

Use of Intravenous Albumin



A Guideline From the International Collaboration for Transfusion Medicine Guidelines

Jeannie Callum, MD; Nikolaos J. Skubas, MD; Aarti Bathla, MPharm, MPH; Homa Keshavarz, PhD; Edward G. Clark, MD; Bram Rochwerf, MD; Dean Fergusson, PhD; Sesmu Arbous, MD; Seth R. Bauer, PharmD; Louise China, MD; Mark Fung, MD; Rachel Jug, MD; Michael Neill; Cary Paine, MD; Katerina Pavenski, MD; Prakesh S. Shah, MD; Susan Robinson, MD; Hua Shan, MD; Zbigniew M. Szczepiorkowski, MD, PhD; Thierry Thevenot, MD; Bovey Wu, MD; Simon Stanworth, MD, PhD; and Nadine Shehata, MD; on behalf of the International Collaboration for Transfusion Medicine Guidelines Intravenous Albumin Guideline Group*

BACKGROUND: Albumin is used commonly across a wide range of clinical settings to improve hemodynamics, to facilitate fluid removal, and to manage complications of cirrhosis. The International Collaboration for Transfusion Medicine Guidelines developed guidelines for the use of albumin in patients requiring critical care, undergoing cardiovascular surgery, undergoing kidney replacement therapy, or experiencing complications of cirrhosis.

STUDY DESIGN AND METHODS: Coauthors oversaw the guideline development process and the panel included researchers, clinicians, methodologists, and a patient representative. The evidence informing this guideline arises from a systematic review of randomized clinical trials and systematic reviews, in which multiple databases were searched (inception through November 23, 2022). The panel reviewed the data and formulated the guideline recommendations using Grading of Recommendations Assessment, Development, and Evaluation methodology. The guidelines were revised after public consultation.

RESULTS: The panel made 14 recommendations on albumin use in adult critical care (three recommendations), pediatric critical care (one recommendation), neonatal critical care (two recommendations), cardiovascular surgery (two recommendations), kidney replacement therapy (one recommendation), and complications of cirrhosis (five recommendations). Of the 14 recommendations, two recommendations had moderate certainty of evidence, five recommendations had low certainty of evidence, and seven recommendations had very low certainty of evidence. Two of the 14 recommendations suggested conditional use of albumin for patients with cirrhosis undergoing large-volume paracentesis or with spontaneous bacterial peritonitis. Twelve of 14 recommendations did not suggest albumin use in a wide variety of clinical situations where albumin commonly is transfused.

INTERPRETATION: Currently, few evidence-based indications support the routine use of albumin in clinical practice to improve patient outcomes. These guidelines provide clinicians with actionable recommendations on the use of albumin. CHEST 2024; 166(2):321-338

KEY WORDS: guideline; intensive care; intravenous albumin; kidney replacement therapy; liver disease; sepsis

ABBREVIATIONS: GRADE = Grading of Recommendations Assessment, Development and Evaluation; ICTMG = International Collaboration for Transfusion Medicine Guidelines; MD = mean difference; RCT = randomized controlled trial; RR = relative risk

AFFILIATIONS: From the Department of Pathology and Molecular Medicine (J. C.), Queen's University and Kingston Health Sciences Centre, Kingston, the Division of Nephrology (E. G. C.), Department of Medicine, University of Ottawa, Ottawa Hospital Research Institute

Summary of Recommendations

Intravenous albumin is a human-derived blood product manufactured from donated human plasma. It is used broadly in hospitalized patients, as well as in outpatients with complications of cirrhosis. Intravenous albumin has been studied in numerous, large, well-designed, randomized controlled clinical trials in multiple patient populations; the data show few applications of albumin that improve patient outcomes. Albumin is more expensive to manufacture and to provide to patients, when compared with crystalloids. The International Collaboration for Transfusion Medicine Guidelines undertook this guideline development process to provide clinicians with actionable recommendations for appropriate use of intravenous albumin.

1. In critically ill adult patients (excluding patients with thermal injuries and ARDS), intravenous albumin is not suggested for first-line volume replacement or to increase serum albumin levels

(D. F.), Ottawa, the Department of Medicine and Department of Health Research Methods (B. R.), Evidence and Impact, Faculty of Health Sciences, McMaster University, Hamilton; the Department of Laboratory Medicine and Pathobiology (K. P.), the Institute of Health Policy, Management, and Evaluation (P. S. S.), the Department of Medicine (N. S.), University of Toronto, the Department of Pediatrics (P. S. S.), the Transfusion Medicine Laboratory (N. S.), Mount Sinai Hospital, Toronto; the Canadian Blood Services (A. B. and H. K.), Ottawa, ON, Canada; the Department of Cardiothoracic Anesthesiology (N. J. S.), Anesthesiology Institute, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University; the Department of Pharmacy (S. R. B.), Cleveland Clinic, Cleveland, the University of Cincinnati College of Medicine (R. J.), Cincinnati, OH; the Department of Pathology and Laboratory Medicine (M. F.), University of Vermont Medical Center, Burlington, VT; the Department of Pathology (H. S.), Stanford University School of Medicine, Palo Alto; the Department of Internal Medicine (B. W.), Graduate Medical Education, Loma Linda University, Loma Linda, CA; the Department of Pathology and Laboratory Medicine (Z. M. S.), Dartmouth-Hitchcock Medical Center, Lebanon, NH; the Division of Nephrology (C. P.), Department of Medicine, University of Washington, Seattle, WA; the Department of Critical Care (S. A.), Leiden University Medical Center, Leiden, The Netherlands; the Department of Hepatology and ILDH (L. C.), The Royal Free NHS Trust and University College London, Department of Clinical Haematology (S. R.), Guy's and St Thomas' NHS Foundation Trust, London, NHS Blood and Transplant (S. S.), the Radcliffe Department of Medicine (S. S.), University of Oxford; the John Radcliffe Hospital (S. S.), Oxford University Hospitals NHS Foundation Trust, Oxford, England; the Service d'Hépatologie (T. T.), Centre Hospitalier Régional et Universitaire de Besançon, Besançon, France; and Patient representative (M. N.).

