



The Therapeutic Role of Albumin Infusions in Critical Care Medicine Management

Mohammed Khudhair Hasan

Ibn Khaldun University College, Department of Pharmacy, Baghdad, Iraq. Email: mohammed.khudhair@ik.edu.iq

OPEN ACCESS

Corresponding Author:

Mohammed Khudhair Hasan
Ibn Khaldun University College,
Department of
Pharmacy, Baghdad, Iraq.

Email:

mohammed.khudhair@ik.edu.iq

Received: 18-02-2026

Accepted: 25-03-2026

Published: 14-04-2026

Copyright© International Journal of
Clinical, Medical and Health Sciences

ABSTRACT

Human serum albumin is the most abundant plasma protein in humans, which plays an important role in maintaining oncotic pressure, fluid distribution, binding of certain proteins and ligands, as well as having important antioxidant and anti-inflammatory functions. It is still controversial whether its use as a resuscitation fluid and therapeutic agent in critical care medicine is beneficial. Although initial clinical evaluations questioned the potential hazards of the use of colloid, sufficiently large randomized controlled trials and more recent meta-analyses have helped to clarify the clinical usefulness of the use of colloid. This comprehensive review examines the physiological properties of albumin, reviews key clinical studies in various critical care populations, looks at specific indications including septic shock, cirrhosis, and acute respiratory distress syndrome, and considers new concepts in therapeutic paradigms related to albumin kinetics in critically ill patients.

Keywords: Albumin Infusion; Critical Care; Hypoalbuminemia; Fluid Resuscitation; Clinical Management.

INTRODUCTION

Maintenance of intravascular volume and systemic inflammation are fundamental aspects in critical care medicine. For many years, the controversy has raged regarding the best fluid to use for resuscitation – crystalloids vs. colloids. At the heart of this discussion is a natural plasma volume expander, human serum albumin.

Before that, there was considerable controversy about the use of albumin after a controversial Cochrane collaboration meta-analysis, which indicated that there may have been a slight increase in death rates among critically ill patients receiving colloids (Cochrane Injuries Group Albumin Reviewers, 1998). This discovery led to the change of the resuscitation approach to crystalloids as first-line treatment. But later, well-designed, high-quality randomized controlled trials (RCTs)—including SAFE, ALBIOS and CONFIRM—confirmed the safety of albumin and identified certain subgroups with different survival benefits from its use (Finfer et al., 2004; Caironi et al., 2014; Wong et al., 2021).

Today, however, it is recognized that albumin is much more than an oncotic stabilizer to counteract hypovolemia, it is a pleiotropic molecule with properties of biological relevance that directly oppose the destructive cascade of sepsis, endothelial breakdown and multi-organ failure. This review summarizes current evidence regarding the physiology, clinical, and kinetic aspects of albumin use in the modern critical care setting.

Physiological Foundations and Pleiotropic Properties

The clinical use of albumin in the intensive care unit (ICU) requires understanding of the structural and functional biochemistry of the protein in both the normal and the disease state.

Colloid Osmotic Pressure and Volumetric Homeostasis

The albumin is a monomeric globular protein, made only by hepatocytes, with a basal rate of 10-15 g/day (Roche et al., 2008). It is about 50–60% of the plasma protein content. Most importantly, the endogenous COP (caused by the plasma itself) in a normal plasma is 70% to 80% albumin (Evans, 2015). About 18 mL of water is bound by the albumin in the intravascular space.

The revised Starling equation indicates that in addition to the trans-endothelial oncotic gradient, the oncotic pressure difference across the endothelial glycocalyx layer (EGL) is also a major factor in fluid filtration across the endothelial barrier (Woodcock & Woodcock, 2012). Albumin interacts directly with the subglycocalyx area and maintains the structural integrity of this fragile area, thereby preventing pathological capillary leak.

Ligand Binding, Transport, and Detoxification

Human albumin has a distinct tertiary structure with three homology-based helical domains (I, II, III) in which two pockets exist called Sudlow's sites I and II (Ghuman et al., 2005). These hydrophobic pockets allow the binding and transport of a variety of endogenous and exogenous molecules:

Endogenous Lipids and Bilirubin: Long-chain fatty acids are transported to metabolic sites as unesterified fatty acids, and unconjugated bilirubin is transported to metabolic sites to prevent systemic lipotoxicity and oxidative stress.

