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# Phases of fluid management and the roles of human albumin solution in perioperative and critically ill patients

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# Phases of fluid management and the roles of human albumin solution in perioperative and critically ill patients

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**ABSTRACT**

**Objective:** Positive fluid balance is common among critically ill patients and leads to worse outcomes, particularly in sepsis, acute respiratory distress syndrome, and acute kidney injury. Restrictive fluid infusion and active removal of accumulated fluid are being studied as approaches to prevent and treat fluid overload. Use of human albumin solutions has been investigated in different phases of restrictive fluid resuscitation, and this narrative literature review was undertaken to evaluate hypoalbuminemia and the roles of human serum albumin with respect to hypovolemia and its management.

**Methods:** PubMed/EMBASE search terms were: "resuscitation," "fluids," "fluid therapy," "fluid balance," "plasma volume," "colloids," "crystalloids," "albumin," "hypoalbuminemia," "starch," "saline," "balanced salt solution," "gelatin," "goal-directed therapy" (English-language, pre-January 2020). Additional papers were identified by manual searching of reference lists.

**Results:** Restrictive fluid administration, plus early vasopressor use, may reduce fluid balance, but in some cases fluid overload cannot be entirely avoided. Deresuscitation, with fluid actively removed through diuretics or ultrafiltration, reduces duration of mechanical ventilation and intensive care unit stay. Combining hyperoncotic human albumin solution with diuretics increases hemodynamic stability and diuresis. Hyperoncotic albumin corrects hypoalbuminemia and raises colloid osmotic pressure, limiting edema formation and potentially improving endothelial function. Serum levels of albumin relative to C-reactive protein and lactate may predict which patients will benefit most from albumin therapy.

**Conclusions:** Hyperoncotic human albumin solution facilitates restrictive fluid therapy and the effectiveness of deresuscitative measures. Current evidence is mostly from observational studies, and more randomized trials are needed to better establish a personalized approach to fluid management.

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## Introduction

Giving fluid therapy to restore and maintain tissue perfusion is standard practice for patients with critical illness or those undergoing surgery[1]. Significant risks of fluid therapies are related to under- or over-administration, as well as their pharmacological side effects. Every day, more than 20% of patients in intensive care units (ICUs) are treated with intravenous fluids; more than 30% receive fluids for volume resuscitation on day 1[2]. In the past, colloid solutions have been used more frequently than crystalloid solutions for volume resuscitation; however, colloids cost more and some are potentially harmful[3]. Today, more crystalloid solutions are used, often buffered solutions instead of saline, and solutions of the natural colloid albumin are favored over synthetic colloid solutions, particularly hydroxyethyl starch (HES)[4–7].

Adverse effects associated with crystalloids result from their distribution into interstitial areas of the subcutis, gut, and lungs[8,9]. In surgery, for example, gastrointestinal recovery is delayed by 2 days if >2 liters of crystalloid is given perioperatively[10], and administration of 6–7 L during open abdominal surgery can lead to inadequate wound healing, pulmonary edema, and pneumonia[9,11,12]. In ICU patients with septic shock, the majority of fluid therapy is given for reasons other than volume expansion; this non-resuscitation portion is perhaps the biggest modifiable target for reducing the risk of fluid overload[13–15].

Regarding colloid fluids, human serum albumin (HSA) solution is the reference solution[16]. It has been determined to be safe for use as a resuscitation fluid in most critically ill patients and may have a role in sepsis[17,18]. HES solutions, in contrast, are associated with increased rates of renal-replacement therapy (RRT) and other adverse events among ICU patients[19]. In a meta-analysis of randomized controlled trials (RCTs), blood loss was greater in patients undergoing major non-cardiovascular surgery who received HES as opposed to crystalloids or HSA solution[20]. With either crystalloids or

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colloids, coagulation is impaired when hemodilution reaches 40%; concomitant hypothermia exacerbates this coagulopathy[9].

Beyond the type of fluid, an important question is the *amount* of fluid to administer, in particular, whether restrictive fluid strategies benefit critically ill and surgical patients. Fluid infusion must be carefully titrated and individualized, as too much or too little fluid can worsen outcomes[1]. Both crystalloids and colloids can cause edema, though the pathophysiological mechanisms differ[9]. Hypotonic HSA solution should be avoided as a resuscitation fluid in patients with traumatic brain injury, based on results from the Saline versus Albumin Fluid Evaluation (SAFE) study[17]. Crystalloids and colloids can be used together to balance the risk of fluid-induced adverse effects, especially in patients who would need large volumes[1]. For example, in surgical patients, switching to a colloid may be necessary when more than 3–4 L of crystalloid have been infused but the patient still requires plasma volume support and blood product transfusion is not indicated[9].

The scope of this narrative review is to describe current volume resuscitation strategies and the roles of HSA solutions. It focuses on hypovolemia and its correction in perioperative and critically ill patients, as opposed to hypervolemia, which can also have detrimental effects in these patients[21,22]. It is important to emphasize that fluid therapy is context-dependent and management varies across different clinical settings – data cannot therefore be easily extrapolated to other patient populations which may be distinct. The manuscript does not aim to systematically review the available clinical evidence in all therapeutic settings and does not encompass HSA in liver disease, for which the reader is referred to other relevant reviews and key guidelines[23–25].

