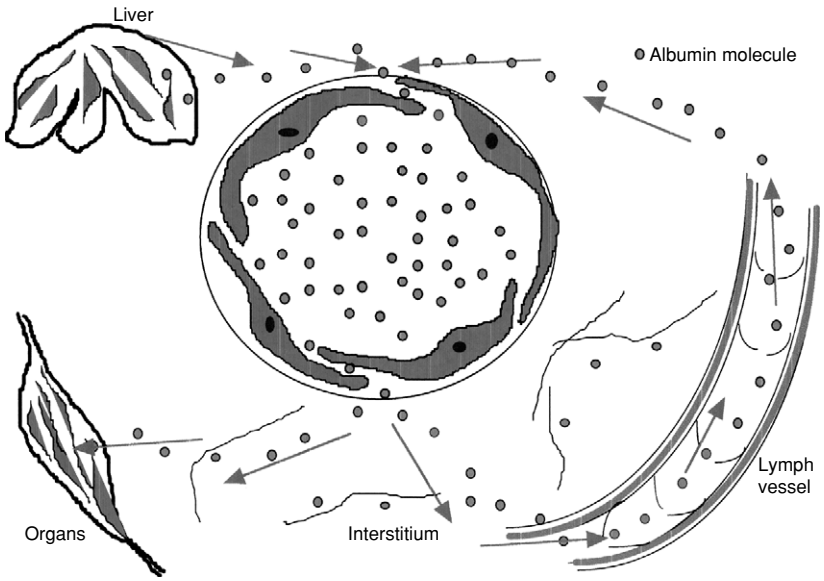

Figure 2: Whole body distribution of albumin. Of the total body albumin, 30–40% exists in the intravascular space and 50–70% in the interstitial space. Intravascular albumin concentrations are maintained during times of albumin loss by moving interstitial albumin into the lymphatics and then the cranial vena cava. When albumin is administered during therapy, the interstitial stores are the first to be replenished.

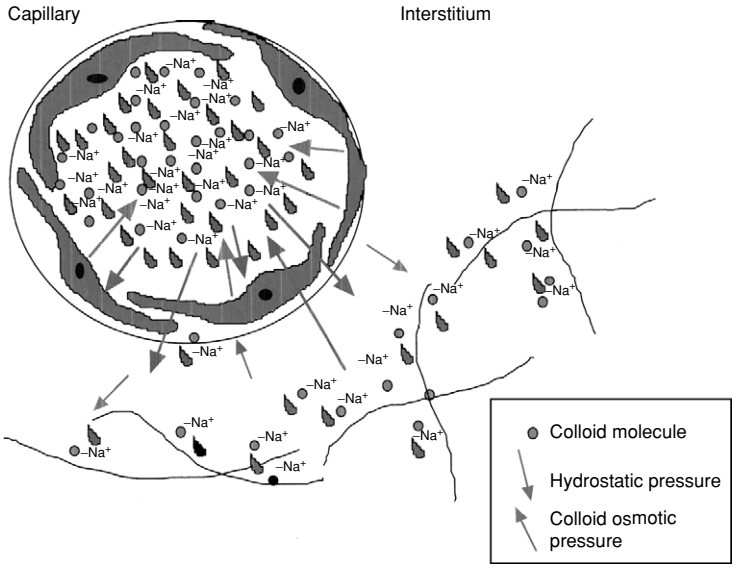

Figure 3: Forces governing distribution of water across the capillary membrane. The capillary membrane is a relatively impermeable barrier to plasma protein solutes (albumin, fibrinogen, globulins). Water will diffuse from a compartment containing less concentration of solutes to a compartment containing greater concentration of solutes (osmosis). In addition to producing colloid osmotic pressure, plasma proteins have a negative charge that attracts sodium ions. This property (Gibbs–Donnan effect) provides an additional pull for water molecules. Hydrostatic pressure is the weight of a fluid against a membrane. Capillary hydrostatic pressure is influenced by mean arterial blood pressure and vascular compliance.

competition between intra- and extravascular albumin in holding water extravascularly.[39] Although intravascular COP is an important factor in determining fluid distribution, other forces such as vascular and tissue permeability to the colloid, fluid hydrostatic pressure, and lymphatic flow contribute to the fluid dynamics within the body.[39]

