JAMA Clinical Guidelines Synopsis

Use of Intravenous Albumin

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GUIDELINE TITLE Use of Intravenous Albumin: A Guideline From the International Collaboration for Transfusion Medicine Guidelines

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DEVELOPER International Collaboration for Transfusion Medicine Guidelines

FUNDING SOURCE Ontario Regional Blood Coordinating Network and International Collaboration for Transfusion Medicine Guidelines

TARGET POPULATION Patients receiving critical care, undergoing cardiovascular surgery or kidney replacement therapy, or experiencing complications of cirrhosis

SELECTED RECOMMENDATIONS

- For patients with cirrhosis and ascites undergoing large-volume paracentesis (>5 L), intravenous albumin is suggested to prevent paracentesis-induced circulatory dysfunction (PICD) (conditional recommendation; very low certainty of evidence [COE]).
- For patients with cirrhosis and spontaneous bacterial peritonitis (SBP), intravenous albumin is suggested to reduce mortality (conditional recommendation; low COE).
- For hospitalized patients with decompensated cirrhosis with hypoalbuminemia (<3.0 g/dL), it is suggested not to use intravenous albumin to increase albumin levels to 3.0 g/dL or greater for reducing infection, kidney dysfunction, or mortality (conditional recommendation; low COE).
- For critically ill adult patients, intravenous albumin in conjunction with diuretics is not suggested for removal of extravascular fluid (conditional recommendation; very low COE).

Summary of the Clinical Problem

Intravenous albumin is used in various clinical scenarios, such as volume resuscitation in hospitalized patients, complications of cirrhosis (ascites, SBP), and hypotension during dialysis.[1] The goal of this guideline was to summarize the known benefits of intravenous albumin, and scenarios in which it is not helpful, to allow for judicious use of this therapy.[1]

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Characteristics of the Guideline Source

The guideline work group included 20 members representing multiple subspecialties, including pediatricians, internists, and intensivists. Two systematic reviews of intravenous albumin were conducted as part of the guideline development process including (1) patients with critical illness or cirrhosis or requiring kidney replacement therapy and (2) patients requiring cardiovascular surgery. Strength of recommendation was rated as strong or conditional based on the confidence of the guideline work group that benefits outweigh risks, and COE was rated as high, moderate, low, or very low based on a GRADE framework[1] (**Table**). This synopsis highlights recommendations for adult patients.

Evidence Base

Forty-seven studies comprising randomized clinical trials (RCTs) and systematic reviews and meta-analyses were used to create the guideline. Among its 14 recommendations, 1 was rated as strong and the remaining 13 recommendations were rated as conditional. Certainty of evidence was rated as low or very low for 12 of the recommendations, with the remaining 2 rated as moderate.

For patients with cirrhosis undergoing large-volume paracentesis (>5 L), albumin is suggested as a plasma volume expander to reduce the risk of PICD, defined for use in clinical trials as a plasma renin level increase of more than 50%. A systematic review and meta-analysis of 3 studies and 432 patients found higher risk of PICD with other plasma expanders (eg, dextrans, polygeline, hydroxyethyl starch solutions) compared with albumin (32.4% vs 14.8%; risk ratio, 1.98; 95% CI, 1.31-2.99).[2] No association was found for albumin compared with other plasma expanders for all-cause mortality (1014 patients) or kidney impairment, defined most commonly as creatinine greater than 1.5 mg/dL (132.6 µmol/L) (1107 patients).

Albumin is suggested for patients with SBP and cirrhosis. An RCT (126 patients) that compared albumin (dosed at 1.5 g/kg on day 1 and 1 g/kg on day 3) plus cefotaxime vs cefotaxime alone reported lower rates of nonreversible deterioration of kidney function during hospitalization (10% vs 33%; $P = .002$) and in-hospital mortality (10% vs 29%; $P = .01$) for those receiving albumin.[3] A second RCT (112 patients) reported that fewer patients developed kidney impairment with albumin and ceftriaxone vs ceftriaxone alone (10% vs 34%;

Table. Guideline Rating[a]

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Fair
Guideline development group composition	Good
Clinical practice guideline–systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Good
Updating	Good
Implementation issues	Good