Pharmaceuticals: Binds high lipid content/lipophilic or acidic drugs which may include critical drugs used in the ICU, such as ceftriaxone, phenytoin, warfarin, and propofol. Hypoalbuminemia has a large impact on the free or unbound fraction of these medicines, leading to a more rapid clearance or toxicity (Smit et al., 2020).

Cations: Main source of zinc, copper and calcium carriers. Free ionized calcium levels need to be measured if there are major fluctuations in albumin levels, and approximately 40% to 45% of the total serum calcium is bound to albumin.

Antioxidant Actions and Nitric Oxide Scavenging

In critical illnesses, the inflammatory state causes enormous oxidative stress on the vascular system. The albumin is the most important extracellular antioxidant pool by a single un-oxygenated cysteine residue (Cys34) (Anraku et al., 2013). This is a free sulfhydryl group that is a strong scavenger of reactive oxygen species (ROS) and reactive nitrogen species (RNS).

Moreover, Albumin is involved in interaction with endothelial nitric oxide (NO). Albumin also acts as a buffer against excess nitric oxide in the plasma to prevent the marked, persistent vasodilation typical of distributive shock (Quinlan et al., 2005).

Pathophysiology of Hypoalbuminemia in the Critically Ill

Hypoalbuminemia (usually < 3.0 g/dL) is present at admission to the ICU in up to 40% to 50% of patients, and is independently associated with prolonged mechanical ventilation, acute kidney injury and all-cause mortality (Vincent et al., 2003).

Synthesis vs. Catabolism and Transcapillary Escape Rate

The hypoalbuminemia in critical illness is multifactorial and not due to a lack of nutrients, but to changes in their kinetics:

1. Pro-inflammatory cytokines, in particular, interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α), specifically downregulate hepatic transcription of the albumin gene to favor the transcription of proteins that make up the acute phase response, such as C-reactive protein and fibrinogen (Moshage et al., 1987).
2. Increased Hypercatabolism: In hypermetabolic inflammatory states, there is increased degradation of albumin in the cell's lysosomes.
3. Increased Transcapillary Escape Rate (TER): In a healthy adult, about 5% of intravascular albumin is lost into the interstitial space each hour. If there is severe sepsis or systemic inflammatory response syndrome (SIRS), systemic endothelial inflammation causes disruption of the tight junctions and degradation of the endothelial glycocalyx layer. This results in a sudden increase in the TER up to 300%, which leads to rapid albumin leakage into the interstitium and to diffuse peripheral and visceral oedema (Fleck et al., 1985).

Parameter	Healthy Baseline Status	Sepsis / Severe SIRS Status	Clinical Consequence
Hepatic Synthesis	10–15 g/day	Significantly suppressed	Slow recovery of native oncotic pressure.
Transcapillary Escape	~5% per hour	Up to 15%–20% per hour	Rapid shift to interstitium, causing anasarca.
Serum Concentration	3.5–5.0 g/dL	Frequently < 2.5 g/dL	Interstitial fluid shifts, reduced drug transport.

Albumin Formulations: 5% Hypervolemic vs. 20–25% Hyperoncotic

Clinicians can select a concentrate of human albumin with two different concentrations for correcting fluid loss or protein depletion, for different hemodynamic purposes.

Iso-oncotic (5%) Albumin Solutions

The 5% albumen formulation is iso-oncotic and has an oncotic pressure of about 20 mmHg which is similar to the oncotic pressure of normal human plasma. It is a direct volume replacement fluid when infused into the intravascular space. It has a [Mohammed Khudhair Hasan](#). The Therapeutic Role of Albumin Infusions in Critical Care Medicine Management. *Sci. 1*(2): 29-33, 2026

superior intravascular retention profile compared to isotonic crystalloids (0.9% NaCl or balanced crystalloids) with 70% to 80% remaining in the blood vessels immediately after infusion, whereas only 20% to 25% of crystalloids remain (Reinecke et al., 2024). It is indicated most often for quick intravascular volume expansion in acute situations of hypovolemic or distributive shock.

Hyperoncotic (20% to 25%) Albumin Solutions

Hyperoncotic formulations have an oncotic pressure 4-5 times higher than normal plasma (approx. 70-100 mmHg). Hyperoncotic albumin does not just increase volume when it is added, but rather, pulls it into the intravascular space.