Starling developed an equation that describes the net effect of protein in solution pulling fluid across a semipermeable membrane against hydrostatic pressure[40] (Figure 3). Starling's law is defined as:

$$V = [kf(P_c - P_{if}) - \sigma(\pi_c - \pi_{if})] - Q_{lymph}$$

where V = net flow, kf = the filtration coefficient (varies from tissue to tissue within the body), P_c and P_{if} is the hydrostatic pressure within the capillary (P_c) and interstitial space (P_{if}), σ is the pore size of the capillary membrane and π describes the colloid effect of protein, such as albumin, in the capillary (π_c) and the interstitium (π_{if}). Finally, Q_{lymph} describes the rate of lymph flow from the interstitium.

Starling's equation predicts that the amount of extravascular fluid flux will be inversely related to capillary oncotic pressure. In normal individuals, plasma albumin and other proteins exert an oncotic pressure and influence the movement of fluid into the interstitial space. Interstitial albumin can circulate back into the vasculature via the lymphatics to maintain a pressure gradient between the plasma and the interstitium.[33] In states of acute hypoalbuminemia, interstitial oncotic pressure can exceed that found intravascularly, resulting in interstitial edema when the capacity of the lymphatic system to return fluid to the vascular space is overwhelmed.[31]

Carrier functions of albumin: Albumin also serves as an important carrier for many endogenous and exogenous substances to locations throughout the body (Table 4). Albumin has binding sites for acidic, basic and neutral substances.[41] By carrying substances in circulation, albumin serves both as a transport vehicle and as a storage reserve, regulating the concentration of a substrate within the body. It also serves as a carrier of substances to the sites of metabolism and elimination from the body (Table 2). Albumin binding and transport of bilirubin, drugs, and long-chain fatty acid anions are the most clinically important functions of albumin in a critically ill patient.[29]

Bilirubin: In states of health, bilirubin binds almost 100% to albumin and is carried to the liver for conjugation and excretion.[29,42] Bilirubin becomes non-toxic when bound to albumin.[41] Certain disease states can result in increased circulating bilirubin levels. When hypoalbuminemia exists, more bilirubin is free (unbound) in circulation, potentiating its toxic effects. Toxic effects of bilirubin in humans include neurologic dysfunction, peracute encephalopathy, renal failure and death.[43] Albumin therapy is commonly used with success in conditions of hemolytic crisis in newborn humans (kernicterus) to prevent the toxic effects of bilirubin.[44] Unfortunately, no studies have investigated the effects of plasma albumin therapy in states of hyperbilirubinemia in veterinary medicine.

Bilirubin demonstrates a strong competitive inhibition with many drugs for the same binding site on albumin. In states of hyperbilirubinemia, competition between drug and bilirubin for the same binding site can potentially increase free bilirubin concentration or displace the

Table 4: Substances which bind with albumin

Endogenous substances
Bilirubin
Divalent cations (Ca^{2+}, Zn^{2+})
Fatty acids
Free radical species
Fat-soluble vitamins
Hormones
Exogenous substances (Drugs)
Antibiotics
Cephalosporins
Penicillins
Sulfonamides
Tetracycline
Anticoagulants
Warfarin
Antiinflammatory
Ibuprofen
Phenylbutazone
Salicylic acid
Antiseizure medications
Phenobarbital
Phenytoin
Benzodiazepines
Diazepam
Cardiovascular-renal
Digitoxin
Furosemide
Hydralazine
Propranolol
Quinidine
CNS Active
Amitryptiline
Chlorpromazine
Thiopental
Hypoglycemic agents
Glipizide
Radiocontrast media

drug from albumin, potentiating toxic side-effects of either bilirubin or the pharmacologically active form of drug. Drugs which compete with bilirubin include non-steroidal anti-inflammatory agents (such as aspirin and phenylbutazone) and warfarin.[45]

Drugs: An important function of albumin is its capacity to bind with exogenously administered drugs. Albumin serves as a vehicle to transport drugs to their site of action and transports metabolites to their sites of excretion. When a drug is bound to albumin, only a small percentage of the drug is free within circulation. It is the unbound form of drug which is pharmacologically active and readily excreted or metabolized. Additionally, the binding of one substance can cause conformational changes in the conformation of albumin, resulting in increased or decreased affinity and binding to other substances.