*Collaborators from the International Collaboration for Transfusion Medicine Guidelines Intravenous Albumin Guideline Group are listed in the Acknowledgments.

CORRESPONDENCE TO: Jeannie Callum, MD; email: jlc17@queensu.ca

Copyright © 2024 The Author(s). Published by Elsevier Inc under license from the American College of Chest Physicians. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

DOI: <https://doi.org/10.1016/j.chest.2024.02.049>

(Conditional Recommendation, Moderate Certainty of Evidence of Effect).

2. In critically ill adult patients with thermal injuries or ARDS, intravenous albumin is not suggested for volume replacement or to increase serum albumin level (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

3. In critically ill adult patients, intravenous albumin in conjunction with diuretics is not suggested for removal of extravascular fluid (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

4. In pediatric patients with infection and hypoperfusion, intravenous albumin is not recommended to reduce mortality (Strong Recommendation, Low Certainty of Evidence of Effect).

5. In preterm neonates (≤ 36 weeks) with low serum albumin levels and respiratory distress, intravenous albumin is not suggested to improve respiratory function (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

6. In preterm neonates (≤ 32 weeks or $\leq 1,500$ g) with or without hypoperfusion, intravenous albumin is not suggested for volume replacement (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

7. In patients undergoing kidney replacement therapy, intravenous albumin is not suggested for prevention or treatment of intradialytic hypotension or for improving ultrafiltration (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

8. In adult patients undergoing cardiovascular surgery, intravenous albumin is not suggested for priming the cardiovascular bypass circuit or volume replacement (Conditional Recommendation, Moderate Certainty of Evidence of Effect).

9. In pediatric patients undergoing cardiovascular surgery, intravenous albumin is not suggested for priming the cardiovascular bypass circuit or volume replacement (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

10. In patients with cirrhosis and ascites undergoing large-volume paracentesis (> 5 L), intravenous albumin is suggested to prevent paracentesis-induced circulatory dysfunction (Conditional

Recommendation, Very Low Certainty of Evidence of Effect).

11. In patients with cirrhosis and spontaneous bacterial peritonitis, intravenous albumin is suggested to reduce mortality (Conditional Recommendation, Low Certainty of Evidence of Effect).

12. In patients with cirrhosis and extraperitoneal infections, intravenous albumin is not suggested to reduce mortality or kidney failure (Conditional Recommendation, Low Certainty of Evidence of Effect).

13. In hospitalized patients with decompensated cirrhosis with hypoalbuminemia (< 30 g/L), repeated intravenous albumin to increase albumin levels to > 30 g/L is not suggested to reduce infection, kidney dysfunction, or death (Conditional Recommendation, Low Certainty of Evidence of Effect).

14. In outpatients with cirrhosis and uncomplicated ascites despite diuretic therapy, intravenous albumin is not routinely suggested to reduce complications associated with cirrhosis (Conditional Recommendation, Low Certainty of Evidence of Effect).

Background

Albumin is administered in a wide spectrum of clinical scenarios including complications of cirrhosis, intradialytic hypotension, volume resuscitation, and priming of cardiopulmonary bypass circuit. Iso-oncotic albumin often is used to maintain intravascular volume in patients with hypovolemia, assuming that crystalloid resuscitation will be ineffective given its shorter intravascular half-life. Hyperoncotic albumin is used to correct low serum albumin levels or to mobilize extravascular fluid.

Hypoalbuminemia is common in acute and chronic illness. Hospitalized patients with hypoalbuminemia have been described as having greater morbidity compared with patients with preserved albumin levels, promoting the use of IV albumin.^{1,2} In the postoperative period, serum albumin levels decreases precipitously by 10 to 15 g/L³; hypoalbuminemia is thought to be the result of suppressed synthesis by inflammatory cytokines⁴ and transcapillary loss.⁵ In addition to its use in patients with hypoalbuminemia, edema, or both, albumin also is used for the prevention and treatment of hypovolemia, particular after administration of large volumes of IV crystalloid solutions.⁶

Practice audits describing the use of albumin show highly variable practice among regions.^{7,8} Albumin is manufactured from large volumes of plasma and is expensive (approximately \$130/25 g United States dollars; warehouse acquisition cost of albumin), with the acquisition cost likely a fraction of the total health care expenditure.⁹ Albumin also can be associated with adverse consequences, including fluid overload,^{10,11} hypotension,¹² hemodilution requiring RBC transfusion,¹³ anaphylaxis,¹⁴ and peripheral gangrene from dilution of natural anticoagulants.¹⁵ Because potential benefits and risks are associated with its use, a multidisciplinary, international guideline panel was convened to develop evidence-based recommendations for the use of albumin in patient populations where it is prescribed commonly. These guidelines are designed to assist clinicians in their decisions on the use of albumin for its most common uses.

Methods

Guidelines Focus

These recommendations apply to patients receiving albumin in critical care settings with hypovolemia, sepsis, hypoalbuminemia, thermal injuries, and ARDS; cirrhosis; intradialytic hypotension; and cardiovascular surgery. These settings were included based on common uses of albumin, the systematic review of the published randomized controlled trials (RCTs), and with input from the panel. We included studies that compared the use of albumin with that of other resuscitation fluids, other pharmaceutical treatments, or standard of care.

Target Population

These guidelines provide actionable recommendations for the most common indications for the use of albumin. The use of albumin for

therapeutic apheresis was excluded because recent guidelines were published.¹⁶

Guidelines Development Process

Panel Composition: This guideline development process was funded by the Ontario Regional Blood Coordinating Network (Ontario, Canada) and the International Collaboration for Transfusion Medicine Guidelines (ICTMG; funded by Canadian Blood Services). Neither entity had any input on recommendations or guidelines content. An international panel of neonatal, pediatric, and adult specialists with expertise in the use of albumin developed the recommendations. This panel included 20 members with expertise in intensive care, hepatology, gastroenterology, nephrology, hematology, pathology, neonatology, transfusion medicine, cardiothoracic anesthesiology, internal medicine, and methodology and a patient representative. A framework and related

clinical questions were developed according to the United States Preventative Services Task Force Criteria. Disclosures were ascertained yearly from all members.

