Intensive Care Med
https://doi.org/10.1007/s00134-022-06655-8

UNDERSTANDING THE DISEASE

Ten myths about albumin

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Albumin plays an important role in critical care as a prognostic marker and therapy. However, the use of human albumin solution (HAS) has varied over time due to the varying and occasionally conflicting conclusions of clinical studies, lack of clear guidance, and misconceptions. In this review, we address ten common (mis-) beliefs and summarise the current evidence (Fig. 1).

Myth #1. Albumin leaks from the intravascular space into the interstitial compartment and contributes to oedema.

No, it does not.

Albumin, a major plasma protein, is essential for maintaining intravascular oncotic pressure. Up to 5% of intravascular albumin leaks per hour into the extravascular space [transcapillary escape rate (TER)] giving a distribution half-time of about 15 h. The TER depends on endothelial barrier function and the glycocalyx, a key component that can be damaged by inflammation. Thus, losses are higher in systemic inflammation, sepsis, postoperatively, and after trauma. Animal data suggest that albumin may protect the glycocalyx. Following extravascular leak, albumin re-enters the bloodstream via the lymphatic system at a rate similar to TER and does not remain in the interstitium (Supplementary Figure S1). Pulmonary vessels show increased permeability for albumin and are less dependent on the glycocalyx. Furthermore, the pulmonary lymphatic system is capable of a sevenfold increase in flow rate. The development of (pulmonary) oedema depends on the balance between the transcapillary difference between intravascular and interstitial oncotic pressures and opposing factors like tissue specific interstitial pressure and lymphatic flow rate. Critical illness impacts the rate of albumin synthesis as well as degradation and impacts both TER and lymph flow resulting in hypoalbuminaemia and altered distribution. In these situations, associated with decreased oncotic pressure, HAS supplementation increases intravascular oncotic pressure and re-establishes the transcapillary oncotic pressure gradient.

Myth #2. Albumin is less effective for intravascular volume expansion than artificial colloids.

No, it's more effective.

Colloids are often used in large-volume fluid resuscitation. The Saline versus Albumin Fluid Evaluation (SAFE) study compared hypotonic HAS 4% versus saline 0.9% in 6997 critically ill patients and showed that the ratio of administered HAS to saline volumes needed to achieve haemodynamic targets in the first 4 days was 1:1.4 [1]. In contrast, the volume ratio of hydroxyethyl starches compared to crystalloids is approximately 1:1.2. Plasma expansion with HAS 20% amounts to twice the infused volume in burn patients and healthy volunteers [2]. The final volume effect depends on TER which is increased in inflammatory conditions.

Myth #3. Albumin administration prevents acute kidney injury.

Yes, in specific settings.

Hypoalbuminemia is associated with an increased risk of acute kidney injury (AKI). HAS administration has been shown to prevent AKI in specific situations. In patients with liver cirrhosis and ascites, large-volume paracentesis combined with HAS is recommended to protect renal function [3]. This applies to patients with cirrhosis and spontaneous bacterial peritonitis, too.

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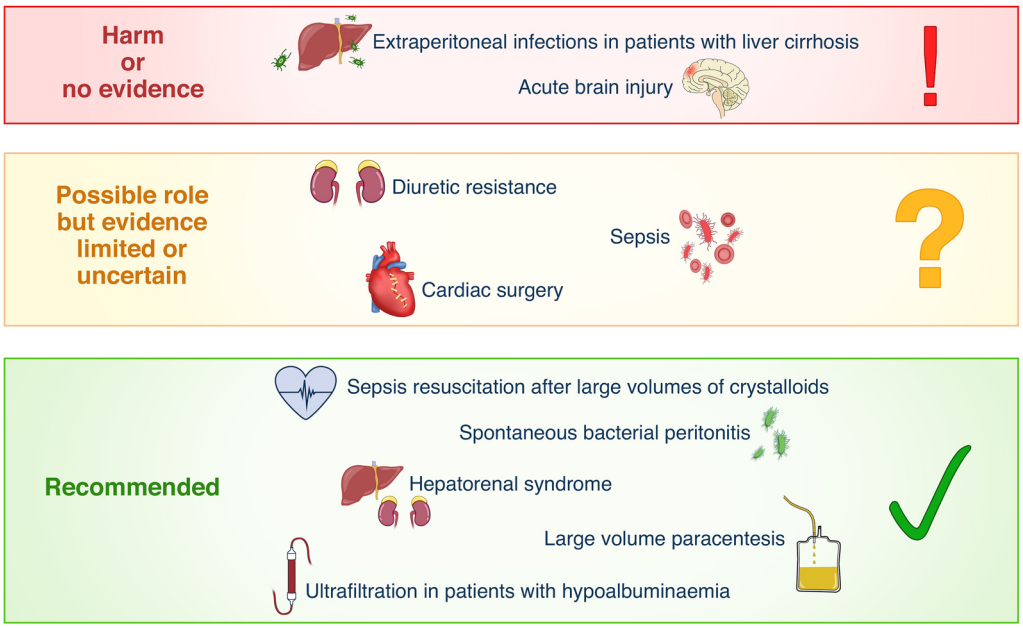