With the presence of hypoalbuminemia, the pharmacodynamics of substrate transport is altered. Adverse drug reactions can occur in states of hypoalbuminemia, or through displacement of drug from albumin.[46] Albumin binding protects a drug from elimination and increases delivery to tissues.[47] Low serum albumin concentration may allow increased free drug concentration, which may potentiate toxicity, and decrease half-life by increasing the amount of drug available for excretion. When albumin binding is subnormal, a reduced dose of albumin-bound drug should be utilized in order to avoid toxicity.[46] The proportion of dosage reduction is not easily predictable however. A recent study investigating the pharmacokinetics of various drugs in canine patients with hypoalbuminemia revealed increased concentrations of unbound drug including diazepam, flunixin, phenylbutazone, and warfarin in dogs with low serum albumin concentration.[19]

Fatty acids and platelet function: By binding to a variety of sites on the albumin molecule, free fatty acids become non-toxic in circulation.[41] Lipemia/hyperlipidemia is a common occurrence in patients with decreased serum albumin. Hyperlipidemia has been implicated as contributing to the pathology associated with Acute Respiratory Distress Syndrome (ARDS) by increasing the concentration of circulating free fatty acids, which may injure the pulmonary endothelium along with leukotrienes and inflammatory cytokines.[41]

Glomerular loss of albumin in nephrotic syndrome has been implicated to contribute to increased platelet aggregation and thrombosis due to an increase in circulating levels of arachidonic acid available for metabolism to prostaglandins, which causes platelet aggregation and thrombosis.[8–12] In states of prolonged hyperglycemia (i.e. uncontrolled diabetes mellitus), the glycosylation of albumin displaces bound arachidonic acid, thus potentiating platelet aggregation through a similar mechanism.[48] Additionally, albumin *in vitro* has been found to have a heparin-like activity by enhancing antithrombin-III (AT-3) activity.[7,49] By potentiating platelet aggregation and decreasing AT-3 activity, hypoalbuminemia may, therefore, contribute significantly to the incidence of thrombotic events seen in nephrotic syndrome, uncontrolled diabetes mellitus,[48] and other diseases associated with hypoalbuminemia.

Free radical scavenger: Another important function of albumin is its capacity to bind toxic substances generated during inflammatory states. The release of free radical species and lipid peroxidation during inflammation is thought to be a major cause of direct and indirect tissue damage.[41] Albumin at the site of inflammation has been

called the 'sacrificial antioxidant'.[41] Small quantities are utilized to scavenge free radical species and bacterial toxins, resulting in the functional destruction of each albumin molecule.[50] Denaturation of albumin at the site of inflammation can occur through changes in temperature and pH. The denaturation releases amino acids that can be utilized for tissue repair. Experimentally, pre-treatment with albumin has been shown to prevent tissue damage and ARDS in endotoxemic sheep.[51] The combination of endotoxin-bound albumin degradation, albumin denaturation, and leakage of albumin from increased vascular permeability all contribute to the hypoalbuminemia observed in patients with systemic inflammatory response syndrome (SIRS).

Albumin in Disease

In states of metabolic stress, albumin synthesis becomes a low priority.[2,26] During acute stress, albumin levels fall transiently when preferential synthesis of acute phase proteins by the liver occurs. If nutrient supply is adequate, albumin synthesis is gradually increased after 16–18 hours[23] However, during most states of disease and surgical trauma, nutrient intake is diminished, resulting in inadequate intake of amino acids available for protein synthesis and inadequate nutrient absorption and utilization. Caloric deprivation resulting from an 18–24 hours fast can cause a decrease in albumin synthesis by as much as 50%.[23] Experimentally, infusion of a complete mixture of amino acids can stimulate albumin synthesis within minutes of infusion.[25] This emphasizes the importance of continuous nutritional support in critically ill animals.