The content is based on PubMed and EMBASE searches for English-language reports published before January 2020 using the terms "resuscitation," "fluids," "fluid therapy," "fluid balance," "plasma volume," "colloids," "crystalloids," "albumin," "hypoalbuminemia," "starch," "saline," "balanced salt solution," "gelatin" and "goal-directed therapy". Additional papers were identified by manual searching of the reference lists of selected articles.

## Fluid management in perioperative and critically ill patients

### *Fluid balance*

For traumatic shock, delayed hemorrhage control and excessive use of crystalloids for preloading are recognized as modifiable predictors of highly lethal hyperacute organ failure (respiratory, renal, and cardiac) due to increased abdominal pressure[26]. Moving away from the decades-old approach of large-volume resuscitation with crystalloids, characterized by edema formation and weight gain, substantially reduced the rate of postinjury abdominal compartment syndrome and morbidity in this indication[26,27]. However, increased body weight is still common following major surgery, and in the acute phase of critical illness can persist for several days; it is typically ascribed to the inflammatory stress response in combination with liberal use of fluid therapy[28,29]. The extent to which the kidneys retain or excrete fluid in the pathophysiology of injury may be particularly relevant for this increase in body weight due to edema formation[28].

Managing volume status in patients with critical illness is a dynamic and delicate exercise that necessitates frequent monitoring and sound clinical judgment[21] .The *"fluid balance method"* is the approach most widely used for managing volume replacement by fluid infusion during intensive care or perioperatively. Perceived needs and losses are summarized continuously and volume is substituted with crystalloids and colloids in proportion to their respective plasma-volume-expanding properties. It is well known that fluid overload, positive fluid balance, morbidity and mortality are interrelated. Organ dysfunction, prolonged mechanical ventilation, and higher mortality may result from volume overload and hypervolemia[21,22]. When compared with zero fluid balance, positive fluid balance after cardiac surgery was associated with increased incidence of acute kidney injury (AKI) [30], suggesting that fluid retention may be causally interrelated with AKI, contributing to renal retention and weight gain.

Modern approaches to volume resuscitation center on the patient's fluid requirement, responsiveness, and tolerance as distinct aspects of care, yet a documented order for strict monitoring of fluid balance (intake versus output) is lacking in a significant number of patients hospitalized with severe illness[31].

Hypovolemia leads to diminished organ perfusion, ischemia, and multiple organ failure, although low blood pressure is not necessarily the result of hypovolemia[1,21,22,32]. In patients with critical illness, fluid balance that is either positive or negative – as opposed to even – is associated with increased mortality within 1 year; RRT reduces the risk related to positive fluid balance[33]. Mortality through 30 days was lower in critically ill patients with influenza whose cumulative fluid balance was negative on days 1–4 after ICU admission[34]. In critically ill children with fluid overload receiving continuous RRT, early fluid removal enhances patient outcomes[35].

### *Phases of fluid management in volume resuscitation*

Fluid resuscitation is imperative for sepsis rescue; however, the fluid type, dosage, and duration are matters of debate[36–38]. The SOSD concept (Salvage, Optimization, Stabilization, De-escalation) first proposed by Vincent and De Backer[39], and later adapted to ROSE (Resuscitation, Optimization, Stabilization, Evacuation) by Malbrain et al. [22], describes the different phases of fluid management in volume resuscitation of critical illness (Table 1). During salvage/resuscitation, optimization, and stabilization, fluid treatment progresses from boluses, to titration, and then to maintenance, respectively. Finally, de-escalation/evacuation, also referred to as "goal-directed fluid removal" or "deresuscitation," involves active fluid removal through diuretics, RRT, and cessation of invasive treatments.

**Table 1.** Concepts of the different phases of fluid management in volume resuscitation of the critically ill patient[22,39].

| SOSD | ROSE | Goals and considerations for fluid therapy in each phase |
|---|---|---|
| EBB PHASE: From boluses, to titration, and then maintenance | | |
| Salvage | Resuscitation | • Rapidly optimize tissue oxygenation to preserve and protect organ function<br>• Give fluid boluses within minutes, guided by dynamic measures of responsiveness<br>• Insufficient resuscitation can lead to microcirculatory dysfunction and exacerbate tissue hypoxia |
| Optimization | Optimization | • Optimize fluid therapy during subsequent hours to prevent organ failure *via* organ support and minimizing second-hit injury through additional boluses, guided by indices of fluid responsiveness<br>• Insufficient resuscitation can lead to microcirculatory dysfunction and exacerbate tissue hypoxia<br>• Conversely, if fluid therapy is too aggressive, interstitial edema and organ dysfunction may worsen |
| Stabilization | Stabilization | • Stabilize organ perfusion and aid recovery from organ dysfunction/failure; ensure that fluid balance is neutral or negative<br>• Within days, identify fluid overload and consider inducing diuresis with diuretics and RRT if AKI is present |
| FLOW PHASE: Goal-directed, active removal of fluid; deresuscitation | | |
| De-escalation | Evacuation | • Restore organ function by attaining negative fluid balance through goal-directed fluid removal<br>• Limit fluid intake by using colloids, especially hyperoncotic solution<br>• Restrict the volume of maintenance fluids and drug diluents administered<br>• Consider deresuscitative measures involving more aggressive fluid removal to limit the possible consequences of fluid overload<br>• Avoid removing too much fluid, as this could lead to hypoperfusion |

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy.

