

## Expert consensus on the use of human serum albumin in critically ill patients

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### Introduction

Human serum albumin (HSA) is a non-glycosylated, negatively charged, single-chain polypeptide composed of 585 amino acid residues with a relative molecular mass of 66.438 kD. It is synthesized by the liver at a rate of approximately 200 mg·kg<sup>-1</sup>·day<sup>-1</sup>, with a half-life of 21 days, and subjected to catabolism in the muscles, liver, and kidneys at a rate of 4% per day.<sup>[1]</sup>

Albumin, accounting for 60% of the total plasma protein, has various physiological functions,<sup>[2]</sup> such as maintaining 70% to 80% of effective plasma colloid osmotic pressure, coordinating vascular endothelial integrity, anti-oxidant and anti-inflammatory activities, maintaining the acid-base balance, and participating in the transport, distribution, and metabolism of a variety of endogenous and exogenous substances.

The normal concentration of plasma albumin is 35 to 50 g/L. In clinical practice, hypoalbuminemia often occurs because of reduced albumin synthesis due to liver dysfunction, redistribution of serum albumin due to capillary leakage, or increased loss via the intestinal and renal routes. Hypoalbuminemia (defined as a serum albumin concentration less than 35 g/L) reportedly has an incidence of 24% to 87% in critically ill patients,<sup>[3]</sup> while severe hypoalbuminemia (a serum albumin concentration less than 25 g/L) has an incidence of 5.0–9.6%.<sup>[4]</sup> Hypoalbuminemia is an independent risk factor for increased short- and long-term mortality and an increased incidence of acute kidney injury (AKI) in patients with acute conditions such as trauma, cardiogenic shock, and sepsis.<sup>[5]</sup> A meta-analysis showed that for every 10 g/L decrease in the serum albumin concentration in critically ill

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patients, there was a 137% increase in in-hospital mortality, an 89% increase in the incidence of comorbidities, and a 72% increase in the length of hospital stay.<sup>[6]</sup> Hypoalbuminemia can also alter the pharmacokinetics of antibiotics, leading to either insufficient or excessively high blood concentrations, thereby resulting in treatment failure or excessive toxicity.<sup>[7]</sup>

HSA is mainly used for fluid resuscitation and the treatment of hypoproteinemia in critically ill patients.<sup>[2]</sup> Existing studies have shown controversial results regarding whether the use of albumin in critically ill patients improves their clinical prognosis.<sup>[8]</sup> Albumin consumption varies greatly among countries,<sup>[9]</sup> and its inappropriate use is frequently seen, with 40% to 90% of reported HSA applications failing to follow clinical guidelines.<sup>[10]</sup> A tertiary hospital in China reported that hypoproteinemia was the most common indication for the use of HSA (35.6%); however, it was also used in 11.8% of patients with serum albumin concentrations more than 40 g/L. The reason for its use was not documented in 22% of cases.<sup>[11]</sup> In clinical practice, guidelines and consensus are lacking regarding the selection of HSA concentration, the timing of administration, dosage, and target concentration. Inappropriate use of HSA will cause adverse effects and increase medical costs inevitably, whereas guidance from clinical pharmacists or hospital standards can help reduce inappropriate HSA use by 30% and decrease medical costs without affecting patient prognosis.<sup>[12]</sup> To further strengthen the standardized application of HSA in critically ill patients and achieve optimal clinical outcomes, the Chinese Society of Critical Care Medicine convened a panel of relevant experts who reviewed and summarized data on the clinical use of HSA, outlined 11 relevant clinical problems, and formulated the “Expert Consensus on the Use of Human Serum Albumin in Critically Ill Patients” using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

**Application Scope of the Consensus**

This consensus is mainly intended to propose recommendations relevant to critically ill patients through establishment of clinical problems, literature search, and comprehensive analysis with respect to 11 aspects: sepsis and septic shock, hemorrhagic shock, cardiac surgery, abdominal surgery, acute brain injury, trauma, burns, acute respiratory distress syndrome, liver disease, extracorporeal circulation, and adverse effects of HSA infusion. This consensus mainly serves as a reference for clinicians and clinical pharmacists on HSA use.

**Development Process of the Consensus**

The writing group, which was established in December 2019, for the “Expert Consensus on the Use of Human Serum Albumin in Critically Ill Patients” consisted of 18 experts in critical care medicine and two experts in evidence-based medicine, and held working meetings on a regular basis to discuss relevant issues. After discussion, the experts agreed that HSA has been widely used for fluid resuscitation and albumin supplementation in critically ill

patients, but controversy persists regarding the applicable population, timing, and administration regimen. Therefore, considering the current practices in clinical diagnosis and treatment as well as existing reports, the writing group believed that it was both necessary and possible to develop an expert consensus and provide recommendations to promote the appropriate and standardized use of HSA in critical care medicine.

The expert group first defined the clinical questions to be addressed and then experts were designated to specific questions after the first meeting. All clinical questions were developed using the Population, Intervention, Comparison, and Outcome (PICO) format, which is beneficial for developing inclusion and exclusion criteria for retrieved literature and identifying relevant studies for inclusion. The evidence was divided into high- and low-level evidence. Expert opinions provided tentative answers to certain clinical questions owing to insufficient literature in this regard.

The writing group identified 11 sections to be included in the consensus based on work experience as well as panel discussion and communication. A working group of 18 experts in critical care medicine was formed, with two experts forming a team in charge of the literature search and review and opinion collection for a specific topic as well as the preparation of the first draft of the relevant consensus items. In addition, one expert from each topic team was responsible for ensuring academic rigor and clinical relevance of the topic as well as consistency with other topics.

Members of the expert group searched the PubMed and Cochrane Library databases for reports published in English or with English abstracts and focused on recent meta-analyses and randomized controlled trials (RCTs) when further screening the search results. After five rounds of discussion in writing group meetings, 25 basic items were identified. The recommendations were assessed and graded using the GRADE methodology in terms of theoretical and scientific validity [Table 1]. This evaluation process was repeated twice to generate a relatively complete list of consensus items. Subsequently, the writing group performed a new literature search and included the latest references in a draft according to the meeting summary, completed the first draft of the consensus by the end of April 2021, and completed the final draft at the beginning of May 2021. The final draft was approved through two rounds of voting, with high levels of consistency achieved for each recommendation.

**Table 1: Expert consensus on the use of human serum albumin in critically ill patients: Recommendation grades.**

Grade	Recommendation	Evidence level
Grade 1+	Strongly recommended	High-level evidence
Grade 2+	Weakly recommended	Low-level evidence
Expert opinion	Expert advice	Insufficient evidence
Grade 2–	Weakly not recommended	Low-level evidence
Grade 1–	Strongly not recommended	High-level evidence

## Recommendations for the Use of HSA in the Treatment of Sepsis and Septic Shock

Fluid management is a key component in the hemodynamic resuscitation of patients with sepsis and septic shock, with timely and effective restoration of plasma volume enabling the correction of tissue hypoxia and maintenance of organ function. The 2016 Surviving Sepsis Campaign (SSC) guidelines clearly recommend crystalloids as the major initial resuscitation fluid and albumin as a supplemental resuscitation fluid. However, there are no clear recommendations regarding the applicable population, timing of initiating administration, optimal concentration, or indications for the discontinuation of albumin for fluid resuscitation in patients with sepsis. In this context, this consensus addressed the above issues and proposed recommendations accordingly.