Decreased synthesis: Albumin synthesis is depressed during periods of inadequate nutrition, inadequate intracellular potassium levels, exposure to toxins, or by exposing hepatocytes to supranormal COP values.[26] Changes in oncotic pressure have been shown to result in inverse changes in albumin synthesis. The changes are largely due to increased extravascular albumin concentration, but can also be associated with the presence of other colloidal substances within the vasculature.[26,28]

Serum albumin levels have often been used to assess liver function. Hepatocellular injury in animals can be a combination of acute and chronic processes, resulting in reduced function. Decreased serum albumin levels are a late marker for hepatic insufficiency because a decrease in plasma albumin concentration does not occur until greater than 75% decline of liver function and end-stage liver disease is present.[48] End-stage hepatic disease can further contribute to hypoalbuminemia through loss of this protein directly into ascitic fluid through the hepatic capsule.[24,29] However, as long as 10–25% of the liver is functioning normally, albumin synthesis and plasma albumin concentrations will be normal due to its movement from the interstitial pool, unless excessive losses are also present.[29]

Albumin is also necessary for the proper integrity, function, and healing of the gastrointestinal tract. Early studies in dogs demonstrated that experimentally induced hypoalbuminemia via selective plasmapheresis resulted in delayed gastric emptying times, gastrointestinal ileus, and marked gastric and intestinal edema.[52] Further, hypoalbuminemia and its consequences in the gastrointestinal tract have been associated with delayed healing of gastrointestinal surgery sites, impaired substrate absorption, and enteral feeding intolerance. The pathology observed was reversible once plasma protein concentrations were restored.[4,6,52,53]

Loss of albumin from gastrointestinal tract: Malabsorptive and secretory forms of diarrhea that result in extensive loss of protein from the gastrointestinal tract can be seen in a wide variety of acute and chronic gastrointestinal diseases in patients with critical illness. Hypoalbuminemia caused by gastrointestinal disease is a multifactorial process. First, in conditions with protein-losing enteropathy, albumin loss through the mucosal surface can be significant. Hypoalbuminemia, with decreased oncotic pressure in the gastrointestinal tract, can result in impaired GI function, including gut stasis. This stasis results in subsequent bacterial translocation, often in combination with malabsorption. Malabsorption subequently results in a decrease in available amino acids necessary for albumin synthesis. Hypoalbuminemia occurs when the rate of loss exceeds the rate of synthesis. The resultant hypoalbuminemia further complicates local gastrointestinal pathology by decreasing COP, contributing to tissue edema and preventing adequate repair of diseased tissues.[4]

Albumin in inflammation: In addition to binding free radicals and toxins, the extravasation of plasma albumin during inflammation provides carrier transport of substances such as zinc, amino acids, fatty acids, and drugs to the site of inflammation. In this way, albumin serves to potentiate wound healing by transporting zinc and energy substrates necessary for collagen cross-linking and membrane synthesis.[5,37,41,53] A change in vascular permeability during inflammatory states may be the most important cause of hypoalbuminemia in many diseases.[54] Significant hypoalbuminemia requiring albumin therapy can occur with acute losses secondary to burns or SIRS diseases such as gastroenteritis, pancreatitis, pyometra, peritonitis, and pleuritis (Table 5).

Table 5: Causes of hypoalbuminemia in systemic inflammatory response syndrome (SIRS)

Decreased production
Leakage from vasculature
Denaturation of albumin at sites of inflammation
Degradation of albumin bound to toxins
Dilution effects of crystalloid therapy

Albumin in critical illness: Hypoalbuminemia may compromise the delivery of zinc, energy substrates, and drugs to and from inflamed tissues, which may explain delayed reparative processes in critically ill patients with total body albumin deficits. In addition, decreased production of albumin occurs during systemic inflammation due to preferential synthesis of acute phase proteins, which exacerbates substrate delivery and contributes to compromised tissue function and repair. Albumin therapy, therefore, may be efficacious in diseases complicated by burn injuries, sepsis, pancreatitis, and ARDS.[41]