### *Ebb phase – salvage/resuscitation, optimization, and stabilization*

In the ebb phase of hemodynamic instability and circulatory shock, the body's response to proinflammatory cytokines results in vasodilatation, reduced oncotic pressure in the capillaries (as a consequence of albumin leak), and compensatory neuroendocrine changes with potential renal dysfunction. Sufficient filling of the patient's circulatory system through fluid infusion is advocated to avoid exacerbating microcirculatory dysfunction and interstitial edema and compromising regional tissue oxygenation. Initially, patients respond to intravenous fluid; however, the effects diminish rapidly over time. According to a recent study in septic shock, less than 5% of patients were fluid responsive after 8 h from presentation[40]. Fluid balance is generally positive in this phase. Outcomes were not improved with early goal-directed therapy versus usual care in patients with septic shock[41]. Excess fluid leads to worse outcomes, and early vasopressor therapy is often required; catecholamines are typically recommended as the first-choice vasopressors in patients with septic shock[37,39,42] .However, the efficacy-to-safety profile of catecholamines has come under increasing scrutiny[37].

There is some evidence of poorly sustained physiological efficacy when fluid bolus therapy is used in critically ill patients[43,44]. However, study methodology is generally heterogeneous in terms of fluids and volumes used and timings of assessments, such that outcomes are conflicting; higher quality RCTs are needed to provide evidence of the physiological effects/benefits of fluid bolus therapy and to better understand the setting-dependent effects of HSA administration[45].

Hemodynamic stabilization is a crucial element of supportive treatments for severe sepsis and septic shock recommended in the Surviving Sepsis Campaign (SSC) treatment bundle[42,46]. Early, aggressive use of crystalloid fluid is potentially detrimental. Accumulation of fluid, which is frequent not only in the salvage phase of resuscitation and in patients undergoing major surgery but also in ICU patients with AKI, is linked to higher mortality and impaired renal recovery[47–49]. Higher fluid balance on day 3 increases the risk of death from sepsis[50]. In the Sepsis Occurrence in Acutely ill Patients (SOAP) observational study, fluid balance was linked to survival in patients with AKI[51]. According to a recent cohort study, positive fluid balance in sepsis patients during the second 24-h period after ICU admission was associated with increased mortality, whereas mortality was decreased if a lower fluid balance was achieved; these effects were not evident in the first 24 h[52]. Given this observational evidence on the association of positive fluid balance with adverse outcomes, prospective RCTs should be able to confirm a causal relationship between a conservative approach to fluid management and increased survival.

### *Flow phase – de-escalation, elimination, and fluid removal*

The goal of fluid therapy following management in the ebb phase is to restore organ function by achieving negative fluid balance *via* goal-directed fluid removal[22]. The flow phase usually occurs when the patient is stable, inflammatory mediators have been attenuated, and the plasma oncotic pressure has been restored. Limiting fluid intake by using colloids, in particular hyperoncotic HSA solution, has been associated with favorable effects[53]. Likewise, minimizing fluid balance at day 3 by restricting maintenance fluids and drug diluents, as well as taking deresuscitative measures, is potentially beneficial in critically ill patients[54].

Caution is recommended to avoid removing too much fluid, as this could lead to hypoperfusion. RCTs have so far

failed to confirm a mortality benefit with conservative versus liberal fluid management[55]. However, observational trials in sepsis, acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), and AKI, have detected a survival benefit with negative fluid balance[30,34,47,48,56–61]. Similarly, mortality after cardiovascular surgery was lower in critically ill patients who achieved early negative fluid balance[62]. Outcomes were also significantly improved in sepsis patients who achieved negative fluid balance during resuscitation; furthermore, the amount of daily or cumulative negative fluid balance correlated with reduced mortality[63]. Conversely, increased long-term mortality has been observed not only in patients with positive fluid balance but also in those with negative fluid balance[33]. Fluid management according to Enhanced-Recovery-After-Surgery (ERAS) protocols, which aim to maintain a euvolemic state and avoid adverse events related to hypervolemia or hypovolemia after surgery, may increase the rate of AKI[64]. Therefore, prospective clinical trials are needed to validate beneficial outcomes observed to date with conservative approaches to fluid management.

The Fluids And Catheters Treatment Trial (FACTT)[65], a landmark study of liberal versus conservative fluid management in adults with ARDS, used fluid restriction and diuretics in the conservative group to maintain lower central venous pressure and pulmonary capillary wedge pressure. The conservative approach resulted in fewer ventilator days, and *post hoc* analysis[57] indicated that negative fluid balance induced by diuretics may enhance survival in patients with AKI. According to a recent pilot study, accumulation of fluid in ICU patients with AKI may be effectively treated by forced fluid removal aiming at 1 mL/kg ideal body weight/hour[66]. Therefore, outcomes in patients with critical illness may be improved by pharmacological fluid management to alleviate excessive accumulation of fluid[67].