Systematic Review of the Evidence: A systematic search for articles published between inception and November 23, 2022, in MEDLINE, EMBASE, Cochrane, the National Health Service Economic Evaluation Database Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Ovid MEDLINE, Ovid MEDLINE epub ahead of print and in-process, and other nonindexed citations was completed with the assistance of an information specialist. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for this review is presented in [e-Appendix 1](#). The guideline development group conducted two systematic reviews: one for patients with critical illness or cirrhosis or requiring kidney replacement therapy (International Prospective Register of Systematic Reviews Identifier: CRD42019145152) and the other for patients undergoing cardiovascular surgery (International Prospective Register of Systematic Reviews Identifier: CRD42020171876). Manually searched references of primary articles, relevant reviews, and additional articles identified by panel members were included. The search strategy is detailed in [e-Appendix 2](#). Study inclusion criteria were: (1) original peer-reviewed published RCTs comparing albumin with an alternative strategy, (2) systematic reviews and meta-analyses reporting on RCTs, or both, (3) including at least one of the following outcomes of interest: mortality, multisystem organ failure, need for kidney replacement therapy or kidney failure, need for vasoactive medications, need for mechanical ventilation, hypotension, hemodynamic metrics, length of stay (hospital and intensive care), quality of life, health care use, and albumin levels; and (4) published in English.

InsightScope screened publications for eligibility and extracted characteristics, outcomes, and risk of bias for all indications, with the exception of studies published between November 2018 and November 2022 and the systematic review for cardiovascular surgery. Quality and risk-of-bias assessment were conducted using the established criteria,^{17,18} presented in detail for all systematic reviews in [e-Appendix 3](#). Discrepancies were resolved by a third reviewer. With the exception of cardiovascular surgery, comprehensive systematic reviews were available for all other settings that were used to develop recommendations. For cardiovascular surgery, where no systematic review had been performed, a systematic review and meta-analysis was conducted.¹⁹ Evidence tables for all indications are presented in [e-Appendix 4](#).

Recommendations

Recommendations are outlined in [Table 1](#).

Clinical Setting 1: Critically Ill Adult Patients

Recommendations: Recommendation 1: In critically ill adult patients (excluding patients with thermal injuries and ARDS), intravenous albumin is not suggested for first-line volume replacement or to increase serum albumin levels (Conditional Recommendation, Moderate Certainty of Evidence of Effect).

Recommendation 2: In critically ill adult patients with thermal injuries or ARDS, intravenous albumin is not suggested for volume replacement or to increase

Grading of the Evidence: Recommendations were formulated on the basis of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) (GRADEpro GDT; McMaster University).²⁰ The evidence certainty was graded as high, moderate, low, or very low certainty based on GRADE criteria.²¹ The panel ranked clinical outcomes (electronic survey) relevant for the development of recommendations according to GRADE criteria. Outcomes were ranked on a nine-part Likert scale for all relevant clinical outcomes identified by panel members (1-3 = low importance, 4-6 = important but not critical, and 7-9 = critical) ([e-Appendix 5](#)). Recommendation strength was evaluated as strong or conditional. A strong recommendation was made according to GRADE if the panel was “confident that the desirable effects outweighed the undesirable effects.” A conditional recommendation was made if the panel concluded that the “desirable effects probably outweigh the undesirable effects,” but the trade-offs were not well defined and the recommendation may not be applicable to all patients.²² The terms *recommend* and *suggest* were used to reflect strong and conditional recommendations, respectively.

Virtual conferences and electronic correspondence were used to discuss the clinical questions and to formulate recommendations. Electronic surveys were sent to all members to assess agreement with recommendations. Disagreements were resolved by discussion. If disagreements could not be resolved, a recommendation was accepted if most members (50% or more of the panel) agreed. Members recorded their disclosures, but none were excluded from voting ([e-Appendix 6](#)). The final guidance document was disseminated widely for public consultation to numerous medical societies ([e-Appendix 7](#)). The reviewers from these societies were sent a survey consisting of open-ended and closed-ended questions to determine agreement with each recommendation and to identify facilitators and barriers to guideline implementation. Comments from reviewers subsequently were discussed by panel members and addressed.

The recommendations in this guidance document will be reviewed every 3 years. If a study is published that may impact the recommendations critically before that time, a comment will be added on the ICTMG website. Recommendations are intended for critical care physicians, nephrologists, hepatologists, gastroenterologists, anesthesiologists, cardiovascular surgeons, general internists, hospitalists, hematologists, pathologists, pharmacists, laboratory technologists, and transfusion medicine physicians. The ICTMG website (<https://www.ictmg.org>) will be used to post implementation tools (eg, podcasts, order sets). The guideline process adhered to the 2011 Institute of Medicine (United States) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines.

serum albumin level (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

Recommendation 3: In critically ill adult patients, intravenous albumin in conjunction with diuretics is not suggested for removal of extravascular fluid (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

Evidence Summary: Sixteen²³⁻³⁸ of 19 systematic reviews were retrieved and included. These reports included a broad critical care patient population, including patients with critical illness, sepsis, thermal injuries, and ARDS. Three of the 19 systematic reviews

TABLE 1] The 14 Recommendations From the Panel, Ordered by Strength of the Recommendations**Moderate Certainty of Evidence**

Recommendation 1: In critically ill adult patients (excluding patients with thermal injuries and ARDS), intravenous albumin is not suggested for first-line volume replacement or to increase serum albumin levels (Conditional Recommendation, Moderate Certainty of Evidence of Effect).

Recommendation 8: In adult patients undergoing cardiovascular surgery, intravenous albumin is not suggested for priming the cardiovascular bypass circuit or for volume replacement (Conditional Recommendation, Moderate Certainty of Evidence of Effect).

Low Certainty of Evidence

Recommendation 4: In pediatric patients with infection and hypoperfusion, intravenous albumin is not recommended to reduce mortality (Strong Recommendation, Low Certainty of Evidence of Effect).

Recommendation 11: In patients with cirrhosis and spontaneous bacterial peritonitis, intravenous albumin is suggested to reduce mortality (Conditional Recommendation, Low Certainty of Evidence of Effect).

Recommendation 12: In patients with cirrhosis and extraperitoneal infections, intravenous albumin is not suggested to reduce mortality or kidney failure (Conditional Recommendation, Low Certainty of Evidence of Effect).