**Recommendation 1: HSA solution is safe as a resuscitation fluid for patients with sepsis (Grade 2+, weak recommendation), and its use in fluid resuscitation in patients with septic shock may reduce mortality (Grade 2+, weak recommendation).**

HSA solution is a commonly used resuscitation fluid in clinical practice, but its role in fluid resuscitation in patients with sepsis remains inconclusive. To date, several RCTs have evaluated the role of HSA solution in fluid resuscitation in patients with sepsis. The Saline versus Albumin Fluid Evaluation (SAFE) study published in 2004 included 6,997 intensive care unit (ICU) patients who were randomized to receive 4% HSA solution or saline for fluid resuscitation and reported similar clinical outcomes for the two groups.<sup>[8]</sup> A subgroup analysis of patients with severe sepsis revealed a decreasing trend of mortality among patients receiving HSA treatment (risk ratio [RR]: 0.87, 95% confidence interval [CI]: 0.74–1.02).<sup>[8,13]</sup> The SAFE study showed that the safety of HSA solution is comparable to that of saline for resuscitation, and HSA use may improve the prognosis of patients with severe sepsis. In the subsequent Albumin Italian Outcome Sepsis (ALBIOS) trial, 1818 patients with sepsis were divided into a group treated with crystalloids alone and a group treated with both crystalloids and 20% HSA solution. The mortalities of the two groups were similar. However, a subgroup analysis of patients with septic shock showed a decrease in mortality among patients treated with HSA solution (RR: 0.87, 95% CI: 0.77–0.99).<sup>[14]</sup> Two large RCTs, namely the Early Albumin Resuscitation during Septic Shock (EARSS) study<sup>[15]</sup> and the Lactated Ringer Versus Albumin in Early Sepsis Therapy (RASP) study,<sup>[16]</sup> evaluated resuscitation effect with HSA solution in patients with septic shock and showed no difference in mortality. Three systematic reviews compared the effect of HSA solution versus crystalloids for fluid resuscitation in patients with sepsis and reported that HSA resuscitation was not superior to crystalloid resuscitation in patients with sepsis but led to lower mortality among patients with severe sepsis and septic shock.<sup>[17–19]</sup> In summary, the existing studies suggest that the safety of HSA solution is comparable to that of crystalloids for resuscitation in patients with sepsis, and its use may reduce the mortality rates of patients with septic shock.

**Recommendation 2: If hemodynamic instability persists in patients with septic shock after 30 mL/kg crystalloid resuscitation, initiation of HSA infusion should be considered (expert opinion).**

No RCT has evaluated the optimal timing of HSA infusion during fluid resuscitation in patients with sepsis. A 30 mL/kg dose of crystalloids is recommended for initial fluid resuscitation by both the 3-h sepsis bundle, based on the 2016 SSC guidelines, and the subsequently updated Hour-1 bundle.<sup>[20,21]</sup> Additionally, the 2016 SSC guidelines recommend additional supplementation with HSA when large amounts of crystalloids are needed for patients with septic shock.<sup>[20]</sup> An estimated 70% to 80% of human plasma colloid osmotic pressure is maintained by albumin, and each gram of albumin retains 18 mL of circulating water, with 10 g of infused albumin expanding the intravascular volume by nearly 200 mL.<sup>[22]</sup> In the SAFE and ALBIOS studies, albumin infusion was performed within 28 days of randomization.<sup>[8,14]</sup> In the EARSS study, HSA infusion was performed within 3 days of randomization.<sup>[15]</sup> Only the RASP study required that HSA infusion be performed within 6 h of randomization. However, in cancer patients with septic shock, resuscitation using HSA solution (*vs.* crystalloids) during the first 6 h did not improve outcomes.<sup>[16]</sup> It should be noted that the patients with septic shock included in the RASP study were cancer patients, which limited the generalizability of those results. There is currently no direct supportive evidence for clinical decision-making regarding the timing of HSA administration during resuscitation in patients with sepsis. Considering the 2016 SSC guidelines and clinical practice, the expert group recommends that albumin should be administered to septic shock patients who remain hemodynamic unstable after resuscitation with 30 mL/kg crystalloids and that hemodynamic instability be defined as follows: (1) failure to maintain a mean arterial pressure (MAP) of 65 mmHg or higher despite the intravenous injection of norepinephrine at a rate of  $0.4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  or more; (2) frequent fluctuations in MAP at around 65 mmHg; and (3) a comorbidity involving obvious capillary leakage. Caution should be addressed in supplementing albumin when the patient has a comorbidity involving impaired myocardial function or cardiogenic shock.

**Recommendation 3: Both low- (4% or 5%) and high-concentration (20% or 25%) HSA solutions can be used for fluid resuscitation in patients with sepsis (expert opinion).**

There have not been any RCTs comparing the efficacy and safety of different concentrations of HSA solutions for fluid resuscitation in patients with sepsis. However, in published large-scale RCTs, low- (4% or 5%) and high-concentration (20% or 25%) HSA solutions have been used as resuscitation fluids, and no serious adverse events have been reported,<sup>[8–16]</sup> confirming that low- and high-concentration HSA solutions are safe in patients with sepsis. Different concentrations of HSA were used in different trials: 4% albumin was used in the SAFE and RASP trials, and 20% albumin was used in the ALBIOS trial. However, these large trials did not perform comparisons between different HSA concentrations. A

recent meta-analysis of 26,351 patients included in 58 clinical trials indicated that there was no significant difference in the fatality rate or amount of resuscitation fluid between patients with sepsis who were administered low- and high-concentration HSA solutions.<sup>[23]</sup> Based on the results of these trials, the expert recommendation is that both low- and high-concentration HSA solutions can be used for fluid resuscitation in patients with sepsis.

**Recommendation 4: HSA infusion can be discontinued in patients with sepsis when serum albumin levels reach 30 g/L or more and hemodynamics are stable (Grade 2+, weak recommendation).**

In a comprehensive meta-analysis of 291,433 critically ill patients from 90 cohort studies, hypoalbuminemia was evaluated as an outcome predictor using multivariate analysis. The results showed that for every 10 g/L decrease in the serum albumin concentration, the length of hospital stay, incidence of comorbidities, and mortality rate increased by 71%, 89%, and 137%, respectively.<sup>[6]</sup> A meta-analysis of nine prospective controlled trials on correcting hypoalbuminemia in critically ill patients showed that the incidence of complications was significantly reduced in patients with serum albumin concentrations of more than 30 g/L after albumin supplementation.<sup>[6]</sup> A prospective observational cohort study of 5894 critically ill adults also showed that hypoalbuminemia at admission was an independent predictor of 30-day all-cause mortality.<sup>[24]</sup> A recent observational study of 136 patients with sepsis showed that albumin levels were associated with short-term mortality risk in patients with sepsis.<sup>[25]</sup> In the ALBIOS trial, the 90-day mortality was significantly elevated in patients with severe sepsis with a serum albumin level of less than 30 g/L at the time of enrollment.<sup>[26]</sup>

**Recommendation 5: When using antibiotics with a high protein binding rate in patients with sepsis, HSA supplementation is recommended for improving drug pharmacokinetics and pharmacodynamics (Grade 2+, weak recommendation).**

Some antibiotics used in patients with sepsis bind to proteins in the blood, including albumin,  $\alpha$ -1-acid glycoprotein, and lipoproteins, with albumin accounting for 60% of all plasma proteins. Some antibiotics such as ceftriaxone sodium, ertapenem, and daptomycin have high protein binding rates of 90%, 90%, and 92%, respectively. Hypoalbuminemia affects the apparent volume of distribution (Vd) and clearance rate (CL) of these drugs.<sup>[27]</sup> The binding rate of ertapenem to albumin is 85% to 95%. Hypoalbuminemia patients with ventilator-associated pneumonia have significantly higher Vd ( $0.21 \pm 0.05$  L/kg *vs.*  $0.07 \pm 0.03$  L/kg) and CL ( $43.23 \pm 23.74$  mL/min *vs.*  $20.21 \pm 0.16$  mL/min) of ertapenem than healthy volunteers.<sup>[28]</sup> The protein binding rate of teicoplanin is 90% to 95%. In critically ill patients, the CL of teicoplanin is higher than that in healthy volunteers ( $18.2$  mL/min *vs.*  $13.4$  mL/min).<sup>[29]</sup> The protein binding rate of ceftriaxone sodium is 85% to 95%. Patients with severe sepsis have higher Vd ( $0.32 \pm 0.05$  L/kg *vs.*  $0.12 \pm 0.01$  L/kg) and CL ( $25.8$  mL/min *vs.*  $13.0$  mL/min) of ceftriaxone sodium

than healthy volunteers.<sup>[30]</sup> Therefore, when patients with sepsis are being treated with antibiotics with high protein binding rates, supplementation with human albumin is recommended to improve drug pharmacokinetics and pharmacodynamics.

