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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Do patients with sepsis benefit from intravenous albumin?

My hospitalized adult patient with sepsis is hypotensive despite adequate resuscitation with intravenous (IV) crystalloid fluid. Should I administer a bolus of IV albumin?

A: In hospitalized patients with sepsis who do not need vasopressors, administration of IV albumin affords no morbidity or mortality benefit compared with IV crystalloid therapy alone.

HOW DO WE DEFINE SEPSIS?

Sepsis is a clinical definition designed to identify patients at high risk of death due to infection. In modern practice, sepsis is most commonly defined as the presence of 2 or more of the following systemic inflammatory response syndrome criteria plus a suspected or confirmed infectious source:

- Heart rate greater than 90 beats per minute
- Respiratory rate greater than 20 breaths per minute
- Temperature above 38°C or below 36°C
- White blood cell count greater than 12×10^9/L or less than 4×10^9/L.[1]

Severe sepsis is defined as sepsis plus evidence of end-organ dysfunction, hypotension, or hypoperfusion; *septic shock* is defined as severe sepsis with hypotension requiring vasopressors despite adequate fluid resuscitation.[1] Treatment is guided by the Surviving Sepsis Campaign 2021 guidelines,[2] with IV fluid resuscitation being a key component of effective management.

WHAT ARE THE TYPES OF IV FLUIDS?

IV fluids can be divided into crystalloid solutions, which are composed of small solutes (ie, electrolytes and glucose) dissolved in water, and colloid solutions, which are composed of large solutes (ie, proteins) dissolved in water. The most commonly used crystalloid solutions include normal saline, lactated Ringer's solution, Plasma-Lyte A, and 5% dextrose in water. The most commonly used colloid solutions include human serum albumin, plasma products, and whole blood.[3]

WHAT IS HUMAN SERUM ALBUMIN, AND HOW DOES IT WORK?

Human serum albumin is a purified human blood product derived from pooled plasma donations. It consists of concentrated large proteins (albumin) dissolved in water. Theoretically, it serves to draw fluid into the blood vessel, thereby increasing IV colloid osmotic pressure and expanding effective circulating volume.[4] However, physiologic studies have shown that these theoretical effects do not consistently translate into the expected clinical effects. For example, in postsurgical cardiac surgery patients, IV albumin is a more effective plasma volume expander than normal saline. Despite this, normal saline has similar effects as albumin on interstitial fluid volume, suggesting that fluid balance is a complex process dependent on mechanisms beyond plasma volume expansion alone.[5]

In the United States, human serum albumin is available in a 5% formulation, with the remainder of the solution composed of 95% normal saline, and in a 25% formulation, with the remainder of the solution composed of 75% normal saline.[6] When the therapeutic goal is to raise the plasma albumin concentration while minimizing infusion of additional sodium and fluid volume, 25% albumin is the preferred formulation. Alternatively, when the goal is to provide patients with additional plasma fluid volume, 5% albumin is preferred.[6]

As a blood product, albumin carries risks, including transfusion-related acute lung injury, transmission of

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diseases for which no screening assay is available such as Creutzfeldt-Jakob disease (though no documented cases exist to date), and higher cost. One bolus of albumin can cost up to 60 times as much as an equivalent bolus of crystalloid solution.[6]

DOES IV ALBUMIN IMPROVE OUTCOMES COMPARED WITH IV CRYSTALLOID?

The utility of albumin in patients with sepsis remains controversial. Multiple randomized controlled trials have investigated albumin as a resuscitation fluid in sepsis dating back to 2004, after consistent implementation of the Surviving Sepsis guidelines. None of these trials has proven albumin to be superior to crystalloid.