Recommendation 13: In hospitalized patients with decompensated cirrhosis with hypoalbuminemia (< 30 g/L), repeated intravenous albumin to increase albumin levels to > 30 g/L is not suggested to reduce infection, kidney dysfunction, or death (Conditional Recommendation, Low Certainty of Evidence of Effect).

Recommendation 14: In outpatients with cirrhosis and uncomplicated ascites despite diuretic therapy, intravenous albumin is not routinely suggested to reduce complications associated with cirrhosis (Conditional Recommendation, Low Certainty of Evidence of Effect).

Very low Certainty of Evidence

Recommendation 2: In critically ill adult patients with thermal injuries or ARDS, intravenous albumin is not suggested for volume replacement or to increase serum albumin level (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

Recommendation 3: In critically ill adult patients, intravenous albumin in conjunction with diuretics is not suggested for removal of extravascular fluid (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

Recommendation 5: In preterm neonates (≤ 36 wk) with respiratory distress and low serum albumin levels, intravenous albumin is not suggested to improve respiratory function (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

Recommendation 6: In preterm neonates (≤ 32 wk or $\leq 1,500$ g) with or without hypoperfusion, intravenous albumin is not suggested for volume replacement (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

Recommendation 7: In patients undergoing kidney replacement therapy, intravenous albumin is not suggested for the prevention or treatment of intradialytic hypotension or for improving ultrafiltration (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

Recommendation 9: In pediatric patients undergoing cardiovascular surgery, intravenous albumin is not suggested for priming the cardiovascular bypass circuit or for volume replacement (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

Recommendation 10: In patients with cirrhosis and ascites undergoing large-volume paracentesis (> 5 L), intravenous albumin is suggested to prevent paracentesis-induced circulatory dysfunction (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

were excluded because they assessed the impact of albumin only on fluid balance,³⁴ gelatin vs colloids,³⁹ or all colloids compared with crystalloids (without reporting albumin vs other fluids).⁴⁰

A systematic review from 2019³⁵ identified 55 RCTs comparing crystalloid with colloids in critical care. Data on mortality were available for 26,329 patients from 46 studies. No mortality benefit was found when crystalloid was compared with albumin (relative risk [RR] 1.02; 95% CI, 0.96-1.10). Crystalloids were less effective than colloids in hemodynamic resuscitation end points (eg, mean arterial pressure) but this did not translate into improvements in patient outcomes. After this systematic review, one RCT was identified that examined 360 patients with sepsis with an underlying diagnosis of cancer (albumin was compared with Ringer's lactate); no

differences in mortality or other outcomes were found.⁴¹

A systematic review from 2018 conducted by the Cochrane collaboration²³ found no difference in mortality in patients in the ICU (20 studies; $N = 13,047$) when patients managed with crystalloids were compared with those managed with albumin at the end of follow-up (RR, 0.98; 95% CI, 0.92-1.06), at 30 days (RR, 0.99; 95% CI, 0.93-1.06), or at 90 days (RR, 0.98; 95% CI, 0.92-1.04) or who needed kidney replacement therapy (RR, 1.11; 95% CI, 0.96-1.27). The largest randomized trial is the Saline Versus Albumin Fluid Evaluation trial published in 2004,¹³ which enrolled 6,997 patients receiving critical care (including a mix of medical and surgical patients) and compared 4% albumin with 0.9% normal saline. No differences were found in outcomes, including 28-day mortality (RR, 0.99; 95% CI, 0.91-1.09).

A 2015 systematic review evaluated the administration of albumin in critical care patients with traumatic injury; the review included five trials comparing albumin with crystalloid and found a higher mortality in albumin-treated patients (RR, 1.35; 95% CI, 1.03-1.77).²⁴ This systematic review was dominated by the Saline Versus Albumin Fluid Evaluation trial (57% of patients).¹³ The Saline Versus Albumin Fluid Evaluation trial subgroup analysis found that patients with traumatic brain injury showed a higher mortality rate (RR, 1.62; 95% CI, 1.12-2.34), but those without traumatic brain injury did not (RR, 1.00; 95% CI, 0.56-1.79).¹³ Hence, it is uncertain whether albumin may be unsafe only in patients with traumatic brain injury as compared with the wider trauma population.

A 2020 systematic review and sequential network analysis of RCTs in the setting of sepsis³⁶ included 23 randomized trials (N = 14,659); the vast majority of the trials used a physiologic target for volume resuscitation or at the discretion of the clinician, rather than a target albumin level. The review found albumin not to be superior to crystalloids for mortality or acute kidney injury. A 2014 systematic review²⁵ included 16 randomized trials (N = 4,190) comparing crystalloid or albumin and found no difference in mortality (RR, 0.94; 95% CI, 0.87-1.01). Two network meta-analyses have been performed and reported no mortality benefit from albumin.^{29,30} The largest randomized trial in sepsis was the Albumin Italian Outcome Sepsis trial,⁴² which randomized 1,818 patients with sepsis at 100 sites to 20% albumin (targeting plasma albumin level of ≥ 30 g/L) vs crystalloid. The Albumin Italian Outcome Sepsis trial did not observe improvements in mortality at 28 days (RR, 1.00; 95% CI, 0.87-1.14) or other important outcomes.

Three systematic reviews found no impact of albumin in critically ill adults on the need for kidney replacement therapy, including two network meta-analyses^{31,36} and the 2018 Cochrane review.²³ A systematic review evaluated the impact of albumin on patient outcomes after thermal injuries.³² The report identified four RCTs and found no impact on the incidence of kidney failure or mortality (RR, 1.41; 95% CI, 0.27-7.38).