### Recommendations for the use of HSA in patients with hemorrhagic shock

In patients with hemorrhagic shock, severe hypovolemia and reactive vasoconstriction can lead to end-organ hypoperfusion, resulting in neurological damage, cardiac arrest, and multiple organ failure. Rapid restoration of blood volume is essential for the treatment of hemorrhagic shock. The 2019 European guideline on management of major bleeding and coagulopathy following trauma<sup>[31]</sup> recommends the use of isotonic crystalloid and balanced electrolyte solutions as fluid therapy for hemorrhagic shock. In addition, the guidelines recommend limiting the use of artificial colloids for fluid resuscitation because multiple studies have shown that colloids failed to significantly improve the prognosis of patients with hemorrhagic shock, and artificial colloids may affect coagulation in these patients.<sup>[32]</sup> However, there is no clear recommendation for whether albumin should be used as a natural colloid for fluid resuscitation in patients with hemorrhagic shock.

**Recommendation 6: The use of HSA solution as a routine fluid for initial resuscitation in patients with hemorrhagic shock with uncontrolled bleeding is not recommended (Grade 2-, weak recommendation).**

As a natural colloid, albumin is the body's principal component for maintaining blood volume and colloidal osmotic pressure. In recent years, several animal studies have shown that infusion of colloidal fluid, particularly HSA, in animals with hemorrhagic shock can increase volume effectively, improve microcirculation, and reduce mortality.<sup>[33]</sup> The SAFE trial<sup>[8]</sup> showed that when 4% HSA solution or normal saline was used for fluid resuscitation and the same therapeutic target was achieved, the infusion volume in the normal saline group was 1.4-times higher than that in the albumin group, indicating that albumin has superior efficacy for the maintenance of blood volume. There was no significant difference in mortality between the albumin and normal saline groups, suggesting that HSA does not present an advantage over normal saline with respect to reducing patient mortality. In 2011, a systematic analysis of 38 RCTs including ICU patients conducted by Roberts *et al.*<sup>[34]</sup> revealed that HSA solution did not present an advantage over other resuscitation fluids in reducing the mortality of patients with hemorrhagic shock. Similar results were also observed in the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial conducted in 2013.<sup>[35]</sup>

Several studies on the effect of colloids (including various artificial colloids and albumin) on coagulation have indicated that artificial colloids may inhibit platelet function, decrease von Willebrand Factor (vWF) and factor VIII activity, and induce hypocoagulation and fibrin polymerization. However, albumin was not found to play

significant roles in these phenomena.<sup>[36,37]</sup> This may be a potential advantage of albumin over artificial colloids for fluid resuscitation in patients with hemorrhagic shock, but this advantage has not yet been demonstrated in RCTs.

**Recommendation 7: HSA infusion is recommended for patients with hemorrhagic shock in whom bleeding has been controlled to correct hypovolemia and hypoalbuminemia (Grade 2+, weak recommendation).**

For patients with hemorrhagic shock in whom bleeding has been controlled, the rapid loss of whole blood is controlled, but hypovolemia leads to redistribution of blood, poor tissue perfusion, and insufficient oxygen supply to cells. In addition, increased capillary permeability caused by inflammation and bleeding persists for a certain period. Timely restoration of plasma volume can improve tissue hypoxia and facilitate the maintenance of organ function. In a model of increased capillary permeability due to sepsis, the expanding effect of 5% HSA was three times higher than that of a crystalloid solution.<sup>[38]</sup> Therefore, colloid fluid resuscitation in shock patients reduces the total infusion volume,<sup>[39]</sup> capillary leakage and tissue edema. In addition, HSA has anti-oxidant effects and maintains the integrity of the vascular wall, which reduces damage to the endothelial glycocalyx during hemorrhagic shock and facilitates endothelial repair.<sup>[40]</sup> Another study showed that HSA has a protective effect on the kidneys in critically ill patients.<sup>[41]</sup> Therefore, HSA infusion is recommended for patients with hemorrhagic shock in whom bleeding has been controlled to correct hypovolemia and hypoalbuminemia.

### Recommendations for the Use of HSA in Cardiac Surgery Patients

Owing to blood cell destruction, blood dilution, massive release of inflammatory mediators, increased capillary permeability, and ischemia-reperfusion injury caused by cardiopulmonary bypass, it is very common for patients to show hemodynamic instability and hypoproteinemia during perioperative period of cardiac surgery.<sup>[42]</sup> Effective fluid management is essential to such patients.

**Recommendation 8: HSA is recommended for fluid resuscitation in patients with perioperative shock during cardiac surgery (Grade 2+, weak recommendation).**

HSA is commonly used as a therapeutic agent for patients with low serum albumin levels, unstable hemodynamics, and fluid resuscitation requirements.<sup>[43]</sup> In a randomized, double-blind, single-center study of 240 patients undergoing elective cardiac surgery, HSA, hydroxyethyl starch (HES), or Ringer's lactate was infused at a maximum of 50 mL·kg<sup>-1</sup>·day<sup>-1</sup> during the perioperative period. The results showed that the total perioperative fluid volume in the HSA group was lower than that in the HES and Ringer's lactate groups.<sup>[44]</sup> In a meta-analysis of 970 patients from 18 clinical trials, compared to albumin group, HES group increased postoperative blood loss by 33.3%, red blood cell transfusion by 28.4%, fresh frozen plasma transfusion by 30.6%, and platelet transfusion by 29.8%.<sup>[45]</sup>

In a large observational study, 6188 adult patients from the Cerner Health Facts<sup>®</sup> database undergoing cardiopulmonary bypass surgery for heart valve and/or coronary artery disease were included. Propensity score matching was performed for 1095 patients who received 5% HSA and crystalloid solutions and 1095 patients who received a crystalloid solution alone on the day of or the day after cardiac surgery. The results suggested that compared to using crystalloid solution alone, using 5% HSA in combination with crystalloid solution reduced the in-hospital mortality and 30-day all-cause readmission rate.<sup>[46]</sup>

Hypoproteinemia is associated with a poor prognosis in cardiac surgery and can lead to increased extravascular lung water and complications such as renal insufficiency.<sup>[47]</sup> A prospective single-center, randomized, double-blind trial involving 220 patients undergoing off-pump cardiac surgery with preoperative serum albumin levels of less than 40 g/L showed that the preoperative transfusion of 20% HSA in patients with serum albumin levels of less than 40 g/L increased intraoperative urine output. The incidence of AKI in the albumin group was lower than that in the control group, and the risk of AKI was reduced by 47%, but there was no significant difference in the incidence of severe AKI between the groups.<sup>[48]</sup> A similar recommendation was made in the 20th International Consensus Conference of the Acute Disease Quality Initiative (limited evidence) in 2017.<sup>[49]</sup> Based on these clinical evidences, we believe that the use of HSA during the perioperative period of cardiac surgery can better promote intravascular volume expansion, thereby reducing the overall need for fluid resuscitation. In patients with hypoalbuminemia (protein levels of less than 40 g/L) undergoing off-pump cardiac surgery, the use of 20% HSA has some protective effects on the kidneys.