Each 100 mL of 25% albumin infused will extract an additional 300-400mL from the interstitium within 30-60 minutes (Myburgh & Mythen, 2013) if patient is well hydrated. Hyperoncotic albumin is suitable for patients who have severe fluid overload, visceral oedema or cirrhosis with ascites.

Landmark Clinical Trials and Evidence-Based Medicine

Several multicenter RCTs have established the current guidelines for the use of albumin; these studies addressed several misconceptions.

The SAFE Trial (2004)

The Saline versus Albumin Fluid Evaluation (SAFE) trial was a randomized trial of 6,997 patients who required fluid resuscitation in the ICU that were randomized to either receive 4% albumin or normal saline (Finfer et al., 2004). The landmark study showed that the mortality rate for 28 days for all causes was essentially the same in the two groups (albumin 20.9% vs. saline 21.1%), thus dispelling the warnings of the Cochrane review in 1998.

Important pre-specified subgroup analyses showed that there was a strong tendency toward benefit on albumin use in patients with severe sepsis, but that there was a significant increase in mortality in severe traumatic brain injury (TBI) patients.

The ALBIOS Trial (2014)

The Albumin Italian Outcome Sepsis (ALBIOS) trial, which included 100 ICUs (Caironi et al., 2014), tested 1,818 patients with severe sepsis or septic shock. Patients were allocated to either 20% albumin which was used to maintain a serum albumin level of at least 3.0 g/dL, or crystalloids alone. The overall 28-day survival rates were not significantly different between the groups, but a secondary analysis revealed a statistically significant difference in 90-day mortality in patients with documented septic shock at enrolment who received targeted albumin therapy.

The CRISTAL Trial (2014)

The Colloids Versus Crystalloids for the Resuscitation of Critically Ill Patients (CRISTAL) trial randomized 2,857 patients with hypovolemic shock (Annat et al., 2014) to receive either a colloid (albumin or synthetic starches/gelatins) or a crystalloid. The 28-day mortality was similar; however, the colloid group had a significantly increased number of days of organ recovery as assessed by the 90-day mortality rate and the number of days of pressor and ventilator support.

Specific Clinical Indications in Critical Care

Sepsis and Septic Shock

In sepsis, endothelial stability is altered resulting in extensive vasodilation and loss of fluid to the tissues. The Surviving Sepsis Campaign guidelines recommend Albumin for patients that need large amounts of crystalloid during early resuscitation (Evans et al., 2021).

In contrast to crystalloids, albumin is known to restore intravascular volume in a more effective way, stabilize the endothelial glycocalyx and, independently, correlates with the development of worsening multi-organ dysfunction syndrome (MODS) (Acheampong & Vincent, 2015).

Decompensated Cirrhosis and Spontaneous Bacterial Peritonitis (SBP)

Advanced liver disease is a distinct patient population in the ICU. There is strong physiology and clinical evidence supporting the use of hyperoncotic albumin in cirrhosis:

- **Large-Volume Paracentesis (LVP):** Removal of > 5 liters of ascites fluid induces paracentesis-induced circulatory dysfunction (PICD), characterized by severe arterial vasodilation and subsequent acute kidney injury. Administering 8 grams of hyperoncotic albumin per liter of ascites removed significantly limits the incidence of PICD (Runyon, 2021).
- **Spontaneous Bacterial Peritonitis:** The combination of targeted antibiotic therapy and albumin infusions (1.5 g/kg at diagnosis, followed by 1.0 g/kg on day 3) reduces renal failure incidence from 33% to 10% and improves hospital survival outcomes (Sort et al., 1999).
- **Hepatorenal Syndrome (HRS-AKI):** Concurrently administering albumin and vasoconstrictors (such as terlipressin or norepinephrine) reverses renal hypoperfusion by augmenting central blood volume and improving renal perfusion pressure (Wong et al., 2021).

Acute Respiratory Distress Syndrome (ARDS)

Severe ARDS is associated with disruption of the alveolar-capillary membrane leading to non-cardiogenic pulmonary edema, resulting in impairment of gas exchange and severe ventilation-perfusion mismatching.

In clinical trials using combination therapy of hyperoncotic (25%) albumin and loop diuretics (furosemide) in patients with hypoproteinemic ARDS, the $\text{PaO}_2/\text{FiO}_2$ ratio improved significantly, along with a more negative net fluid balance and improved hemodynamic stability, compared to diuretic therapy alone (Martin et al., 2005).