The first of these trials was the 2004 Saline versus Albumin Fluid Evaluation (SAFE) study.[7] This study explored whether albumin improved outcomes in all comers to the intensive care unit (ICU) compared with normal saline. Nearly 7,000 patients, 20% of whom had sepsis, were randomized to receive all ICU fluid resuscitation with either 4% albumin or normal saline for up to a 28-day period. Patients admitted for burns, liver transplantation, and cardiac surgery were excluded. The study found no difference between the albumin and saline groups in mortality, hospital length of stay, ICU length of stay, duration of mechanical ventilation, or duration of renal replacement therapy. The SAFE study established that albumin does not improve outcomes in undifferentiated ICU patients. However, a subgroup analysis of patients admitted for severe sepsis identified a trend toward decreased mortality in patients treated with albumin compared with patients treated with normal saline.[7]

The Albumin Italian Outcome Sepsis (ALBIOS) trial[8] sought to address the question of albumin efficacy in sepsis. ALBIOS was a 2014 multicenter, open-label, randomized controlled trial in which 1,818 patients admitted to the ICU for severe sepsis were randomized to either 20% albumin plus crystalloid resuscitation or crystalloid resuscitation alone. Patients in the albumin group received up to 300 mL of 20% albumin daily for up to 7 days to maintain a serum albumin level of at least 3 g/dL, which ensured consistent and adequate replacement of albumin. Of note, IV albumin was not provided specifically as a fluid bolus for early fluid resuscitation. As in the SAFE study,[7] patients admitted for burns, liver transplantation, and cardiac surgery were excluded. Despite these additional steps, this trial[8] found no significant difference in mortality, organ dysfunction, ICU length of stay, or hospital length of stay in the albumin group compared with the crystalloid group. A post hoc analysis in 1,121 patients with septic shock found a 6.3% absolute reduction in 90-day mortality in patients who received albumin. However, the authors cautioned readers about the generalizability of this result and recommended further confirmation.[8]

Two recent meta-analyses examined the question of colloid vs crystalloid fluid resuscitation. Martin and Bassett[9] found that undifferentiated critically ill patients who received colloid fluid had higher central venous pressure, mean arterial pressure, and cardiac index compared with patients who received crystalloid fluid alone. There was no statistically significant difference in mortality. This meta-analysis suggests that resuscitation with colloid fluid may afford improved hemodynamics compared with crystalloid fluid; however, the applicability of these results to patients with sepsis is limited by the study's broad inclusion criteria. Geng et al[10] found that patients with septic shock who were given 20% albumin had lower 90-day mortality compared with those treated with crystalloid fluid alone. However, there was no statistically significant difference in mortality among patients with sepsis or severe sepsis. While this suggests a potential benefit of colloid fluid in appropriate patients with septic shock, it reaffirms that colloid fluid does not confer mortality benefit in septic patients without shock.

Given the lack of consensus and randomized controlled trial data to support the use of albumin as a first-line resuscitation fluid in sepsis, the Surviving Sepsis Campaign guidelines[2] suggest using a balanced crystalloid solution such as lactated Ringer's or Plasma-Lyte A. These guidelines are based on the Isotonic Solutions and Major Adverse Renal Events Trial (SMART),[11] which showed a mortality benefit in a subset of patients with sepsis who were treated with balanced crystalloid solutions instead of normal saline.

ARE THERE OTHER INDICATIONS FOR ALBUMIN?

While not clearly indicated for patients with sepsis, there are some evidence-based indications for administration of human serum albumin. For example, it has US Food and Drug Administration approval for use after large-volume paracentesis in patients with cirrhosis, as it has been shown to decrease postprocedural hemodynamic shifts and improve mortality.[12] In patients with cirrhosis, human serum albumin has been shown to decrease rates of kidney injury and mortality in both spontaneous bacterial peritonitis and hepatorenal syndrome.[13,14] When human serum albumin is used for these indications, the goal is to reduce the deleterious effects of abnormal hepatic physiology on

the circulatory system, thereby conferring renal protection and improving hemodynamics.

THE BOTTOM LINE

In the vast majority of patients hospitalized with sepsis, fluid resuscitation with IV albumin confers additional risk associated with transfusion of human blood products, substantially higher cost, and no proven morbidity or mortality benefit compared with IV crystalloid fluid. Hypotensive patients with sepsis should receive fluid resuscitation with crystalloid fluids alone. Patients who remain hypotensive despite adequate fluid resuscitation should receive vasopressors without delay.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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