### Recommendations for the Use of HSA in Critically Ill Patients Undergoing Abdominal Surgery

Patients undergoing abdominal surgery are often in a hypermetabolic state, with decreased anabolism and sustained negative nitrogen balance. In addition, surgical trauma leads to a systemic inflammatory response with the release of inflammatory mediators and cytokines. Thus, it can increase vascular permeability and capillary leakage while the plasma albumin concentration is decreased. Therefore, hypoproteinemia is often seen in critically ill patients after abdominal surgery.

**Recommendation 9: Close monitoring of albumin levels in critically ill patients during the perioperative period of abdominal surgery is recommended to prevent hypoalbuminemia, for reducing the risk of gastrointestinal fistula and infection in the surgical area, and improving prognosis (Grade 2+, weak recommendation).**

In 2017, a European prospective study including 138 patients undergoing major abdominal surgery showed that a decrease of 10 g/L or more in the serum albumin concentration on the first postoperative day was associated

with a three-fold increase in the risk of overall postoperative complications. Thus, this finding can be used to identify patients at high risk of developing postoperative complications.<sup>[50]</sup>

Low perioperative albumin levels in critically ill patients undergoing abdominal surgery are associated with postoperative pancreatic fistula after pancreatic surgery. A retrospective study involving 247 patients undergoing pancreaticoduodenectomy noted that the postoperative serum albumin level (odds ratio [OR]: 2.819) was an independent risk factor for pancreatic fistula after the operation.<sup>[51]</sup>

Management of preoperative albumin levels can reduce the occurrence of infection. A total of 268 patients in a retrospective study were divided into the intra-abdominal infection (IAI) group (38 cases) and non-IAI group (230 cases). The preoperative serum albumin level was found to be an independent risk factor predicting IAI after hepatectomy (OR: 0.91, 95% CI: 0.83–0.99).<sup>[52]</sup> Postoperative monitoring of albumin levels also helps to predict postoperative infections. A prospective study including 105 patients who underwent laparoscopic colorectal cancer resection between August 2014 and September 2016 found that regular monitoring of albumin levels in the early postoperative period may be beneficial for detecting postoperative infection-related complications.<sup>[53]</sup>

Critically ill patients undergoing major abdominal surgery were divided into a successful weaning group and a weaning failure group. Multivariate logistic regression analysis indicated that low postoperative serum albumin level was a risk factor for weaning failure in critically ill patients undergoing major abdominal surgery (OR: 0.812, 95% CI: 0.664–0.993).<sup>[54]</sup> A meta-analysis of 90 cohort studies showed that the mortality increased by 137% for every 10 g/L decreases in the serum albumin level (OR: 1.89, 95% CI: 1.51–2.36).<sup>[6]</sup> In a retrospective study of 362 critically ill patients undergoing emergency gastrointestinal surgery who were admitted to the ICU between January 2007 and December 2011, patients were divided into the survival and non-survival groups. Multivariate logistic regression analysis found that preoperative hypoalbuminemia was an independent risk factor for in-hospital mortality after emergency gastrointestinal surgery (OR: 9.954, 95% CI: 1.603–61.811). Dynamic monitoring of perioperative protein levels aids in risk stratification and the provision of optimal perioperative care.<sup>[55]</sup>

**Recommendation 10: HSA is recommended for fluid resuscitation in critically ill patients with hypoalbuminemia during the perioperative period of abdominal surgery (Grade 2+, weak recommendation).**

One hundred ICU patients undergoing abdominal surgery were divided into albumin treatment group and control group based on whether they received albumin infusion at serum albumin concentrations  $\leq 30$  g/L. Albumin infusion was found to improve organ function in critically ill patients with hypoalbuminemia compared to the control group.<sup>[56]</sup> A prospective study included patients with cirrhosis awaiting liver transplantation from 2012 to

2016, in which 82 patients who developed acute kidney injury-hepatorenal syndrome (AKI-HRS) prior to liver transplantation and received terlipressin and albumin during the study period were treated according to whether they responded to terlipressin and albumin therapy (a response was defined as a decrease of 26.5  $\mu\text{mol/L}$  in serum creatinine concentration from the basal value) and were divided into a response group (43 patients) and a non-response group (39 patients), and finally 30 patients in each of the two groups underwent renal transplantation after treatment. An additional 259 patients without AKI-HRS who underwent liver transplantation during the study period were used as a control group to assess transplantation outcomes. The frequency of renal replacement therapy in the non-response group was found to be higher than that in the response group, and the incidence of chronic kidney disease at 1 year after liver transplantation was significantly higher in the non-response group than that in the response group. Multivariate analysis indicated that non-response to terlipressin and albumin was an independent predictor of chronic renal insufficiency at 1 year after transplantation (sub-distribution hazard ratio [SHR]: 2.76), whereas the risk did not increase in responders (SHR: 1.53). Thus, response to terlipressin and albumin in patients with AKI-HRS reduces the need for renal replacement therapy after liver transplantation and reduces the risk of chronic renal failure within 1 year postoperatively.<sup>[57]</sup> In one randomized controlled study, 67 patients with end-stage liver disease who underwent *in situ* liver transplantation were randomized into two groups, with the restricted fluid resuscitation group given albumin, frozen plasma and concentrated red blood cells, and the unrestricted fluid resuscitation group given 10 mL·kg<sup>-1</sup>·h<sup>-1</sup> of saline, and compared with the unrestricted fluid resuscitation group, fluid resuscitation with human albumin in the perioperative period of liver transplantation was found to stabilize hemodynamics, reducing the risk of postoperative pulmonary insufficiency.<sup>[58]</sup>

**Recommendation 11: HSA supplement is recommended for critically ill patients undergoing abdominal surgery when the perioperative serum albumin level is  $< 30$  g/L, and perioperative albumin levels should be maintained above 30 g/L (Grade 2+, weak recommendation).**

A retrospective study of living donor liver transplantation at a large hospital between May 2008 and August 2012 enrolled 998 patients and divided them into  $< 30$  g/L group (522 patients) and  $\geq 30$  g/L group (476 patients) based on the lowest albumin level on post-operative day 2. Patients in the albumin  $< 30$  g/L group were found to have significantly longer lengths of ICU stay than patients in the albumin  $\geq 30$  g/L group.<sup>[59]</sup> Albumin infusion can be initiated intraoperatively for patients undergoing abdominal surgery, especially in critically ill and hypoproteinemic patients. A systematic review of 79 randomized trials involving 4755 patients indicated that maintaining protein levels above 30 g/L during the perioperative period is beneficial in reducing perioperative fluid requirements, reducing intraoperative intestinal edema, reducing clinical complications, and protecting organ function.<sup>[60]</sup>

### Recommendations for the Use of HSA in Patients with Acute Brain Injury

Acute brain injury includes stroke, traumatic brain injury (TBI), central nervous system infection, and metabolic encephalopathy, which are characterized by high rates of mortality and disability.<sup>[61]</sup> Fluid therapy is the basic treatment protocol for acute brain injury, including volume resuscitation and maintenance, controlling intracranial pressure (ICP), preventing delayed cerebral ischemia, and even acting as a factor of neuroprotection. HSA has been used for a long time in the treatment of patients with craniocerebral injury. In 1994, Asgeirsson *et al* proposed the “Lund concept” that maintaining normal colloid osmotic pressure by infusion of HSA and correction of anemia could reduce secondary brain injury.<sup>[62,63]</sup> This has greatly promoted the clinical use of HSA, but whether human albumin can improve the prognosis of craniocerebral injury is still controversial.