In a 2022 systematic review evaluating the impact of albumin and diuretics, as compared with diuretics alone, in mechanically ventilated patients (three trials; N = 129), albumin reduced hypotensive episodes, but did not shorten the duration of mechanical ventilation or improve the mortality rate.³⁸ A 2014 systematic review

evaluated the impact of albumin, as compared with crystalloid, in patients with ARDS.³³ Three RCTs (N = 204) were included; no difference in mortality was found (RR, 0.89; 95% CI, 0.62-1.28). Similarly, a 2014 systematic review that included two small RCTs (N = 70) found no difference in ventilator-free days or mortality when albumin with diuretics, as compared with diuretics alone, were used to improve respiratory status in critically ill patients.³⁴

A 2014 systematic review evaluated the impact of albumin with furosemide, compared with furosemide alone, to facilitate fluid removal in patients with hypoalbuminemia and hypervolemia.³⁷ The systematic review identified 10 studies (N = 343). Although urine output was higher at 6 h in the patients receiving albumin-furosemide, no difference was found in urine output at 24 h. One RCT of 49 patients with edema receiving critical care was identified subsequent to this systematic review that compared albumin and furosemide with furosemide alone; no difference in urine output at 8 h was found.⁴³

Rationale for Recommendations: A substantial amount of evidence from RCTs in critically ill adult patients across a wide range of patient subgroups provides little supportive evidence for the use of albumin as fluid replacement to reduce mortality, the need for kidney replacement therapy, or other outcomes considered important or critical for decision-making by the panel. Given the wide CIs for the estimates from the systematic reviews, all recommendations were considered conditional because of the residual uncertainty.

In systematic reviews evaluating the role of albumin in patients with sepsis, the use of albumin has not been found to be associated with improved outcomes, although a benefit has not been excluded because of the wide CI in the most recent systematic review.³⁶ The Surviving Sepsis Campaign guidelines published in 2021⁴⁴ recommend albumin in addition to crystalloids when patients require large volumes of crystalloids (Weak Recommendation, Moderate-Quality Evidence). Specific formulations of albumin (4%-5% or 20%-25%), volumes or doses, serum albumin targets, or a combination thereof were not described. The guidelines state, “The lack of proven benefit and higher cost of albumin compared to crystalloid contributed to our strong recommendation for the use of crystalloids as first-line fluid for resuscitation in sepsis and septic shock.”⁴⁴ More studies will be needed to evaluate the role and timing of albumin as a rescue fluid in patients

with sepsis failing front-line crystalloid resuscitation, particularly given the considerably higher cost of albumin compared with crystalloids, the risks of albumin, and the lack of benefit shown in RCTs.

Clinical Setting 2: Critically Ill Pediatric Patients With Severe Infection

Recommendation: **Recommendation 4: In pediatric patients with infection and hypoperfusion, intravenous albumin is not recommended to reduce mortality** (Strong Recommendation, Low Certainty of Evidence of Effect).

Evidence Summary: A single systematic review⁴⁵ identified three RCTs that compared albumin with crystalloid in critically ill children.⁴⁶⁻⁴⁸ All RCTs enrolled children primarily in African countries with either severe malaria or febrile illness with impaired perfusion. The first trial enrolled 61 children with severe malaria and found no difference in mortality when albumin was compared with crystalloid.⁴⁷ The second trial enrolled 150 children with severe malaria and found an improvement in the mortality with albumin as compared with crystalloid.⁴⁸ A mortality difference was not found in a large, well-designed RCT (Fluid Expansion as Supportive Therapy; N = 3,141) that included children with severe febrile illness with impaired perfusion (60% had malaria).⁴⁶ This RCT had three arms comparing saline bolus, 5% albumin bolus, and no bolus. The trial was terminated by the independent data safety monitoring committee at the fifth interim analysis based on data from 2,995 children and after 3,141 of 3,600 planned patients were enrolled because of excess mortality in the patients treated with both the albumin bolus (RR, 1.45; 95% CI, 1.10-1.92) and the saline bolus (RR, 1.44; 95% CI, 1.09-1.90) compared with children who received no bolus. No mortality difference was found when the albumin bolus arm was compared with the crystalloid bolus arm (RR, 1.00; 95% CI, 0.78-1.29) at 48 h. Similar differences in mortality were observed between groups at 28 days, again with an excess mortality in the albumin and saline bolus groups compared with the no bolus group (RR, 1.40 [95% CI, 1.08-1.80] and 1.38 [95% CI, 1.07-1.78]). Children treated with both saline and albumin boluses showed higher rates of respiratory and neurologic dysfunction and of hyperchloremic acidosis and a greater reduction in hemoglobin levels.⁴⁹

Rationale for Recommendations: The systematic review of the literature for pediatric patients receiving critical care found fewer RCTs as compared with studies

of adult patients. Among them, a very large trial of children with febrile illness and hypoperfusion found excess mortality when either an albumin bolus or a crystalloid bolus strategy was compared with a no bolus strategy. Given the extensive, albeit indirect, literature base in adult critical care showing no improvement in mortality or other important outcomes and the above large trial in children suggesting excess mortality with a front-line albumin bolus strategy, pediatric intensivists probably should not use albumin as a first-line treatment outside of a clinical trial for severe infections in critically ill children. Because most children enrolled in these RCTs had malaria, it is uncertain if the results are applicable to all critically ill children with infections or the broader pediatric critical care population. In addition, the increased mortality in the Fluid Expansion as Supportive Therapy trial may be the result of the bolus administration, rather than the type of fluid, with substudies of the Fluid Expansion as Supportive Therapy trial showing that the bolus of either fluid type was associated with higher rates of cardiovascular collapse.⁵⁰

Clinical Setting 3: Neonates in Critical Care

Recommendation 5: In preterm neonates (≤ 36 weeks) with low serum albumin levels and respiratory distress, intravenous albumin is not suggested to improve respiratory function (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

Recommendation 6: In preterm neonates (≤ 32 weeks or $\leq 1,500$ g) with or without hypoperfusion, intravenous albumin is not suggested for volume replacement (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