Currently, there is wide debate whether albumin replacement therapy is necessary in all situations of critical illness. One study documented no benefit of albumin replacement therapy on clinical outcome in critically ill humans.[5] One criticism of this study is that aggressive albumin replacement was not attempted, and the authors assumed that further replacement would not improve clinical outcome. A second study failed to demonstrate the added benefit of albumin replacement in decreasing post-operative ileus.[53] Although post-operative ileus did not improve, albumin replacement was thought to improve bowel function as determined by normal flow of barium through the small intestine. The Cochrane review, a meta-analysis that investigated the use of different colloid solutions including albumin in human patients with critical illness, concluded that albumin supplementation increases the relative risk of death, however, mechanisms for why mortality was increased with albumin supplementation were not defined.[53–56] Since this study was published, other researchers have found fault with the data analysis, therefore, questioning the validity of the Cochrane reviewers' conclusions.[57–59] Other meta-analyzes have found no increased risk of death with albumin supplementation in human patients with critical illness.[60–62] Clearly, further prospective studies need to be performed to investigate the use of albumin replacement in both human and veterinary patients with critical illness.

Morbidity and mortality: An important consistent finding in hypoalbuminemic patients is a decrease in intravascular COP and the potential for translocation of fluid from the vasculature into the interstitial space and body cavities.[60] An acute decrease in albumin concentration by one-third results in a loss of colloid-bound intravascular water by the Gibbs–Donnan effect.[63] The decrease in intravascular COP contributes to decreased distension of vessel walls, which may contribute to increased pore size, rendering the vascular endothelium more permeable to fluid shifts into the interstitium, resulting in tissue edema or ascites. Treatment of patients with overzealous crystalloid administration can further contribute to decreased intravascular COP by diluting plasma proteins in circulation. The combination of decreased COP and increased total extracellular water content can potentiate interstitial fluid overload and the life-threatening complications associated with edema, such as respiratory failure or cerebral dysfunction. Both acute and chronic decreases in intravascular COP may predispose patients to inadequate circulating fluid volume, which can result in tissue ischemia and delayed wound healing.[2] In humans[5,13–15,65] and in animals,[16,17] hypoalbuminemia and decreased COP have been found to be associated with increased morbidity and mortality. Serum albumin levels less than 2.0 g/dl have been positively correlated with increased morbidity and mortality in human patients.[1,39] Albumin replacement may, therefore, be an important adjunct to therapy in many disease states complicated by hypoalbuminemia.

Recommendations for Albumin Therapy

A wide variety of clinical diseases are characterized by hypoalbuminemia and the resultant decrease in COP. When the cause of hypoalbuminemia is known, therapy should always be directed at treating the cause(s) of increased loss and/or decreased production. During times of acute albumin loss, such as hemorrhagic shock or systemic inflammatory disease states, inadequate or overzealous crystalloid fluid administration in critically ill patients can result in poor tissue perfusion, leading to multiple organ system dysfunction and death.[65] Briefly, inadequate crystalloid fluid administration during hemorrhage or intravascular fluid loss often is associated with peripheral tissue vasoconstriction, impairing oxygen and nutrient delivery to sites normally perfused by peripheral vascular beds. Conversely, overzealous crystalloid fluid administration can dilute plasma proteins in circulation, resulting in decreased intravascular COP. The decrease in COP allows leakage of fluid into the interstitium, impairing the area available for nutrient exchange. Both can result in impaired tissue perfusion with subsequent cellular dysfunction. The use of albumin therapy in the critically ill hypoalbuminemic patient is

an appropriate adjunct therapy to promote normal drug and electrolyte delivery, and to potentiate the scavenging of free radicals at sites of inflammation. Since albumin contributes approximately 80% to COP, replacement of the protein using blood component therapy can result in an improvement of COP and decreased vascular fluid loss if a healthy vasculature is present. However, appropriate administration of synthetic colloids in the hypoalbuminemic patient are typically more effective than plasma infusions alone in restoring and maintaining intravascular volume without causing volume overload and its complications including pulmonary or cerebral edema.[52,63–76] It is important to note, however, that colloids must be used with some caution in patients with cardiac dysfunction, as attraction or retention of fluid within the vascular space can lead to intravascular volume overload in some situations.