**Recommendation 12:** *HSA is not recommended as the first choice for fluid resuscitation in patients with acute brain injury (Grade 2-, weak recommendation).*

Several national guidelines and expert consensus preferentially recommend the use of crystalloids for fluid resuscitation. However, it is not appropriate to extrapolate the results of clinical trials on fluid resuscitation in critically ill patients with acute brain injury, because the proportion of patients with acute brain injury in such studies is relatively low. One subgroup analysis of the SAFE trial showed a higher morbidity and mortality rate (33.2%, 20.4%) with low-dose 4% albumin ( $n = 214$ ) compared to saline ( $n = 206$ ) after TBI.<sup>[8]</sup> Furthermore, the ALIAS study published in 2006 showed that the use of high-dose 25% albumin ( $n = 82$ ) after cerebral infarction was associated with a better prognosis.<sup>[64]</sup> Combined data analysis of the 2016 ALIAS trial found that the use of 25% HSA at a dose of 2 g/kg did not improve 90-day outcomes but was associated with an increased incidence of cerebral hemorrhage and pulmonary edema in stroke patients.<sup>[65]</sup> A single-center retrospective study ( $n = 42$ ) in 2004 and a multicenter propensity score matching study of patients with subarachnoid hemorrhage ( $n = 5400$ ) in 2013 both indicated that the use of high-dose HSA was associated with better neurological outcomes compared to crystalloids.<sup>[66,67]</sup> In contrast, a propensity score matching study ( $n = 123$ ) conducted in 2013 in patients with subarachnoid hemorrhage showed that HSA had no effect on the occurrence of delayed cerebral ischemia/cerebral infarction after subarachnoid hemorrhage but was associated with worse National Institutes of Health Stroke Scale scores at 6 weeks.<sup>[68]</sup> The role of HSA in subarachnoid hemorrhage and ischemic stroke remains controversial, and confirmation through large-scale, multicenter RCTs is needed. Currently, HSA is not recommended as the first choice for fluid resuscitation in patients with acute brain injury.

**Recommendation 13:** *HSA is safe for use in patients with cerebral hemorrhage and may improve neurological prognosis (expert opinion).*

In 1994, Tone *et al*<sup>[69]</sup> reported that using 25% albumin (50–100 mL/day) combined with furosemide (20–40 mg/day) for

2 weeks ( $n = 11$ ) in 22 cases of basal ganglia hemorrhage following hematoma removal operation resulted in less midline shift in CT scans, and fewer patients showed a vegetative state or died compared to the control group ( $n = 11$ ). In 2002, Huang *et al*<sup>[70]</sup> reported 20 patients with cerebral hemorrhage who were rapidly administered 20% HSA (50 mL) or 40 mg furosemide intravenously and received continuous electroencephalography (EEG) monitoring. An increase in  $\alpha$ -wave and a decrease in  $\delta$ -wave in the focal hemisphere were observed in 14 patients treated with albumin, whereas no significant change in EEG was observed after furosemide infusion. A rodent model study published in 2005 confirmed that infusion with 25% albumin (1.25 g/kg body weight) improved neurological prognosis and blood-brain barrier integrity in rats with cerebral hemorrhage.<sup>[71]</sup> We recommend 25% HSA infusion in the early phase of cerebral hemorrhage to improve neurological functional prognosis.

**Recommendation 14:** *The use of HSA alone for reducing ICP in patients with traumatic brain injury is not recommended (expert opinion).*

When HSA is applied in clinical practice, physicians are more concerned about whether it can decrease the ICP. In 2013, Cooper *et al*<sup>[72]</sup> reported a re-analysis of the SAFE study, randomly selecting 321 patients who underwent ICP monitoring. They found there was a significant linear increase in mean ICP and significantly more deaths in the HSA group compared with normal saline group when ICP monitoring was discontinued during the first week. Currently, there are few studies on whether albumin could be used to reduce ICP, and the designs of these studies are not suited to specifically evaluate the effect of HSA on ICP. Clinical studies comparing the conventional hypertonic salt/mannitol group with the hypertonic salt/mannitol combined with HSA group are expected, as this protocol is more clinically relevant and has more research value. Based on the existing evidence, the use of HSA alone to reduce ICP in patients with traumatic brain injury is not recommended.

### Recommendations for the Use of HSA in Trauma Patients

Patients with multiple injuries often experience severe blood loss and fluid loss and require large amounts of fluid replacement. 20% HSA is a hypertonic solution, and 100 mL of 25% HSA solution can expand the blood volume by 400 mL within 25 min. Therefore, hypertonic HSA solutions can be used for small-volume resuscitation and rapid correction of hypovolemia. However, the safety and efficacy of HSA for fluid resuscitation in trauma patients remain controversial.

**Recommendation 15:** *The use of HSA for initial fluid resuscitation in trauma patients is not recommended (Grade 2-, weak recommendation).*

There have been many studies on the use of HSA for fluid resuscitation in trauma patients [Supplementary Digital Content, Table 1, <http://links.lww.com/CM9/A699>]. As early as 1995, the American University Hospital Consortium (UHC) guidelines for the use of HSA, nonprotein

colloids, and crystalloid solutions indicated that nonprotein colloids should be considered for adult patients with hemorrhagic shock in whom the infusion of 4 L crystalloid solution is ineffective after 2 h, and 5% HSA solution should be considered only when nonprotein colloids are contraindicated.<sup>[73]</sup> In the 2004 SAFE study, 6997 critically ill patients, including 1186 trauma patients, were randomly grouped and resuscitated with 4% HSA and saline, respectively, and in a subgroup analysis of trauma patients, no significant difference was found in the 28-day morbidity and mortality between the two groups. Although the HSA group had a higher mortality (RR: 1.36, 95% CI: 0.99–1.86), the mortality of the two groups were similar (RR: 1.00, 95% CI: 0.56–1.79) after patients with traumatic brain injury were excluded.<sup>[8]</sup> In a follow-up study of 460 cases of patients with traumatic brain injury (Saline or Albumin for Fluid Resuscitation in Patients with Traumatic Brain Injury [SAFE-TBI] study), the 2-year mortality rate in the HSA group was significantly higher than that in the normal saline group (RR: 1.63, 95% CI: 1.17–2.26).<sup>[74]</sup> The results of the SAFE study showed that HSA is as safe as normal saline as a resuscitation fluid for trauma patients, but its use may lead to adverse outcomes in patients with traumatic brain injury. The 2012 “Consensus Statement of the European Society of Intensive Care Medicine Task Force on Colloid Volume Therapy in Critically Ill Patients” also did not recommend the use of HSA solution for fluid resuscitation in patients with traumatic brain injury.<sup>[75]</sup> Subsequently, the 2013 CRISTAL study included 2857 critically ill patients, including 177 trauma patients, who were randomly divided into a crystalloid resuscitation group and a colloid resuscitation group. The study found that there was no significant difference in the 28-day mortality between the two groups, but the colloid group had a significantly lower 90-day mortality rate than the crystalloid group.<sup>[35]</sup> It is worth noting that the colloidal resuscitation solutions in the CRISTAL study included HSA, dextran, gelatin, and hydroxyethyl starch, etc. The resuscitation effect of the HSA solution was not clearly stated and still needs to be further investigated.