Evidence Summary: A Cochrane systematic review evaluated the use of albumin in preterm neonates (≤ 36 weeks' gestation at birth) with hypoalbuminemia (two RCTs enrolling 64 preterm neonates).⁵¹ Only one study reported mortality rates and no difference was found. No other important differences in outcomes were observed. A Cochrane systematic review of RCTs of early volume expansion compared normal saline, plasma, albumin, plasma substitutes, or blood with no treatment or another fluid treatment in preterm neonates (≤ 32 weeks or $\leq 1,500$ g).⁵² Early volume expansion was defined as > 10 mL/kg of body weight in the first 3 days. The studies included variable indications for the administration of IV fluids. Eight studies were identified, with four studies evaluating albumin with a comparative arm (two vs normal saline, one vs plasma,

and one vs no treatment). The two studies (N = 102 and N = 63) comparing 5% albumin with normal saline in hypotensive infants found no difference in mortality (RR, 1.02; 95% CI, 0.50-2.06) or any other patient-important outcomes. The one study (N = 25) comparing 20% albumin with no treatment in normotensive infants also found no difference in mortality (RR, 0.92; 95% CI, 0.23-3.72). Finally, one trial (N = 20) in hypotensive infants compared plasma with albumin and found no difference in duration of ventilation (mortality not reported). Since the publication of these two Cochrane reviews, a single RCT (N = 33) was identified comparing 5% albumin with normal saline (both 10 mL/kg) for term infants with dehydration, metabolic acidosis, and diarrhea and found no differences in outcomes.⁵³

Rationale for Recommendations: Few RCTs have evaluated the impact of albumin compared with other alternative fluids in preterm or term neonates with either hypoalbuminemia or hypovolemia. Very little evidence is available in the literature to guide the use of albumin in term neonates. All trials in the two systematic reviews included small numbers of neonates, preventing any definitive conclusions. Indirect evidence from the adult and pediatric literature, the costs of albumin, and the lack of trials assessing the potential harms of albumin should be considered when including albumin in neonatal fluid protocols.

Clinical Setting 4: Patients Undergoing Kidney Replacement Therapy

Recommendation: Recommendation 7: In patients undergoing kidney replacement therapy, intravenous albumin is not suggested for prevention or treatment of intradialytic hypotension or for improving ultrafiltration (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

Evidence Summary: A single Cochrane systematic review was identified evaluating the use of albumin, compared with an alternative strategy, for the treatment of intradialytic hypotension.⁵⁴ The review identified a single (N = 45) randomized crossover trial of 5% albumin compared with normal saline and did not find a difference in the primary outcome (percentage target ultrafiltration achieved) or other clinical outcomes.⁵⁵ Two small crossover trials identified in this review evaluated 20% albumin as compared with gelatin (N = 10) and a three-arm study compared 20% albumin with both saline and hydroxyethyl starch (N = 10).^{56,57} These RCTs suggested that BP was maintained better

with albumin vs other fluid, but found no improvements in other outcomes, including improving ultrafiltration. Finally, a 2021 randomized crossover trial involving 65 hospitalized patients requiring hemodialysis with serum albumin levels of < 30 g/L⁵⁸ found that hypotension, lowest intradialytic systolic BP, and ultrafiltration rate were improved with 25% albumin compared with saline.

Rationale for Recommendation: Intradialytic hypotension and fluid overload are experienced commonly during kidney replacement therapy.^{59,60} Patients with intradialytic hypotension are at greater risk of morbidity and mortality.⁶¹ Given the costs of albumin, the need for thrice weekly treatment for patients receiving maintenance hemodialysis, and the lack of evidence to support superiority over less costly fluid alternatives, alternative fluids or treatments need to be considered. The annual cost of 25 g of albumin given with thrice-weekly maintenance dialysis is estimated at \$20,000 per patient (United States dollars). Midodrine (an oral vasopressor) given alone or in combination with use of a high dialysate calcium concentration and lower dialysate temperature has been explored as a therapeutic option to mitigate intradialytic hypotension.⁶²⁻⁶⁴ In patients prescribed kidney replacement therapy, higher dialysate calcium, lower dialysate temperature, individualized ultrafiltration rates, or a combination of these strategies may mitigate intradialytic hypotension.⁶⁵⁻⁶⁷ Further studies are needed to understand the pathophysiology of intradialytic hypotension⁶⁸ to determine if albumin prevents intradialytic hypotension or improves ultrafiltration,⁶⁹ mitigates associated symptoms, or improves patient-important outcomes.

Clinical Setting 5: Patients Undergoing Cardiac or Vascular Surgery

Recommendations: Recommendation 8: In adult patients undergoing cardiovascular surgery, intravenous albumin is not suggested for priming the cardiovascular bypass circuit or volume replacement (Conditional Recommendation, Moderate Certainty of Evidence of Effect).

Recommendation 9: In pediatric patients undergoing cardiovascular surgery, intravenous albumin is not suggested for priming the cardiovascular bypass circuit or volume replacement (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

Evidence Summary: A systematic review and meta-analysis of RCTs in pediatric and adult patients undergoing cardiovascular surgery was performed.¹⁹ We identified 43 randomized studies (N = 3,862), comparing albumin with gelatin, starches, or crystalloid solutions for priming the cardiopulmonary bypass circuit, volume expansion, or both. The majority of the trials were conducted in patients undergoing on-pump cardiac surgery, with the exception of two RCTs conducted in patients undergoing off-pump cardiac surgery.^{70,71}

Albumin infusion did not result in a lower mortality rate when compared with other fluids (risk difference, 0.00; 95% CI, -0.01 to 0.01; N = 2,711). No differences were found for the rates of kidney failure (risk difference, 0.01; 95% CI, -0.01 to 0.03; N = 1,703), blood loss (mean difference [MD], -0.04 L; 95% CI, -0.04 to 0.01 L), ICU length of stay (MD, -0.12 days; 95% CI, -0.31 to 0.06 days; N = 1,371), hospital length of stay (MD, 0.02 days; 95% CI, -0.95 to 1.00 days; N = 870), blood component use (MD, 0.03 L; 95% CI, -0.03 to 0.08 L; N = 1,547), or cardiac index (MD, 0.07 L/min/m²; 95% CI, -0.10 to 0.25 L/min/m²; N = 499). Fluid balance was lower with albumin compared with alternative solutions (MD, -0.55 L; 95% CI, -1.06 to -0.40 L; N = 450). The largest trial enrolled 1,386 patients and compared 4% albumin (20% albumin diluted in Ringer's lactate) with Ringer's lactate for both the pump prime and for fluid resuscitation⁷²; albumin-treated patients showed higher rates of bleeding, re sternotomy, and infection.