Interventions currently being tested in RCTs include discontinuation of maintenance fluids, concentration of intravenous drugs, and diuretic titrations commenced when fluid balance is more than 2 L positive from ICU admission or upon evidence of edema in more than one anatomical site on ICU day 3 or later[68]. Deresuscitation strategies involving more aggressive removal of fluid after stabilization are increasingly evaluated as tools for limiting the possible consequences of fluid overload[69].

## Fluid therapy for plasma volume expansion

Prompt restoration or expansion of plasma volume can help to avoid tissue hypoxia and conserve organ function. Delayed fluid resuscitation may increase organ dysfunction and inflammation, especially in patients with septic shock[18]. Therefore, once infused, exogenous fluid therapy should ideally persist in the plasma for a prolonged duration.

### *Plasma volume expansion with crystalloids*

The distribution phase of crystalloids yields a plasma volume expansion capacity of 50–60% of the infused volume for the duration of the infusion; this capacity decreases to 15–20% within 30 min of stopping the infusion[70]. Small volume infusions of crystalloid undergo minimal distribution to the interstitium, whereas rapid infusions can lead to edema. Elimination of fluid during general anesthesia is slow because arterial pressure is reduced by vasodilatation, while hemorrhage has less effect on fluid kinetics. The half-life of saline is almost double that of Ringer's solutions. Capacity to expand the plasma volume is similar between Ringer's and glucose solutions, though it fades faster after the end of the infusion with glucose[70].

### *Plasma volume expansion with colloids*

The observed ratio (1:1.3–1:1.4) of colloid to crystalloid needed to attain similar hemodynamic endpoints in trials is narrower than predicted (1:3–1:5), likely due to endothelial permeability[2]. Colloids persist in the intravascular space for longer than crystalloids, but their hemodynamic effects are influenced by several factors: normal metabolic processing of colloids; leakage across the endothelium when permeability is increased, e.g. in sepsis; and external loss, e.g. due to hemorrhage or burns[18]. Because of their side effects, artificial and semisynthetic colloids should no longer be used in critically ill patients[19,36], and their ongoing use outside the ICU is controversial and subject to tightened regulatory restrictions[71].

### *Capillary leak and global capillary leak syndrome*

Novel markers that might be useful to clinicians when selecting appropriate volume therapy include the capillary leak, extravascular lung water, and pulmonary permeability indices[72,73]. Capillary leak is an inflammatory condition with diverse triggers that results from a common pathway which includes ischemia-reperfusion, toxic oxygen metabolite generation, and cell wall and enzyme injury, leading to loss of capillary endothelial glycocalyx and barrier function. Capillary leak is the abnormal loss of fluid, electrolytes and protein from the blood vessels and into the interstitium, potentially resulting in edema[72].

Global increased permeability syndrome (GIPS) involves persistent systemic inflammation and continuing transcapillary leakage of albumin, with net fluid balance becoming increasingly positive. Following the initial insult and ischemia-reperfusion injury, GIPS represents a "third hit". Fluid overload should be avoided in this setting in particular[72,73].

### *The endothelial glycocalyx and fluid dynamics*

Endothelial functions including inflammation and permeability are determined by the glycocalyx, a network of proteoglycans and glycoproteins that coats the luminal surface of vascular endothelium (Figure 1)[74,75]. The predominant proteoglycans of the glycocalyx are the transmembrane-bound-syndecan and the membrane-bound glypican, bound to which are glycosaminoglycan side chains, mostly heparan sulfate but also others such as hyaluronic acid and chondroitin sulfate. Diverse glycoproteins are found in the glycocalyx, including the cell adhesion molecules as well as receptors

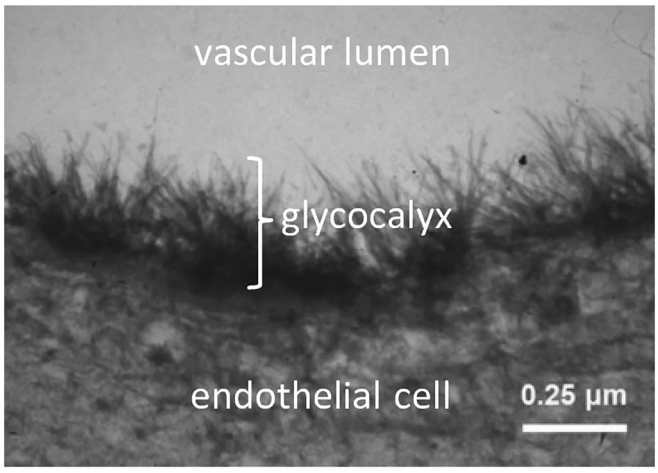


**Figure 1.** Electron micrograph of the endothelial glycocalyx in healthy rat aorta. Image reproduced without modification from Wiesinger et al.[74], under a Creative Commons Attribution 3.0 Unported (CC BY 3.0) License (https://creativecommons.org/licenses/by/3.0/). Copyright © 2013 Wiesinger et al. This reuse has not been endorsed by the licensor. The source reference is "Nanomechanics of the endothelial glycocalyx in experimental sepsis" in *PLoS One* and is available at https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0080905