Trauma patients often suffer from hypoalbuminemia due to massive blood loss, capillary leakage, and hypermetabolism after trauma.<sup>[76]</sup> When the serum albumin level is less than 10 g/L, the mortality could reach up to 70%. The American UHC “Guidelines for the Use of Albumin, Nonprotein Colloid, and Crystalloid Solutions” and the 2018 Scottish “Clinical Guidelines for Human Albumin Use” recommend that HSA can be used in patients with severe hypoalbuminemia with serum albumin levels of below 15 g/L or hemodynamically unstable patients with hypoalbuminemia.<sup>[73,77]</sup> Therefore, whether an exogenous infusion of HSA can improve the prognosis of trauma patients with hypoalbuminemia is an important issue to clinicians.

**Recommendation 16:** *HSA can be used for trauma patients with severe hypoalbuminemia and unstable hemodynamics (Grade 2+, weak recommendation).*

A study based on the data from the 2006 SAFE trial found that critically ill patients in the ICU, including trauma patients, had similar 28-day mortality rates after resusci-

tation using HSA solution or normal saline, regardless of the baseline serum albumin concentration (above or below 25 g/L).<sup>[78]</sup> In a systematic review, a total of 161 trauma and surgery patients were included from five RCTs. The results showed that although HSA could not improve mortality effectively, it could help maintain colloid osmotic pressure more effectively than crystalloid fluids, improving intestinal edema and increasing cardiac output in trauma and surgery patients, which was beneficial for circulatory stability.<sup>[79]</sup> Therefore, the HSA solution can be used for trauma patients with severe hypoalbuminemia and unstable hemodynamics.

### Recommendations for the Use of HSA in Patients with Severe Burns

Burn patients, especially those with moderate or severe burns, require fluid resuscitation during the shock period (24–72 h after injury). There have been controversies both domestically and internationally regarding the types of resuscitation fluids for this period, especially colloids (plasma, HSA, artificial plasma). Clinical staff still cannot reach a consensus on whether colloid resuscitation is needed and what kind of colloid resuscitation is more suitable.

**Recommendation 17:** *The combined resuscitation with crystalloid and colloidal fluids is recommended for patients with severe burns in the shock stage (Grade 2+, weak recommendation). Plasma is the preferred colloidal solution, and 5% human albumin solution is an alternative option in case of insufficient plasma supply (expert opinion).*

In the shock stage among patients with severe burns, capillary permeability increases, and the circulating fluid flows out of the blood vessels, resulting in reduced blood concentration and body fluid loss. Since the lost composition of the circulating intravascular fluid is plasma-like material containing large amounts of electrolytes and proteins (mainly albumin), rehydration resuscitation should be supplemented with both electrolyte solutions and colloidal solutions.<sup>[80]</sup> Although the National Institutes of Health workshop in 1978 did not reach a consensus on a specific formula and fluid type for resuscitation of burn patients, the most commonly used burn resuscitation formula today is sodium lactate Ringer solution (lactated Ringer's, containing sodium 130 milliequivalents per liter [mEq/L]). Although hypotonic compared to plasma, this solution is effective in treating hypovolemia and extracellular sodium deficiency due to thermal injury.<sup>[80]</sup>

The use of colloidal fluids in burn resuscitation remains controversial. The use of large amounts of crystalloid fluids during burn resuscitation reduces the plasma protein concentration, further promoting fluid outflow and the development of edema in blood vessels. Theoretically, the use of colloidal fluids (plasma or HSA) to supplement plasma protein could reduce this effect, as these fluids are more consistent with the lost body fluid. Therefore, the early calculation formula developed by the United States Army Institute of Surgical Research Burn Center included a large quantity of colloidal fluids.<sup>[81]</sup> Some prospective



studies have confirmed that colloidal fluids have little clinical benefit in burn patients (especially when used within 12 h of burn injury) and may even increase the alveolar exudative inflammation.<sup>[82-84]</sup> However, some prospective randomized clinical studies have confirmed that colloid fluid resuscitation strategies using plasma, HSA, and high molecular weight glucose polymers such as dextran and HES can reduce the resuscitation fluid volume, incidence of edema, patient weight gain, peak intra-abdominal pressure, and peak inspiratory pressure and increase the clearance of bases from blood.<sup>[85-89]</sup> In the study of Zdolsek *et al.*,<sup>[90]</sup> fifteen burn patients and 15 healthy volunteers were administered an intravenous infusion of 20% HSA at a dose of 3 mL/kg over 30 min. Blood and urine samples were collected to compare plasma dilution, plasma albumin levels, and colloidal osmotic pressure. The goal was to compare the changes in plasma volume expansion and colloidal osmotic pressure after administering a standard dose of 20% HSA to burn patients and volunteers and to estimate the capillary leakage of albumin and fluid. The results showed that after the two groups were administered a 20% HSA solution, the plasma volume was expanded by almost 15%, which was equivalent to twice the infused volume. Urine output was more than 2.5 times that of infused volume. The rates of capillary albumin leakage in the burn patients and volunteers were  $3.4 \pm 1.5$  g/h and  $3.7 \pm 1.6$  g/h, respectively ( $P=0.61$ ), which corresponded to  $(2.4 \pm 1.0)\%$  and  $(2.5 \pm 1.2)\%$  per hour of the intravascular pool, respectively ( $P=0.85$ ). The median half-lives of plasma volume expansion in the two groups were 5.9 and 6.9 h, respectively ( $P=0.56$ ). Furthermore, 20% HSA was an effective volume expander at 1 week post-burn injury, and there was no difference between burn patients and healthy volunteers.<sup>[90]</sup> In China, most hospitals use crystalloid solutions combined with plasma and/or HSA after 8 to 12 h of crystalloid resuscitation in patients with severe burns. However, RCT data on infusion in burn patients are lacking, and the studies cited above-involved limitations such as small sample sizes and small burn areas. The colloid resuscitation strategy used in clinical practice of using plasma initially is based on theoretical research and practical experience, but there is no rigorous corroborating evidence to confirm that plasma resuscitation is superior to albumin resuscitation.

Since there is no interstitial edema in the early stage of burns, infusion of high-concentration HSA can help maintain blood volume. However, it can cause dehydration and damage cells. Moreover, 5% HSA is isotonic with plasma, and this allows the infusion rate to be increased. Therefore, infusion of 5% HSA is recommended in the first 24 h of burn injury, but the infusion of high-concentration HSA is not recommended. In American burn centers, 5% HSA in Ringer's lactate is routinely used for resuscitation 17 to 24 h after burn injury.<sup>[81]</sup>

**Recommendation 18:** *HSA can be used in patients with severe burns during the period of shock (Grade 2+, weak recommendation).*

A retrospective analysis including 40 patients admitted to the burn ICU within the first 12 h post-burn injury showed

that the resuscitation volume during the first 24 h was 2.58 mL/kg per body burned surface area, which is significantly lower than the volume recommended using the Parkland formula. During resuscitation, base excess (120%) and the lactate clearance rate (29%) were significantly increased. It also revealed that 20% HSA can be used for fluid resuscitation and for limiting the infusion volume within 48 h of burn injury.<sup>[91]</sup> In addition, several meta-analyses and reviews have revealed that HSA can reduce the volume of fluid required in burn patients in the early period of shock.<sup>[92-101]</sup>

Patients in another before-after study were divided into two groups. Those admitted before March 2007 were treated with Ringer lactate within the first 24 h after burn injury, and the others admitted after March 2007 were treated with 5% HSA and Ringer lactate. It showed that the use of HSA within the first 24 h of burn injury was associated with lower mortality, a shorter duration of mechanical ventilation, and less vasopressor use.<sup>[102]</sup>

**Recommendation 19:** *Burn patients with serum albumin concentrations below 30 g/L should be treated with hypertonic HSA (concentration above 10%) (expert opinion).*

A systemic non-infectious inflammatory response exists in burn patients with the hypermetabolic state which is characterized by impaired capillary permeability, edema, significant loss of serum albumin, and an increased risk of infection.<sup>[103-105]</sup> Therefore, when the serum albumin concentration is less than 30 g/L, the patient should be treated with hypertonic HSA at a concentration of more than 10% in order to ensure the nutritional support and the efficacy of antibiotics with high protein binding rate.<sup>[106]</sup> Owing to the recovery of capillary function in the late stage of severe burns and the infusion of a large volume of crystalloids, patients experience a decrease in plasma protein content and colloid osmotic pressure, thus resulting in interstitial edema. Hence, the treatment in this stage mainly aims to maintain plasma colloid osmotic pressure and resolve interstitial edema. Therefore, high-concentration HSA (25% or 20%) should be infused in the late stage of burns, while low-concentration HSA infusion should be avoided.