Fig. 1 Albumin therapy in critical care

Additional data suggest that HAS may also be effective in preventing AKI in cardiac surgery patients [4]. In contrast, the Albumin Italian Outcome Sepsis (ALBIOS) trial in patients with severe sepsis or septic shock and hypoalbuminaemia showed no difference in AKI or need for kidney replacement therapy (KRT) between patients who received HAS 20% versus the standard care group [5]. Importantly, no adverse effects on renal function have been shown in any randomized controlled trials (RCTs) either.

Myth #4. Albumin improves survival in sepsis.

Maybe, but it is still uncertain.

Subgroup analysis of the SAFE study suggested that HAS 4% administration for up to 28 days spent in the intensive care unit (ICU) in patients with sepsis reduced mortality compared to crystalloid [1]. The ALBIOS trial showed a trend toward better survival in sepsis patients who received HAS 20% to correct hypoalbuminaemia; subgroup analysis demonstrated lower mortality in patients with septic shock [5]. However, the Lactated Ringer Versus Albumin in Early Sepsis Therapy (RASP) study which compared HAS 4% versus crystalloid alone during the first 6 h after ICU admission in 360 cancer patients with severe sepsis or septic shock, confirmed no difference in 7-day or 28-day survival [6]. A recent RCT investigating the effect of HAS 5% versus saline 0.9% in 154 cirrhotic patients with sepsis related hypotension showed improved haemodynamic stabilisation and 7-day survival in the HAS group [7].

Myth #5. Albumin improves the effects of diuretics.

Yes, but only temporarily.

Severe hypoalbuminemia contributes to diuretic resistance. Potential reasons include the delivery of reduced amounts of diuretics to tubules (furosemide binds to albumin to reach the proximal tubule via renal blood flow), potentially reduced intravascular volume available for fluid removal, and binding of furosemide to albumin in the intratubular space in patients with proteinuria. A RCT in 40 mechanically ventilated patients with acute lung injury and hypoproteinaemia showed that the addition of albumin to furosemide therapy significantly improved oxygenation with a greater net negative fluid balance and better haemodynamic stability [8].

A meta-analysis of 13 RCT's including 9 studies with crossover design investigating co-administration of loop diuretics and HAS versus loop diuretics alone in adult patients concluded that combination therapy may increase diuresis and sodium excretion by 31.5 mL/h and 1.76 mEq/h, respectively. The treatment effect was more pronounced in patients with serum albumin

levels < 2.5 g/dl and higher prescribed albumin infusion doses (> 30 g), but the heterogeneity was high [9]. Importantly, the effect on urine output was more prominent in the first 12 h after co-administration.

Myth #6. Albumin administration improves fluid removal during KRT

Yes, it does.