In conditions with increased vascular permeability, albumin leaks through enlarged capillary pores into the interstitium. The use of large molecular weight synthetic colloids such as hydroxyethyl starch, containing molecules of greater than 69,000 Daltons might be used instead, to help restore and maintain intravascular fluid volume and COP. In the treatment of SIRS, synthetic colloids can be beneficial in maintaining COP until the inciting cause of increased vascular permeability resolves. Acute hypovolemia will result in decreased COP if measures are not taken to restore adequate circulating volume. In patients with a healthy vasculature, the use of crystalloids and colloids can restore circulating volume, blood pressure, and COP. In dogs, shock doses of crystalloids have been recommended at rates of 90 ml/kg/hr. The use of crystalloids in combination with plasma or synthetic colloids such as hydroxyethyl starch or dextrans can achieve the therapeutic goals of restoring intravascular volume and COP.[66,68] The volume of crystalloid fluids can be decreased by 40–60% when administered along with synthetic or natural colloids.[67] The benefit of using synthetic colloids along with crystalloids is that smaller volumes of crystalloids are required to achieve the same therapeutic end points of fluid/volume resuscitation, thereby theoretically avoiding interstitial edema and its potential complications.[66]

Attempts to increase serum albumin concentrations in the face of a whole body deficit can be complicated, as infused albumin will replenish the extravascular interstitial pool before an increase in serum albumin is accomplished.[66] In patients with a healthy vasculature, infused albumin can help increase COP.[66] However, in normoalbuminemic patients, or in patients with increased vascular permeability, infused albumin will not necessarily result in increased COP. Since the majority of albumin (60%) is found extravascularly, calculated serum albumin deficits actually represent only a fraction (40%) of the total body deficit.

In humans, the goal of albumin supplementation is to maintain a plasma albumin concentration equal to 2.5 ± 0.5 g/dl or a plasma oncotic pressure equal to 20 mmHg if albumin is used primarily for its colloidal properties.[42] In animals, the goal of albumin therapy is to maintain an adequate intravascular volume without inhibiting albumin synthesis. The goals of albumin therapy are to provide a carrier substrate and to contribute to COP if other colloids are not available for use. In human, patients whose COP is maintained using synthetic colloids, an increase in morbidity and mortality is still observed when plasma albumin falls below 2.0 g/dl.[70] Extrapolating from human recommendations, the goal of albumin supplementation in animals should be to raise plasma albumin to 2.0–2.5 g/dl and maintain a plasma COP between 13 and 20 mmHg. Concentrated 25% human albumin is ideal for resuscitating hypovolemic human patients with peripheral edema. There are anecdotal reports of using single-dose concentrated human albumin solutions in dogs with doses extrapolated from the human literature. Published recommended doses, based on clinical experience, for supplementation with 5% and 25% human albumin concentrate in dogs are 10 ml/kg and 2 ml/kg, respectively.[71] Concentrated canine or feline albumin solutions unfortunately are not commercially available for use in veterinary medicine. At this time, plasma transfusion is the sole source of species-specific albumin replacement.

In addition to albumin replacement, plasma infusion has other benefits. Plasma contains macroglobulins, coagulation proteins, antithrombin, and other proteins. Resuscitation with large volumes of non-albumin containing fluids and crystalloids may exacerbate hypoalbuminemia through dilution and limit the ability of albumin to transport toxic substances, hormones and therapeutic drugs.[41] The use of plasma alone to increase COP is expensive. In the authors' view, combination fluid therapy can be utilized and may have advantages to monotherapy. Crystalloids can be given to increase interstitial and intravascular volume. Synthetic colloids can be given to increase intravascular volume and COP, and fresh frozen plasma can be given to provide albumin (up to 2.0 g/dl), antithrombin-3, and coagulation proteins. If adequate supplies of blood products are unavailable to meet the patient's needs, plasma or whole blood can be used along with synthetic colloids such as hydroxyethyl starch (recommended rate 20–30 ml/kg/day) to increase plasma COP, decrease interstitial edema, and maintain adequate circulating fluid volume.

The rate and amount of plasma administered should be based on a patient's need and underlying pathology.[69] Approximately 22.5 ml/kg of plasma is required to increase plasma albumin 0.5 g/dl.[73] The plasma dose range administered to hypoalbuminemic dogs was extremely varied in a recent study, ranging from 2.3 to 38 ml/kg,[18] demonstrating a need for specific guidelines for plasma therapy for albumin replacement in the critically ill veterinary patient. Plasma can be administered at a rate equal to 4–6 ml/min in acute crises such as hypovolemic shock.[69–74] For normovolemic animals, plasma infusion can range from 6 to 22 ml/kg in a 24-hour period. The following formula can be used to predict the number of milliliters of plasma required to increase recipient plasma total solids (TS), assuming no interstitial deficit and no ongoing loss.