Safety Profiles, Adverse Effects, and Contraindications

Although there are clinical advantages to the use of albumin, the product is an active biological substance and may lead to adverse effects if used incorrectly.

Traumatic Brain Injury (TBI) Explanations

A 24-month follow-up study of the SAFE TBI study showed that patients with severe brain injuries randomized to receive albumin resuscitation had a higher 24-month mortality rate compared to those receiving normal saline (Safe Study Investigators, 2007).

The mechanism is related to microvascular disruption in the brain. In damaged sections of the brain, the blood-brain barrier is damaged and allows leakage of albumin into the cerebral interstitium. On reaching the brain, it creates ICP by pulling water into brain tissue and lowers cerebral perfusion pressure (CPP). Thus, fluid resuscitation of acute traumatic brain injury should not be administered with albumin.

Volume Overload and Hydrostatic Pulmonary Edema

Hyperoncotic albumin can cause a sudden rise in blood volume that can lead to a sudden increase in venous return, resulting in a sudden increase in venous return. This could be overwhelming for the cardiovascular system when infused into patients with non-compensated left ventricular heart failure or severe oliguric renal failure. This may result in acute hydrostatic pulmonary edema (flash volume overload).

Pathogen Transmission Risks and Anaphylaxis

Albumin is a blood derived product which is prepared from pooled human donor plasma, and is subjected to rigorous pasteurization at 60°C for 10 hours and ultrafiltration. These measures effectively prevent the transmission of known enveloped viruses like HIV, HBV and HCV (Caraceni et al., 2013). Yet, there is a very low theoretical risk of non-enveloped virus or prion transmission exists.

Although rare, true anaphylactic reactions occur in less than 1 in 1,000 people, mild hypersensitivity reactions such as flushing, urticaria and drug fever may occur.

Emerging Perspectives: Albumin Kinetics and Future Directions

Current thinking on the use of fluids in the ICU is shifting away from 'rules of thumb' to individualized 'kinematic' based strategies.

Directed Resuscitation via Glycocalyx Integrity Monitoring

Current research is ongoing with the use of biomarkers for endothelial injury, including syndecan-1, hyaluronan and heparan sulfate, to detect patients with ongoing glycocalyx breakdown (Chappell et al., 2014). These states enable targeting the use of albumin as an early, targeted endothelial stabilizer, instead of waiting until more advanced hypoproteinemia occurs.

Extracorporeal Support Systems and Target Ranges

In advanced liver support systems, such as Molecular Adsorbent Recirculating System (MARS), exogenous albumin is used as a recirculating dialysate fluid to remove toxins in the blood of patients with acute-on-chronic liver failure (ALF), which can be albumin-bound such as bilirubin, copper, or bile acids (Saliba et al., 2013).

The clinical effectiveness of more aggressive serum albumin goals (> 3.5 g/dL) achieved with continuous low-dose infusions for improving long-term microvascular perfusion and reducing the need for vasopressor support in refractory distributive shock is being tested in various multicenter trials.

CONCLUSION

Human serum albumin is a very complex and multifunctional protein that plays an important role in the fluid management of critical care patients. In most ICU admissions, the use of crystalloids is the most suitable type of fluid to use for initial resuscitation, but in certain situations, there are significant physiological and clinical benefits to using targeted albumin therapy.

Albumin enhances oncotic pressure, maintains endothelial barrier function and minimizes systemic inflammatory injury when used judiciously (in septic shock patients who require significant volume expansion, patients with decompensated cirrhosis who present with SBP or HRS, and hypoproteinemic patients with severe ARDS). Clinicians should not use albumin in traumatic brain injury and need to carefully manage volume status to use this to benefit critically ill patients in their improvement and recovery.