[a] Cifu AS, Davis AM, Livingston EH. Introducing JAMA Clinical Guidelines Synopsis. *JAMA*. 2014;312(12):1208-1209. doi:10.1001/jama.2014.12712

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P = .002) (kidney impairment defined as a 50% increase in serum urea nitrogen or creatinine for those with preexisting kidney insufficiency or serum urea nitrogen >30 mg/dL or creatinine >1.5 mg/dL for those without prior kidney insufficiency).[4] In that study, patients in the albumin and ceftriaxone group also had decreased in-hospital mortality compared with those receiving ceftriaxone alone (10% vs 33%; *P* = .01).[4] The frequency of alternative plasma expander use in the group receiving ceftriaxone alone was not reported.

Intravenous albumin for hospitalized patients with cirrhosis and serum albumin levels less than 3.0 g/dL is not suggested. In an open-label RCT, 777 patients were randomized to receive daily 20% albumin infusions (goal serum level of 3.5 g/dL) plus standard care or standard care alone.[5] Standard care was use of intravenous albumin for SBP, for hepatorenal syndrome, and after large-volume paracentesis. Patients were treated with daily albumin infusions for 14 days or until discharge, whichever occurred first. The primary composite end point of new infection, kidney dysfunction, or death measured between days 3 and 15 did not significantly differ between groups (29.7% with albumin vs 30.2% with standard care; odds ratio, 0.98; 95% CI, 0.71-1.33).

For critically ill adults, use of albumin with diuretics is not suggested for extravascular fluid removal. A nonblinded RCT compared diuresis with 20 mg of intravenous furosemide plus either 100 mL of 20% albumin or 100 mL of half normal saline in 49 patients admitted to an intensive care unit with serum albumin less than 4.0 g/dL, generalized edema, and need for diuretics.[6] In this study, patients were most commonly admitted to the hospital for treatment of cancer, pulmonary edema, pulmonary embolism, and cerebral hemorrhage. No primary outcome was specified. There was no statistically significant difference in urine output 8 hours after treatment (2396 [SD, 992] mL in the albumin group vs 2073 [SD, 844] mL in the half-normal saline group).

Benefits and Harms

These guidelines highlight the few conditions in which evidence supports use of intravenous albumin, as well as when it should be avoided. Appropriate use can reduce costs when efficacy is not superior to less-expensive crystalloids. The guidelines were formed based on a small number of studies, and available data on adverse events are limited, complicating assessment of net benefits and risks. The guideline lists potential adverse events from albumin as volume overload, hemodilution, anaphylaxis, and peripheral gangrene from dilution of circulating anticoagulants.[1]

Discussion

Across patients of all ages, albumin was suggested only for those with cirrhosis who are undergoing large-volume paracentesis (>5 L) or those with cirrhosis and SBP to reduce important primary outcomes of kidney injury or mortality. However, the evidence for these suggestions is supported by only a few RCTs with small sample sizes. The guideline suggested not using albumin in all other settings, including for volume replacement in patients with hypovolemia and hypoalbuminemia. For the indication of large-volume paracentesis, PICD was used as a surrogate outcome measure in clinical trials, but the association of renin levels with clinical outcomes, such as hospital readmission, and prognosis, such as mortality, require validation.[2,7-9] The guideline does not specify a role for measuring renin levels to evaluate for PICD in patients undergoing large-volume paracentesis, as there is also uncertainty about whether preventing postparacentesis plasma renin increases of 50% or more reduces clinically relevant outcomes such as recurrent ascites, kidney failure, hospital admission, or death.

Areas in Need of Future Study or Ongoing Research

Uniform criteria about outcomes (including clinical, therapeutic hemodynamic, urinary output, and laboratory data) should be developed and agreed on for both clinical trials and clinical practice. Additionally, more studies are needed comparing alternative regimens of fluid resuscitation, such as crystalloid, for the described indications. It would also be beneficial to clarify optimal dosing, frequency, and duration of intravenous albumin, particularly among patients with cirrhosis and its complications who have an insufficient response to crystalloids. Although therapy with albumin is commonly used for patients with hepatorenal syndrome, no RCTs of albumin vs placebo for treatment of hepatorenal syndrome were identified; further study would better clarify potential benefits and harms of this management strategy.

ARTICLE INFORMATION

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