Rationale for Recommendations: Despite the common use of albumin during cardiovascular surgery,⁷³ little evidence supports the use of albumin to improve patient outcomes. The largest study to date performed in 1,386 patients at a single center, Albumin in Cardiac Surgery,⁷² found increased morbidity when albumin was compared with Ringer's lactate. Albumin in Cardiac Surgery was performed predominantly in low-risk cardiac surgery, and therefore, its role in improving outcomes in high-risk cardiac surgery has yet to be studied (a 590-patient RCT is underway, Albumin in Cardiac Surgery Australia; Identifier, ACTRN12619001355167).⁷⁴

Clinical Setting 6: Patients With Cirrhosis

Recommendations: Recommendation 10: In patients with cirrhosis and ascites undergoing large-volume paracentesis (> 5 L), intravenous albumin is suggested to prevent paracentesis-induced circulatory

dysfunction (Conditional Recommendation, Very Low Certainty of Evidence of Effect).

Recommendation 11: In patients with cirrhosis and spontaneous bacterial peritonitis, intravenous albumin is suggested to reduce mortality (Conditional Recommendation, Low Certainty of Evidence of Effect).

Recommendation 12: In patients with cirrhosis and extraperitoneal infections, intravenous albumin is not suggested to reduce mortality or kidney failure (Conditional Recommendation, Low Certainty of Evidence of Effect).

Recommendation 13: In hospitalized patients with decompensated cirrhosis with hypoalbuminemia (< 30 g/L), repeated intravenous albumin to increase albumin levels to > 30 g/L is not suggested to reduce infection, kidney dysfunction, or death (Conditional Recommendation, Low Certainty of Evidence of Effect).

Recommendation 14: In outpatients with cirrhosis and uncomplicated ascites despite diuretic therapy, intravenous albumin is not routinely suggested to reduce complications associated with cirrhosis (Conditional Recommendation, Low Certainty of Evidence of Effect).

Evidence Summary: We identified a 2019 Cochrane systematic review including 27 RCTs (N = 1,592) examining the use of any plasma volume expanders in patients with cirrhosis undergoing paracentesis.⁷⁵ In general, enrolled patients were undergoing large-volume paracentesis (> 5 L), and the most commonly used albumin doses were either 6 to 8 g of albumin per 1 L of fluid removed or a standard dose of 20 to 40 g. Compared with no plasma expander, no statistically significant effect of using hyperoncotic (20%-25%) albumin on mortality (RR, 0.52; 95% CI, 0.06-4.83), kidney impairment (RR, 0.32; 95% CI, 0.02-5.88), or recurrence of ascites (RR, 1.3; 95% CI, 0.49-3.42) was found. Compared with hyperoncotic albumin, use of other fluids showed uncertain effects on mortality (RR, 1.03; 95% CI, 0.82-1.30), kidney impairment (RR, 1.17; 95% CI, 0.71-1.91), and recurrence of ascites (RR, 1.14; 95% CI, 0.96-1.36). Paracentesis-induced circulatory dysfunction was more frequent with nonalbumin plasma expanders (RR, 1.98; 95% CI, 1.31-2.99) compared with albumin. A 2020 systematic review focused on the impact of different therapies (albumin, other fluids, vasoactive drugs) on the rate of postparacentesis circulatory dysfunction and identified nine RCTs (N = 620).⁷⁶ Albumin at a dose of 8 g/L was found to be

superior to other volume expanders for the prevention of postparacentesis circulatory dysfunction (rise in plasma renin activity by $\geq 50\%$ of baseline). Similar to the Cochrane review, uncertainty regarding the role of albumin as compared with alternative treatments was noted for the prevention of complications after paracentesis. RCTs comparing high-dose albumin (6-8 g/L of ascitic fluid removed) with low-dose albumin (2-4 g/L of ascitic fluid removed) found no difference in the rate of paracentesis associated circulatory dysfunction, although uncertainty exists regarding the risk to benefit profile of the two doses, given the small sample size (two studies [N = 120]; RR, 1.00; 95% CI, 0.22-4.49).⁷⁵

Two systematic reviews (in 2013 and 2020) identified five open-label RCTs in patients with spontaneous bacterial peritonitis both using variable doses and duration of hyperoncotic albumin (eg, 0.5-1.0 g/kg every 3 days for a maximum of 21 days; 1.5 g/kg on day 1 and 1.0 g/kg on day 3).^{77,78} Albumin reduced the rate of kidney impairment (OR, 0.21; 95% CI, 0.11-0.42) and mortality (OR, 0.34; 95% CI, 0.19-0.60).⁷⁸ The largest randomized trial⁷⁹ randomized 126 patients to albumin (plus antibiotics) or antibiotics alone (without an explicit fluid resuscitation for the control arm). Patients treated with albumin showed lower rates of kidney impairment (10% vs 33%; $P = .002$) and in-hospital mortality (10% vs 29%; $P = .01$). The second largest trial randomized 118 patients to albumin (plus antibiotics) or antibiotics alone (without an explicit fluid resuscitation for the control arm).⁸⁰ The primary end point of in-hospital mortality was not different (13% albumin vs 11% antibiotics alone; $P = .66$).

A 2020 systematic review and meta-analysis of RCTs comparing albumin plus antibiotics with antibiotics alone in patients with cirrhosis and extraperitoneal infections found no effect on mortality or kidney impairment, but observed higher rates of pulmonary edema with albumin (three studies [N = 406]; OR, 5.17; 95% CI, 1.62-16.47).⁸¹ A 2019 systematic review in the same population also found no improvements in outcomes when albumin with antibiotics was compared with antibiotics alone.⁸² Subsequent to this 2020 systematic review, two randomized trials have been published (308 and 100 patients, respectively) comparing albumin with crystalloid in patients with cirrhosis and hypotension resulting from sepsis.^{83,84} Both trials included patients with sepsis from all causes, including a small proportion (20%-25%) with spontaneous bacterial peritonitis. In the larger trial, survival at 7 days was not improved in the albumin-

treated patients (saline, 39.0% vs albumin, 43.5%; $P = .42$, Fisher exact test); longer-term outcomes were not reported. In the second, smaller trial, albumin was superior to crystalloid for reversal of hypotension without initiation of vasopressors at 3 h (22% vs 62%; $P < .001$), but this improvement in hemodynamics did not reduce the rate of dialysis, length of stay, or mortality at 28 days.⁸⁴ In the latter trial, patients randomized to albumin vs crystalloid showed higher rates of circulatory overload.