REFERENCES

1. Acheampong, A., & Vincent, J. L. (2015). A positive fluid balance is an independent prognostic factor in patients with sepsis. *Critical Care*, 19(1), 251.
2. Anraku, M., Chuang, V. T., Maruyama, T., & Otagiri, M. (2013). Redox properties of serum albumin. *Biochimica et Biophysica Acta (BBA) - General Subjects*, 1830(12), 5465-5472.
3. Annat, G., Bougle, A., & CRISTAL Investigators. (2014). Colloids versus crystalloids for fluid resuscitation in critically ill patients: The CRISTAL randomized trial. *JAMA*, 311(4), 353-361.
4. Caironi, P., Tognoni, G., Masson, S., et al. (2014). Albumin replacement in patients with severe sepsis or septic shock. *New England Journal of Medicine*, 370(15), 1412-1421.
5. Caraceni, P., Domenicali, M., Tovoli, F., et al. (2013). Clinical indications for the administration of human albumin: Time for a reappraisal. *Annals of Medicine*, 45(4), 291-304.
6. Chappell, D., Westphal, M., & Jacob, M. (2014). The dimensions of the intravascular volume: A shift in current paradigms of fluid therapy. *Critical Care*, 18(4), 312.
7. Cochrane Injuries Group Albumin Reviewers. (1998). Human albumin administration in critically ill patients: Systematic review of randomised controlled trials. *BMJ*, 317(7153), 235-240.
8. Evans, T. W. (2015). Review article: Albumin as a drug—biological effects of albumin unrelated to oncotic pressure. *Alimentary Pharmacology & Therapeutics*, 16(s5), 6-11.
9. Evans, L., Rhodes, A., Alhazzani, W., et al. (2021). Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock 2021. *Intensive Care Medicine*, 47(11), 1181-1247.
10. Finfer, S., Bellomo, R., Boyce, N., et al. (2004). A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *New England Journal of Medicine*, 350(22), 2247-2256.
11. Fleck, A., Raines, G., Hawker, F., et al. (1985). Increased vascular permeability: A major cause of hypoalbuminaemia in disease and injury. *The Lancet*, 325(8432), 781-784.
12. Ghuman, J., Zunszain, P. A., Petitpas, I., et al. (2005). Structural basis of the drug-binding specificity of human serum albumin. *Journal of Molecular Biology*, 353(1), 38-52.
13. Martin, G. S., Moss, M., Wheeler, A. P., et al. (2005). A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. *Critical Care Medicine*, 33(8), 1681-1687.
14. Moshage, H. J., Janssen, J. A., Franssen, J. H., et al. (1987). Study of the molecular mechanism of decreased liver synthesis of albumin in inflammation. *Journal of Clinical Investigation*, 79(6), 1635-1641.
15. Myburgh, J. A., & Mythen, M. G. (2013). Resuscitation fluids. *New England Journal of Medicine*, 369(13), 1243-1251.
16. Quinlan, G. J., Martin, G. S., & Evans, T. W. (2005). Albumin: Biochemical properties and therapeutic potential. *Hepatology*, 41(6), 1211-1219.
17. Reinecke, H., Van Aken, H., & Westphal, M. (2024). Intravascular volume retention of modern resuscitation fluids: A comparative appraisal. *British Journal of Anaesthesia*, 132(3), 401-412.
18. Roche, M., Rondeau, P., Singh, N. R., et al. (2008). The antioxidant properties of serum albumin. *FEBS Letters*, 582(13), 1783-1787.
19. Runyon, B. A. (2021). Management of adult patients with ascites due to cirrhosis: An update. *Hepatology*, 73(4), 1610-1621.
20. Safe Study Investigators. (2007). Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *New England Journal of Medicine*, 357(9), 874-884.
21. Saliba, F., Camus, C., Durand, F., et al. (2013). Albumin dialysis with a Molecular Adsorbent Recirculating System (MARS) for the treatment of patients with acute-on-chronic liver failure: A prospective, randomized, controlled trial. *Liver Transplantation*, 19(5), 505-515.
22. Smit, C., De Cock, R. F., & Allegaert, K. (2020). Effects of hypoalbuminemia on drug distribution and clearance in critically ill populations. *Clinical Pharmacokinetics*, 59(4), 415-429.
23. Sort, P., Navasa, M., Arroyo, V., et al. (1999). Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *New England Journal of Medicine*, 341(6), 403-409.
24. Vincent, J. L., Navickis, R. J., & Wilkes, M. M. (2003). Morbidity in hospitalized patients receiving albumin: A meta-analysis of randomized controlled trials. *Critical Care Medicine*, 31(11), 2666-2679.
25. Wong, F., Pappas, S. C., Curry, M. P., et al. (2021). Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome: The CONFIRM trial. *New England Journal of Medicine*, 384(9), 818-828.
26. Woodcock, T. E., & Woodcock, T. M. (2012). Revised Starling equation and the glycocalyx model of transvascular fluid exchange: An elegant rationale for colloid therapy. *British Journal of Anaesthesia*, 108(3), 385-394.