### Recommendations for the use of HSA in Patients With Acute Respiratory Distress Syndrome

In patients with acute respiratory distress syndrome (ARDS), the rising permeability of the alveolar-capillary barrier can assist the infiltration of protein-rich fluids to enter into the alveoli. The presence of alveolar exudates and inactivation of pulmonary surfactants can lead to life-threatening hypoxemia, impaired carbon dioxide excretion, and reduced lung compliance. Thus, whether albumin infusion can improve the outcome of patients with ARDS remains unclear.

**Recommendation 20:** *HSA administration is recommended for patients with ARDS and hypoproteinemia to improve oxygenation (Grade 2+, weak recommendation).*

Compared to crystalloids, colloids have the beneficial effects of reducing alveolar–capillary permeability, tissue damage, and inflammatory cell infiltration. In the presence of increased capillary leakage, the extravasation of colloid molecules may increase tissue edema, and the use of synthetic colloids (HES and gelatin) is related to the increased incidence of renal injury and death in patients with sepsis. To avoid these side effects of synthetic colloids, studies have been performed to explore the use of HSA in ARDS patients.

Four RCTs<sup>[9,107-109]</sup> and one meta-analysis<sup>[110]</sup> revealed the following findings: (1) effects on mortality: HSA treatment did not significantly affect the 28-day mortality of ICU patients compared with crystalloids therapy (RR: 0.77, 95% CI: 0.57–1.02,  $P = 0.05$ ); and (2) effects on oxygenation: Two RCTs revealed that HSA treatment improved the oxygenation index in ARDS patients with hypoproteinemia at 24 h after albumin infusion (weighted mean difference [WMD] = 56 mmHg, 95% CI: 47–66 mmHg,  $P < 0.001$ ), 48 h after albumin infusion (WMD = 62 mmHg, 95% CI: 47–77 mmHg,  $P < 0.001$ ), and 7 days after albumin infusion (WMD = 20 mmHg, 95% CI: 4–36 mmHg,  $P = 0.017$ ). However, no difference was found in the oxygenation index between patients treated with HSA and those treated with crystalloids after 72 h (WMD = 10 mmHg, 95% CI: -3–23 mmHg,  $P = 0.131$ ).<sup>[107,108]</sup> Considering the small number of relevant studies and insufficient number of enrolled cases, additional clinical trials are needed to verify the above findings.

### Recommendations for HSA Use in the Critically Ill Patients with Severe Cirrhosis

Critically ill patients with decompensated cirrhosis accompanied by other complications (such as variceal rupture and bleeding, hepatic encephalopathy, and HRS) or extrahepatic organ failure are often admitted to ICU for organ support and other treatments as well as perioperative management for liver transplantation.<sup>[111]</sup> A meta-analysis of 2523 cases revealed that the ICU mortality, in-hospital mortality, and 6-month mortality of cirrhosis patients were 42.7%, 54.1%, and 75.1%, respectively.<sup>[112]</sup> Decreased levels and impaired synthesis function of albumin were observed and they were associated with increased risks of mortality among cirrhosis patients.<sup>[113]</sup> Despite the extensive clinical use of HSA for increasing serum albumin levels in cirrhosis patients, widely accepted recommendations are still lacking.

**Recommendation 21:** Critically ill patients with severe cirrhosis induced massive ascites are suggested to be infused with albumin liquids after large-volume paracentesis (LVP) (Grade 2+, weak recommendation).

Large-volume paracentesis (LVP) is currently the optimal treatment for cirrhosis with massive ascites, and HSA infusion after LVP may improve post-paracentesis circulatory dysfunction (PICD) and survival rates.

The human albumin for the treatment of ascites in patients with hepatic cirrhosis (ANSWER) study, an RCT enrolled 440 cirrhosis patients with ascites demonstrated that

compared with the patients treated with standard medical treatment (SMT) alone, the risk of refractory ascites was decreased by 57% (HR: 0.43, 95% CI: 0.29–0.62), and the death was decreased by 38% (HR: 0.62, 95% CI: 0.40–0.95) in the patients combined with albumin infusion together. Also, subsequent LVP operation was avoided by additional albumin infusion (HR: 0.48, 95% CI: 0.35–0.64).<sup>[114]</sup> A meta-analysis by Bernardi *et al*<sup>[115]</sup> with 1225 cirrhosis patients (17 RCTs) showed that the incidence of PICD (OR: 0.39, 95% CI: 0.27–0.55) and mortality (OR: 0.64, 95% CI: 0.41–0.98) were decreased by 61% and 36% respectively with albumin infusion after LVP operation.

However, a meta-analysis by Kutting *et al*<sup>[116]</sup> in 2017 included 21 RCTs with 1277 cirrhosis patients without hepatocellular carcinoma showed that the survival rate was not significantly improved by albumin infusion after LVP operation (OR: 0.78, 95% CI: 0.55–1.11,  $P = 0.17$ ). Similar results were also observed in the other two meta-analyses by Simonetti *et al* ( $n = 977$ , 27 RCTs, 2019)<sup>[117]</sup> and Benmassaoud *et al* ( $n = 3,521$ , 49 RCTs, 2020).<sup>[118]</sup> The discrepancies between the findings of different meta-analyses may be attributed to the inclusion of two controversial RCTs in the meta-analysis studies, to some extent with different control groups, one was compared with diuretics<sup>[119]</sup> and another was with mannitol.<sup>[120]</sup> And albumin use could significantly reduce mortality if the above two RCTs are excluded in the meta-analyses.

Therefore, albumin infusion after LVP operation in critically ill patients with cirrhosis and massive ascites can reduce the risk of refractory ascites, decrease the incidence of PICD, and improve the survival rate.

**Recommendation 22:** HSA infusion combined with terlipressin therapy is recommended for hepatorenal syndrome (HRS) patients (Grade 2+, weak recommendation).