involved in intercellular signaling, fibrinolysis, and coagulation. Also incorporated into the glycocalyx scaffold network are various other molecules derived from the endothelium or plasma, including serum albumin[76]. Understanding the effects of the glycocalyx on oncotic pressure differences across blood vessel walls led to the "revised" or "extended" Starling equation of transvascular fluid exchange[77,78], although Hahn et al. noted that this principle may not fully account for the dynamic nature of the circulatory system and clinical observations in fluid therapy studies[79].

## Mechanistic considerations for human albumin solutions

### Effects on endothelial integrity

There is weak evidence that exogenous fluid infusion causes the release of atrial natriuretic peptide that damages the endothelial glycocalyx and contributes to shedding of this layer[80]. It has been hypothesized from studies in sheep that fluid resuscitation leading to paradoxical increases in vasopressor requirements may be due to release of atrial natriuretic peptide triggering glycocalyx shedding, which might account for reports that cardiovascular collapse rather than fluid overload contributed most to excess mortality with rapid fluid resuscitation in a secondary analysis of the Fluid Expansion as Supportive Therapy (FEAST) trial[81,82]. Other preclinical studies have shown that HSA solution, which reduces vascular permeability and adhesion of leukocytes and platelets, better preserves and restores the endothelial glycocalyx than does HES; however, the mechanism of this effect of HSA is not yet fully understood and has been referred to as "the colloid osmotic pressure paradox"[75]. Accelerated vascular leakage as a consequence of deterioration of the endothelial glycocalyx layer by fluid infusion has yet to be convincingly demonstrated[70].

### Inhibition of matrix metalloproteinase

Low protein content of plasma causes shedding of the endothelial glycocalyx since matrix metalloproteinase (MMP) is uninhibited and free to cleave components of the glycocalyx away from the endothelium. Protein can exert this protective effect by binding lipid mediators such as sphingosine 1-phosphate (S1P) which can inhibit MMP, thereby preventing shedding of the glycocalyx and enabling its concurrent replenishment through Golgi-mediated translocation of new components[75]. S1P is mostly derived from red blood cells and platelets and its release from these sources is facilitated by plasma proteins, mostly high-density lipoprotein and albumin[83]. Without albumin, the release of S1P from red blood cells is reduced 25-fold[84].

### Inhibition of heparin-binding protein

A high plasma level of heparin-binding protein (HBP) is associated with the severity of sepsis, and may be useful as a biomarker for detecting organ dysfunction among patients ranging from those with suspected infections to those with septic shock[85,86]. An *in vitro* study by Fisher et al. showed that when present at a threshold concentration of 20–30 g/L, HSA solution suppressed the capacity of HBP to increase endothelial cell permeability, suggesting that HBP inhibition may be a mechanism through which HSA solution exerts therapeutic efficacy in septic shock[87].

### Albumin kinetics

It remains to be determined whether the effects observed with HSA solution *in vitro* in protecting the endothelium and restoring the glycocalyx also occur *in vivo*, which would have implications not only for capillary leak but also albumin kinetics[74,75]. In healthy volunteers and in patients on day 1 following major open abdominal surgery, a 30-min intravenous infusion of 3 mL/kg body weight 20% HSA solution expanded the volemic state for almost 2 h, with no important differences in the kinetics of 20% HSA solution between the two study groups[88]. The half-life of the plasma volume expansion was a median 10.3 (interquartile range 5.3–17.6) h in the post-surgery group and 7.6 (3.5–9.0) h in the healthy volunteers[89]. In patients with septic shock, infusion of 20% HSA solution improved endothelial function versus saline by restoring microcirculatory blood flow in the skin[90].

### Healthy volunteers

Bolus infusion of 20% HSA solution is effective and safe in healthy subjects, as demonstrated in a randomized, double-blind, cross-over study which compared the pulmonary and hemodynamic effects of commonly available crystalloid and colloidal solutions, i.e. 30 mL/kg of 0.9% saline, Hartmann's solution, 4% HSA solution, and 6 mL/kg of dose-equivalent 20% HSA solution[91]. Another study in healthy volunteers showed that infusion of 20% HSA solution significantly increased plasma volume by recruiting interstitial fluid[92]. Maximum plasma dilution was attained 20 min post-infusion, and the expansion of plasma volume lasted far beyond 5 h.

### Prognostic value of hypoalbuminemia

Albumin has a variety of biological properties and functions[93], including regulating colloid osmotic pressure, binding and transporting substances such as drugs and hormones in blood, antioxidant activity, modulating nitric oxide, and buffering capabilities, which may be especially relevant in critically ill patients[93].