Hypotension during KRT limits fluid removal, prolongs the duration of fluid overload, and is a risk factor for non-recovery of renal function. HAS has been used to promote plasma refilling and to prevent intradialytic hypotension. In a randomised, crossover trial, 65 AKI or end-stage kidney disease (ESKD) patients with hypoalbuminaemia (albumin < 3 g/dl) receiving intermittent haemodialysis were randomised to receive 100 mL of either 0.9% saline or HAS 25% at the initiation of each dialysis session [10]. Analysis of 249 sessions showed significantly fewer episodes of hypotension and better fluid removal in patients who received HAS. Similarly, a secondary analysis of the 'Randomized Evaluation of Normal versus Augmented Level (RENAL) replacement therapy' trial demonstrated that 51% of 1508 patients had received 4% or 20% HAS [11]. Administration of HAS 20% was associated with a more negative fluid balance compared to HAS 4%, without any difference in mortality or renal recovery.

Myth #7. Albumin decreases mortality in liver cirrhosis.

Yes, but only in specific subgroups.

In patients with liver cirrhosis, albumin is recommended for specific indications, including large-volume paracentesis, hepatorenal syndrome (in combination with vasopressor support) and spontaneous bacterial peritonitis (SBP) and but not for patients with infections different from SBP [3]. A meta-analysis of nine clinical trials with 1231 patients concluded that long-term HAS administration (> 1 month) was effective in reducing 1-year mortality of liver cirrhosis patients by 43% compared to standard medical care [11]. However, studies reporting short-term HAS therapy (< 1 month) showed no effect on mortality. A subsequent RCT in 777 patients with decompensated cirrhosis and hypoalbuminaemia comparing HAS substitution versus standard care also showed no significant benefit but more serious adverse events in the HAS group [12].

Myth #8. Albumin increases mortality in traumatic brain injury (TBI)

Maybe, but we are not sure.

In BaSICS, comparing hypotonic balanced crystalloids with saline 0.9%, TBI patients treated with saline had significantly better 90-day survival [13]. The SAFE-TBI study (a post hoc follow-up analysis of 460 patients from the SAFE trial [1]) reported higher mortality in those who received HAS 4% compared with saline 0.9%. However, the low osmolality of HAS used (266–267 mOsmol/L H_2O) may have been suboptimal for patients with TBI. Experimental studies directly comparing commercially available hypotonic HAS 4% used in SAFE with isotonic HAS 4% (theoretical osmolarity, 288 mOsmol/kg) showed higher intracranial pressure (ICP) with hypotonic HAS, suggesting that tonicity rather than albumin itself impacts ICP [14].

Myth #9. Albumin substitution to correct hypoalbuminemia from all causes reduces mortality.

No, it does not.

Hypoalbuminaemia is associated with worse outcomes. A secondary analysis of the SAFE study comparing fluid resuscitation with HAS 4% versus saline 0.9% showed no difference in mortality, irrespective of patients' baseline serum albumin concentration [1]. The subsequent ALBIOS study in critically ill patients with sepsis also concluded that administration of HAS 20% to maintain serum albumin concentration at 30 g/L did not improve 28- and 90-day survival compared with crystalloids alone [5]. The same was true for hospitalised patients with decompensated liver cirrhosis when targeting a serum albumin level > 30 g/L [7].

Myth #10. Albumin administration increases sodium chloride load.

Probably, but it is not relevant.

The infusion of chloride-rich solutions has been associated with adverse outcomes in critically ill patients. Although some studies have suggested that chloride-rich fluids may adversely affect renal function, recent trials showed no measurable risk with use of saline 0.9% in moderate quantities (median volume of 2.9 L in first 3 days in the "Balanced Solution Versus Saline in Intensive Care Study" (BaSICS) [13].

Some commercial HAS 4% and 5% products have high sodium chloride contents. HAS with a higher tonicity contains less chloride. When both 4% and 20% HAS were used as part of a chloride-limiting strategy in the "Limiting IV Chloride to Reduce AKI after Cardiac Surgery" (LICRA) trial, HAS 20% was associated with

a significantly lower incidence of hyperchloremia but there was no difference in adverse renal outcomes [15].

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06655-8.

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Funding
None.

Declarations

Conflicts of interest
MJ has received speaker's fees from CLS Behring. CJW has received fees for speaking and consulting from CSL Behring, and fees for speaking from Biotest. MO reports no conflict of interests.

Publisher's Note

Published online: 05 March 2022

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