AKI is very common among patients with decompensated cirrhosis and the incidence is about 20% to 80% which easily leads to HRS with high mortality.<sup>[121]</sup> The levels of serum creatinine and mortality could effectively be decreased in HRS patients by HSA therapy with terlipressin. A recent RCT including 300 patients with type I HRS indicated that 32% of patients treated with albumin and terlipressin and 17% of patients treated with albumin alone reversed HRS ( $P = 0.006$ ) (HRS reversal was defined as serum creatinine level  $\leq 1.5$  mg/dL [132.6  $\mu\text{mol/L}$ ] at two consecutive detections at least 2 h interval). In addition, in cirrhotic patients with systemic inflammatory response syndrome (SIRS), the HRS reversal rates were 37% and 6% under the two treatment options, respectively ( $P < 0.001$ ).<sup>[122]</sup>

A study by Facciorusso *et al*<sup>[123]</sup> including a total of 739 patients from 13 RCTs with type I HRS revealed that 3-month mortality was significantly decreased by albumin and terlipressin therapy rather than with albumin alone (OR: 0.65, 95% CI: 0.41–1.05). In another meta-analysis with 770 HRS patients from 13 RCTs exhibited that the HRS reversal rate was significantly higher in the patients

with albumin and terlipressin therapy compared with albumin alone (OR: 4.72, 95% CI: 1.72–12.93,  $P = 0.003$ ) or with midodrine and octreotide therapy (OR: 5.94, 95% CI: 1.69–20.85,  $P = 0.005$ ). HRS reversal rate was defined as over 50% reduction in serum creatinine level or serum creatinine level of  $\leq 1.5$  mg/dL (132.6  $\mu\text{mol/L}$ ), however, no benefit was observed in the HRS recurrence and mortality improvement.<sup>[124]</sup> A meta-analysis that included 25 RCTs with a total of 1263 HRS patients reported that a higher recovery rate was revealed in the patients with albumin and terlipressin treatment than that with albumin, midodrine and octreotide treatment (HR: 0.04, 95% CI: 0.00–0.25) or with albumin and octreotide therapy (HR: 0.26, 95% CI: 0.07–0.80), however, there was no significant difference in mortality.<sup>[125]</sup> Therefore, combined administration of albumin with terlipressin is recommended to treat HRS patients induced by decompensated cirrhosis.

The risk of AKI in cirrhosis patients might be decreased by albumin therapy. A recent RCT demonstrated that a decreasing trend in the incidence of AKI (10.5% vs. 14.4%, adjusted OR: 0.68, 95% CI: 0.44–1.11) and mortality (7.9% vs. 8.3%, OR: 0.95, 95% CI: 0.56–1.59) was observed in the additional albumin treatment compared with the standard treatment in hospitalized patients with cirrhosis.<sup>[126]</sup>

### Recommendations for the Use of HSA in Critically Ill Patients on Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) has become an important technology for extracorporeal life support in treating patients with severe respiratory and/or circulatory failure in critical care medicine. However, only a few critically ill patients on ECMO and undergoing HSA therapy were included in the published studies. Thus, data from RCTs with high-level evidence about the pathophysiologic states are still lacking.

**Recommendation 23:** *HSA should not be added to the priming of ECMO circuits to prevent fibrinogen deposition or platelet adhesion (expert opinion).*

HSA was added to the priming of ECMO circuits in the 1980s to cover the polymer surfaces and it was thought as an adjunctive therapeutic agent in patients with suspected heparin-induced thrombocytopenia (HIT).<sup>[127–130]</sup> However, the major difference between ECMO and cardiopulmonary bypass is that the ECMO circuit is a closed-loop and that ECMO involves a much longer operating time. Due to the persistence of procoagulant proteins such as fibrinogen in the blood, the presence of albumin on the polymer surface does not persist, and the albumin gradually disappears as it is replaced by fibrinogen, a phenomenon also known as the Vroman effect.<sup>[131]</sup> Various extracorporeal life support circuits manufactured using new-generation surface-active or surface-passive coating technologies have been successfully applied in clinical practice. Therefore, the addition of HSA to the priming solution has a limited protective effect on blood during long-term ECMO operation, and evidence on this aspect is still lacking.

**Recommendation 24:** *The combined use of HSA and crystalloids is recommended for ECMO patients receiving fluid resuscitation (expert opinion).*

The phenomenon of hypoxia and hypoperfusion have already existed before ECMO has been effectively established, resulting in capillary leakage and intravascular volume loss and redistribution. The process of re-oxygenation or reperfusion may deteriorate this situation in the early stage of extracorporeal circulation and cause an insufficient circulating blood volume in the right heart and blood vessels. Thus, fluid resuscitation in the early stage of ECMO is needed.<sup>[132]</sup> Consensus on fluid resuscitation strategies during ECMO operation is still controversial. One retrospective study included 283 veno-arterial ECMO patients with a positive fluid balance at 12 h after cannulation revealed that fluid resuscitation with a mix of HSA (10 g albumin/L) and crystalloids ( $v/v = 1/2$ ) led to a higher in-hospital survival rate than fluid resuscitation with crystalloids alone (38.4% vs. 25.7% before propensity score matching [PSM],  $P = 0.026$ ; and 43.9% vs. 27.6% after propensity score matching,  $P = 0.025$ ). Multivariate logistic regression suggested that the fluid resuscitation strategy consisting of HSA could improve the in-hospital survival rate with an OR of 4.33 (95% CI: 2.01–9.33) before PSM and an OR of 3.10 (95% CI: 1.15–6.38) after PSM. The subgroup analysis indicated that more benefit could be acquired to elderly patients with hyperlactacidemia, low Sequential Organ Failure Assessment (SOFA) score and lower survival after veno-arterial ECMO (SAVE) score.<sup>[133]</sup>

### Recommendations for the Management of Adverse Effects of HSA infusion

**Recommendation 25:** *Assessment and prompt management of the adverse effects of HSA infusion are recommended (expert opinion).*

As a composition extracted from human blood, adverse effects (ADEs) of HAS infusion are unavoidable. Approximately 0.1% of patients develop allergic reactions such as flushing, urticaria, fever, chills, nausea, vomiting, tachycardia, and hypotension. These ADEs usually disappear when the infusion rate is reduced or when the infusion is stopped. In rare cases, anaphylactic shock may occur. Edema and fluid overload are also common ADEs, the occurrence of which depends on the infused volume, infusion rate, and the patient's clinical condition. In the event of ADEs, albumin infusion should be stopped, and the patient's intravascular volume should be reassessed and properly managed. Moreover, attention should be paid to avoid the incidence of AKI when administering high-concentration HSA for fluid resuscitation in shock patients. A single-center retrospective cohort study of 11,512 patients with postoperative shock revealed that patients who received fluid resuscitation with high-concentration (25%) HSA had a significantly higher risk of AKI than patients who did not (OR: 1.10, 95% CI: 1.04–1.17).<sup>[134]</sup> As shown in another multicenter, prospective, observational study that included 1013 ICU patients needing fluid resuscitation for shock, resuscitation with high-concentration HSA was significantly associated

with adverse renal events (OR: 5.99, 95% CI: 2.75–13.08).<sup>[135]</sup> A recent meta-analysis of 58 clinical trials including 26,351 patients showed no significant difference in the incidence of AKI between patients with sepsis receiving fluid resuscitation with crystalloids and those receiving fluid resuscitation with low-concentration HSA.<sup>[25]</sup>

## Conclusion

In summary, HSA has been applied in clinical practice since the 1940s. Because of its ability to regulate colloid osmotic pressure, antioxidant properties, and its capacity to regulate and buffer the concentration of nitric oxide, it is widely used in treating critically ill patients nowadays. However, the clinical implementation of HSA in the ICU remains controversial because of the advantages and disadvantages in different populations.

Based on the analysis of available literature, the consensus writing group provided a total of 25 graded recommendations on how to use HSA in critically ill patients. Future studies should continue to focus on which kind of critically ill patients are most likely to benefit from the administration of HSA and other issues that are of particular clinical concern but only supported by low levels of evidence from the available literature. Besides the RCTs with large sample size on critically ill patients, it will be necessary to further elucidate the molecular and physiological bases underlying the beneficial effects of albumin as well as the importance of its pleiotropic effects. Moreover, such studies should provide deeper insights into the mechanisms underlying the development of hypoproteinemia, clarify the supplementation doses and action targets of albumin, and explore whether different concentrations of HSA have different effects on clinical outcomes.

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## Conflicts of interest

None.

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