It is known that low levels of serum albumin, which are common in patients with critical illness, are associated with poor outcomes[94–96]. Some evidence indicates that the transcapillary escape rate of albumin increases in tandem with disease severity[97]. A recent study by Gradel et al. measured daily mean levels of serum albumin, C-reactive protein (CRP), and hemoglobin (Hb) for 30 days before and after community-acquired bacteremia, as well as correlations between serum albumin and CRP and serum albumin and Hb; CRP was the first factor that contributed to variations in serum albumin[98]. The rapid decrease in serum albumin, without sudden changes in CRP or Hb, suggests that hypoalbuminemia is a marker of transcapillary leakage.

Elective surgical patients whose initial postoperative serum albumin concentration is less than 27 g/L are at greater risk of fluid overload[99]. Using HSA solution as volume expanders may offer some benefit over crystalloid solutions[42,100,101]; furthermore, the literature supports multiple secondary benefits of HSA solution in specific surgical and ICU settings, such as sepsis and organ dysfunction[102].

### Lactate-to-albumin and C-reactive protein-to-albumin ratios

Serum albumin concentration is predictive of noradrenaline and fluid requirements, and also the change in lactate level, within the first 24 h after ICU admission[103]. Serum lactate and albumin levels diverge during critical illness and an increased ratio of lactate-to-albumin correlates with the development of multiple organ dysfunction syndrome (MODS) and mortality in severely septic and other critically ill patients[104–106]. In a large, multicenter, retrospective study, the lactate-to-albumin ratio demonstrated superior clinical utility for predicting 28-day mortality in critically ill sepsis patients when compared with a single lactate measurement; this prognostic value was evident irrespective of the initial lactate level and the presence of hepatic or renal dysfunction[107]. Use of the lactate-to-albumin ratio to guide fluid management in critical illness has not yet been reported.

The inflammation-based Glasgow Prognostic Score, which is derived from CRP and albumin measurements, predicts poor outcomes in many cancers and in ICU patients with cardiovascular conditions[108,109].

## Effects of human albumin solutions for fluid management

HSA solutions have been used worldwide for treating critically ill patients since the 1940s. Intravenous administration of HSA solution increases circulating serum albumin levels in critically ill patients[17,110]. Treatment guidelines for management of critically ill patients recognise a role for HSA in the management of patients with sepsis, albeit mostly with weak recommendations based on moderate or low quality of evidence[42,111–113]. Guidelines from the SSC suggest albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in sepsis patients when substantial amounts of crystalloids are required (weak recommendation, low quality of evidence)[42], and clinical practice parameters from the American College of Critical Care Medicine (ACCM) state that albumin or isotonic crystalloid may be used for fluid resuscitation of pediatric or neonatal patients with septic shock (strong recommendation, based on cohort and case-control sudies)[111].

As well as the important differences in the therapeutic effects of HSA solutions between discrete clinical settings, it should be noted that commercially available HSA products vary in composition based on manufacturer and country. The therapeutic and functional properties of HSA products can be affected by purification and manufacturing processes and so the commercially available products from manufacturers in different countries may not be interchangeable with each other or with endogenous albumin[114].

### Hyperoncotic or isooncotic human albumin solutions for fluid therapy

Use of HSA solution has been debated but large multicenter RCTs have generated valuable data regarding its safety and have helped to define the patient groups most likely to benefit[115]. Equally, it should be acknowledged that some RCTs involved relatively small numbers of patients and some larger studies retrospectively analyzed outcomes. Clinical studies with HSA described in the following section are summarized in Supplementary Table S1, which covers the design, patient population (including hypoalbuminemia where documented), and outcomes.

### Critical illness

The SAFE trial studied the effects of 4% HSA or saline in critically ill patients. Mortality at 28 days and hospital outcomes were similar for both treatments[17]. At baseline, patients in both groups had hypoalbuminemia, but a subsequent analysis found that outcomes were similar in patients with serum albumin $\leq$2.5 or $>$2.5 g/dL[116]. A small pilot study of 20% HSA in critically ill patients with hypoalbuminemia reported an improvement in organ function and a less positive fluid balance compared with a control group receiving Ringer's lactate for fluid therapy[117]. In ICU patients, resuscitation with 20% HSA solution decreased the volume of resuscitation fluid required and the cumulative fluid balance at 48 h after admission, and there was no evidence of harm compared with 4–5% HSA solution in patients with serum albumin 3.0 g/dL at baseline[118]. In a retrospective study of hemodynamic and biochemical responses in critically ill patients, fluid bolus therapy with 100 mL of 20% HSA solution was equivalent to 500 mL of 4% HSA solution, and delivered much less fluid, sodium, and chloride[119].

### Sepsis or septic shock

Evidence for HSA therapy in patients with sepsis includes three large-scale clinical trials – the Albumin Italian Outcome Sepsis (ALBIOS) study[120] and the Early Albumin Resuscitation during Septic Shock (EARSS) study[121], which both used 20% HSA and involved patients with hypoalbuminemia at baseline, and a pre-specified sub-set analysis from the SAFE study[122]. The effect of HSA on mortality did not achieve statistical significance in primary analyses of the individual trials. In ALBIOS, a *post hoc* analysis of the subgroup of patients with septic shock showed significantly reduced mortality at day 90 with albumin vs crystalloids (43.6% vs 49.9%). In SAFE, multivariate analysis to adjust for baseline characteristics (in patients with complete data, $n = 919$) gave an adjusted odds ratio for death for albumin versus saline of 0.71 (95% confidence interval 0.52–0.97; $p = .03$). Although there were differences in design and endpoints for these three studies, an exploratory meta-analysis suggested that the pooled relative risk of mortality was significantly lower across the three trials (0.92, 95% confidence interval: 0.84–1.00; $p = .046$) in patients with severe sepsis who received HSA[123].