[ml plasma = desired recipient TS g/dl
−recipient TS g/dl ×weight (kg) ×50/donor TS g/dl].

However, this equation assumes that albumin is roughly equal to one-half of plasma total solids. Therefore, it may not be valid if hyperglobulinemia with concurrent hypoalbuminemia exist. The volume of plasma required may vary depending on the rate of ongoing albumin loss and the magnitude of total body (i.e. interstitial and intravascular) albumin deficit.

In states of chronic hypoalbuminemia such as end-stage hepatic disease or protein-losing glomerulopathies, albumin administration via plasma becomes both costly and transient, as infused plasma albumin is quickly lost into ascitic fluid, urine, or moved extravascularly to replace interstitial albumin deficits.[26,42,44] Albumin therapy therefore may be more effective in treating acute losses such as those observed in systemic inflammatory disease states and hemorrhagic shock.[68]

Adjunct therapy: The importance of adequate nutritional support in critically ill animals to provide amino acid sources necessary for albumin synthesis and repair of diseased tissues cannot be overemphasized. Utilizing enteral nutrition when it can be accomplished via a functioning gastrointestinal tract should be considered in addition to analgesics to decrease discomfort/pain, and appetite stimulants (cyproheptadine,[a] anabolic steroids such as Winstrol-V[b]) that stimulate appetite and provide the nutrients necessary for protein synthesis and repair of diseased tissues. In anorexic patients, the use of feeding tubes (esophagostomy, gastrostomy or jejunostomy), can provide nutrients without the added stress of forced alimentation. The use of enteral nutrition for direct stimulation of enterocytes can help to prevent intestinal mucosal atrophy and subsequent bacterial translocation, both of which can contribute to sepsis and SIRS.[74–76] In situations where enteral feeding tubes cannot be placed or tolerated, parenteral nutrition is an alternative means of providing nutrients to a critically ill patient.

Monitoring: Physiological parameters which should be measured for end-points of plasma resuscitation include plasma albumin concentration, antithrombin levels, COP, and coagulation profiles. Perfusion parameters such as heart rate, respiratory rate and effort, and central venous pressure should also be closely monitored, to prevent overhydration and its negative consequences.

Conclusions

Albumin is one of the most important proteins in the body, contributing to a variety of functions, including maintenance of colloid osmotic pressure, substrate transport and delivery, and mediator of wound healing. Numerous conditions in both critically ill human and veterinary patients can result in decreased circulating albumin concentrations and depletion of total body albumin stores. Deficits in albumin have been correlated with increased morbidity and mortality in both human and veterinary patients.[17,70] Regarding the benefits and risks of albumin replacement in various critical illnesses, the jury is still out. It is the authors' opinion that in critically ill veterinary patients with hypoalbuminemia, use of a synthetic colloid alone to maintain COP, in combination with plasma therapy to maintain adequate circulating albumin levels and with crystalloid fluids to maintain circulating vascular volume, is the best approach to successful fluid therapy. Plasma transfusions alone are an ineffective means of increasing intravascular protein levels, particularly if ongoing loss is occurring. Colloid oncotic pressure should be provided, instead, with synthetic colloids and nutrition to assist in endogenous albumin synthesis. In this combination strategy, plasma is not used primarily for its oncotic effects, but rather, is used to increase plasma albumin for its other important functions, including drug carrying capacity, blood pH buffering, and mediation of coagulation and wound healing.[18] Albumin replacement, in combination with other fluids, may be an important adjunctive therapy to consider in disease states complicated by hypoalbuminemia.

Footnotes

[a] Cyproheptadine (Periactrin, Dose 2–4 mg PO, once to twice daily), Merck & Co, West Point, PA

[b] Winstrol-V (Stanozolol, Dose 2 mg PO BID or 25 mg deep IM, may be repeated weekly), Upjohn, Kalamazoo, MI

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