### Infectious diseases and febrile illness

Observational data showed that children with severe dengue virus infection who received 20% HSA solution had better lactate clearance and shorter durations of mechanical ventilation, ICU stay and hospital stay than children treated with 5% HSA solution[124]. Improved lactate clearance, a viable surrogate marker of resuscitation adequacy[125,126], also suggests that 20% HSA solution is superior to 5% HSA solution in fluid therapy of severe dengue infection[124]. The FEAST trial evaluated the role of fluid bolus therapy in the resuscitation of children in Africa with shock and life-threatening infections with severe febrile illness and impaired perfusion (mostly malaria), and reported higher 48-h mortality in those who received boluses of either saline or 5% albumin, as compared with a no bolus control group who received maintenance fluids[127]. A recent reanalysis of the FEAST trial found that worsening hyperchloremic acidosis, due to the chloride content of the saline or 5% albumin boluses, was a major contributor to the increased mortality risk[128]. This raises the possibility that lower-volume fluid therapy with buffered solution or higher-percentage HSA solution might help to minimize mortality in this setting, although this requires further study[128,129].

### Cardiac surgery

In cardiac surgery incorporating extracorporeal circulation, crystalloid priming is associated with a transient increase in serum lactate levels and a greater need for volume substitution with crystalloid fluid during surgery, as compared with 5% HSA solution priming[130]. However, in an observational study of children after cardiac surgery, using 5% HSA solution for resuscitation, as opposed to crystalloids, was not associated with lower fluid intake[131]. In an open-label, single-center study involving post-cardiac surgery patients, resuscitation with small volumes of 20% HSA solution provided equivalent optimization of cardiac output and correction of hypotension, but with less fluid accumulation, as compared with crystalloid therapy alone[132]. Patients treated with 20% HSA solution also received fewer vasopressors and had shorter ICU stays. The investigators did not see an increase in adverse events with 20% HSA solution; there was no difference in renal dysfunction between the groups[132].

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) provides blood flow and perfusion pressure for patients in cardiogenic shock or undergoing extracorporeal cardiopulmonary resuscitation[133,134]. In a recent single-center retrospective study, low preimplantation serum levels of albumin were strongly associated with mortality[134]. A separate retrospective study compared fluid resuscitation with HSA solution versus crystalloid in patients on VA-ECMO, and found that those who received both HSA solution and balanced crystalloids (on a 1:2 volume basis; 10 g HSA solution per liter of fluid therapy) showed greater hospital survival than those treated solely with balanced crystalloids[133].

### Negative fluid balance and fluid removal

Clinical examination, bedside tools, and radiological findings are used to evaluate fluid status, detect fluid overload, and prompt fluid removal in critically ill patients; the most popular strategy for ongoing management is fluid balance. RRT is used before more diuretic therapy in oligo-anuric patients, or if the response to diuretic therapy is inadequate[135]. Furosemide is easily the most common diuretic used in the ICU[136].

Edema is common in patients with nephrotic syndrome thought to be related to hypoalbuminemia due to renal albumin loss, and HSA solution has been used to treat diuretic-resistant edema in this setting. A recent Cochrane review included a RCT with 26 patients that compared HSA solution plus furosemide versus placebo[137]. The investigators observed increased initial weight loss in the HSA solution group, but it remains unclear whether HSA solution is effective in patients with nephrotic syndrome as the study was deemed to be at high risk of performance bias and selective reporting.

Martin *et al* showed improved fluid balance, oxygenation, and hemodynamics in 37 patients with ALI/ARDS and hypoalbuminemia (serum albumin 1.8 g/dL) treated with HSA solution and furosemide[138]. In a later study, the same group randomly assigned 40 mechanically ventilated patients with ALI/ARDS and serum total protein levels $<6.0$ g/dL (serum albumin $\sim 1.7$ g/dL) to receive furosemide with either HSA solution or placebo over 72 h, titrated according to fluid loss and to normalize serum total protein[139]. Addition of HSA solution to furosemide therapy significantly increased oxygenation, serum total protein, and net fluid loss. Fluid bolus administration was greater in the furosemide plus placebo group, as these patients developed hypotension more frequently and had fewer shock-free days, consistent with differences in organ failure by the end of the study, although the study was not sufficiently powered for clinical endpoints[139].

Combining high positive end-expiratory pressure, hyperoncotic HSA solution for small volume resuscitation, and furosemide or ultrafiltration for fluid removal has been tested in ALI patients with hypoalbuminemia at baseline by Cordemans et al.[59]. Compared with matched controls, patients who received this combined "PAL-treatment" approach exhibited reductions in cumulative fluid balance, extravascular lung water index, and intraabdominal pressure. Clinical outcomes were also improved, such as fewer days in the ICU and on mechanical ventilation and lower 28-day mortality, without compromising organ function.

In ICU patients with hypoalbuminemia, the diuretic effect is similar when 60 mg furosemide is mixed with either HSA solution or fresh frozen plasma in patients with creatinine clearance (CCr) >20 mL/min; however, when CCr ≤20 mL/min, the diuretic effect is superior with furosemide plus HSA solution[140]. Oczkowski et al.[141] conducted a pilot RCT to test the feasibility of a larger trial aimed at establishing whether combining diuretics with hyperoncotic HSA solution as opposed to saline improves diuresis and expedites withdrawal of mechanical ventilation in adults with critical illness and hypoalbuminemia. The study design could not demonstrate adequate feasibility, but patients who received HSA solution demonstrated more significant increases in colloid osmotic pressure and serum albumin. The results add to the current understanding that severely low levels of albumin hamper furosemide secretion in the tubular lumen, resulting in diuretic resistance[142,143]. The degree of diuretic resistance may be dependent upon the severity of hypoalbuminemia, which itself may be an essential effect modifier of interactions between HSA solution and furosemide[144]. Further studies are needed to evaluate whether a furosemide stress test could be used to distinguish patients with diuretic resistance[145].

### *Human albumin solution for renal protection*

Oliguria as a trigger for fluid therapy has recently been called into question[36], and using urine output as a hemodynamic target to guide fluid resuscitation may even increase the rate of AKI[146]. AKI is common in patients with critical illness, particularly those with sepsis. Along with hypovolemia, with which it often coexists, sepsis is one of the most frequent causes of AKI in ICUs. Effective fluid therapy is essential to resuscitate and stabilize patients with sepsis-induced hypoperfusion of the kidneys. However, positive fluid balance is associated with AKI risk and negatively predicts recovery of renal function[147]. Some evidence for an increase in adverse renal events for artificial hyperoncotic colloids and hyperoncotic HSA was reported from a prospective cohort study[148], but this had a high risk of bias[149]. Evidence from RCTs at low risk of bias supports the renal safety of hyperoncotic albumin[118,120,121].

AKI occurs in around 30% of cardiac surgery patients and is associated with increased ICU stay, healthcare costs, and mortality[150,151]. A retrospective analysis of a cardiac surgery cohort identified perioperative transfusion of packed red blood cells and postoperative use of furosemide as modifiable risk factors for AKI[152]. Production of free radicals and increased oxidative stress have also been shown to mediate AKI in patients undergoing cardiac surgery[153]. Therefore, the antioxidant properties of albumin[154] make it an attractive option for use in cardiac surgery settings, although no RCTs have shown improved outcomes directly due to the oxygen radical scavenging properties of albumin. Hypoalbuminemia has been associated with AKI and need for RRT in the cardiac surgery population[155–158]. In patients with hypoalbuminemia undergoing off-pump coronary artery bypass graft procedures, preoperative treatment with 20% HSA solution reduced the incidence of postoperative AKI versus treatment with saline alone, but this study does not establish that albumin prevents lipid peroxidation of oxygen free radicals, nor rule out that an increased chloride load with saline alone may have led to hyperchloremic acidosis and decreased renal blood flow[159].

Patients with AKI have reduced response to furosemide, and lack of furosemide responsiveness is predictive of AKI development in children undergoing cardiac surgery[160,161]. In adults, unresponsiveness in a furosemide stress test (urine output below 200 mL in 2 h after treatment with 1 mg/kg intravenous furosemide in furosemide-naive patients or 1.5 mg/kg in patients who had received furosemide within the past 7 days) identifies patients at high risk for AKI progression and subsequent use of RRT[145]. Whether or not hyperoncotic HSA solution ameliorates AKI progression in this scenario awaits further study.

For critically ill patients with fluid overload in whom pharmacological therapy fails or produces an inadequate response, mechanical removal of fluid should be considered as a means to optimize fluid balance, though further work is needed to better understand its appropriate clinical application[162].

## Conclusions

Hypovolemia in critically ill patients is difficult to assess and contributes to poor outcomes, while management in clinical practice is hampered by low quality of evidence, with real risks of treatment-related harm. Topics of onging research and debate include triggers and targets for volume resuscitation, as well as the volumes and types of fluid to administer. Hypovolemia is a readily reversible causative factor in the developent of shock and a liberal approach to volume resuscitation is typical, with intravenous fluid boluses constituting initial therapy in various hemodynamic scenarios. However, positive cumulative fluid balance is also common in patients with critical illness and is consistently associated with worse outcomes, particularly in sepsis, ARDS, and AKI. Correctly identifying the critically ill patient with fluid overload who requires an individualized approach to fluid management is a key factor in enabling the clinician to make good decisions at the bedside. Evidence and biological rationale supports the use of HSA solution in septic shock when considering colloid therapy. Observed benefits of small volume resuscitation with hyperoncotic HSA solution come mainly from studies at risk of bias, and should be confirmed in a high-quality RCT.

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