We identified one RCT, Albumin to Prevent Infection in Chronic Liver Failure (N = 777), that evaluated the role of hyperoncotic albumin to target an albumin level of > 30 g/L (median, 200 g albumin over 14 days) as compared with no albumin in hospitalized patients with decompensated cirrhosis and hypoalbuminemia (< 30 g/L).¹⁰ No difference was found in the primary end point (composite of new infections, kidney dysfunction, or death between days 3 and 15) between groups (OR, 0.98; 95% CI, 0.71-1.33). More severe or life-threatening serious adverse events were reported in the albumin-treated patients, primarily a numerical increase in pulmonary edema.

A 2021 systematic review was identified that evaluated albumin in patients with hepatic encephalopathy.⁸⁵ The review identified two RCTs (N = 176). Albumin resulted in a reduction in hepatic encephalopathy (RR, 0.60; 95% CI, 0.38-0.95) and mortality (RR, 0.54; 95% CI, 0.33-0.90). The first open-label trial randomized 120 patients to albumin (1.5 g/kg/d for up to 10 days and lactulose) vs lactulose alone.⁸⁶ Complete resolution of hepatic encephalopathy by day 10 was seen in 75% of the albumin-lactulose group vs 53% of the lactulose alone group ($P = .03$). Mortality was 18% in the albumin-lactulose group vs 32% in the lactulose alone group at day 10 ($P = .04$). The second masked RCT of albumin (1.5 g/kg on day 1 and 1.0 g/kg on day 3) vs normal saline enrolled 56 patients.⁸⁷ No difference was found in the rate of resolution of hepatic encephalopathy at day 4 (albumin, 58% vs saline, 53%; $P = .7$). The mortality rate was lower in albumin-treated patients at 90 days (23% vs 47%) and transplant-free survival was improved ($P = .02$, Kaplan-Meier estimate). A 2021 systematic review of RCTs and cohort studies evaluating the role of albumin in prevention and treatment suggested that albumin may assist with the resolution or prevention of hepatic encephalopathy and may reduce mortality⁸⁸; only the two RCTs identified in the aforementioned systematic review were identified for the treatment of hepatic

encephalopathy.⁸⁵ In the subsequent large Albumin to Prevent Infection in Chronic Liver Failure trial,¹⁰ the subgroup (N = 149) of patients admitted with hepatic encephalopathy randomized to albumin as compared with placebo did not show an improvement in the composite end point of new infections, kidney dysfunction, or death between days 3 and 15 (adjusted OR, 0.91; 95% CI, 0.44-1.86). Subsequent to the two systematic reviews, a single RCT was identified that randomized 48 outpatients with hepatic encephalopathy to weekly hyperoncotic albumin for 5 weeks as compared with saline and found improvements in cognitive function with albumin.⁸⁹

A 2021 systematic review of RCTs evaluating outpatient hyperoncotic albumin for patients with cirrhosis and ascites identified five trials (N = 716).⁹⁰ The systematic review found no difference in mortality at 12 to 36 months (RR, 0.88; 95% CI, 0.67-1.14) or any other outcome, with the exception of reducing the need for paracentesis (RR, 0.56; 95% CI, 0.48-0.67). Two large randomized trials were included in the review.^{91,92} The first unmasked trial randomized 440 patients with cirrhosis and uncomplicated, persistent ascites despite diuretic therapy to albumin (40 g twice weekly for 2 weeks and then 40 g weekly for up to 18 months) or no albumin.⁹² Patients randomized to albumin experienced longer time to first paracentesis; required fewer paracenteses; were less likely to demonstrate hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, nonperitonitis infections, hyponatremia, or episodes of kidney dysfunction; experienced fewer days in hospital; and showed lower all-cause mortality (77% vs 66% survival at 18 months; hazard ratio, 0.62; 95% CI, 0.40-0.95). The most important limitation of this study is that the albumin-treated patients underwent weekly health care interactions and the control group did not, raising the concern that the observed differences may have been the result of increased health care exposure. The second trial randomized 196 outpatients with cirrhosis and ascites awaiting liver transplantation to oral midodrine and albumin as compared with placebo tablets and a 0.9% saline infusion and found no difference in patient outcomes.⁹¹ The dose of albumin given as part of the intervention was lower (40 g every 15 days). The study improved on the methodology of the first trial by achieving masking to treatment assignment and ensuring the same health care exposure in both study groups.

Rationale for Recommendations: Approximately one-third of albumin is used for patients with cirrhosis,⁸ and although this practice is exceedingly common, the certainty of evidence supporting this therapy in this population is insufficient to allow for strong recommendations. Although the use of albumin for large-volume paracentesis is a commonly accepted clinical practice and is endorsed by guidelines,⁹³⁻⁹⁵ the reported trials have important limitations that affect the certainty in outcomes. These trials included a small number of patients and findings for most patient-important outcomes (mortality, kidney dysfunction) were imprecise, leaving residual uncertainty regarding true clinical benefits and harms. Albumin, as compared with other fluid expanders, may be superior for the prevention of paracentesis-induced circulatory dysfunction (rise in serum renin level on the sixth day after paracentesis), but whether this translates to improvement in patient-important outcomes is less certain. Plasma renin levels are predictive of greater morbidity in patients with cirrhosis.⁹⁶⁻⁹⁸ The panel suggested continuing this commonly accepted practice for patients undergoing large-volume paracentesis, but believed the data supported only a conditional recommendation based on low-quality evidence. Further trials are needed urgently to clarify if albumin improves patient important outcomes, to elucidate the optimal dosing strategy, to further the understanding of the safety profile of the treatment, and to evaluate alternative fluids and therapies. It is unclear if improving laboratory measures of paracentesis-induced circulatory dysfunction will translate into reductions in renal failure, hospital admission, or other patient-important outcomes. The panel also highlighted the need to personalize the use of albumin, the dose after paracentesis, or both, considering the patient's baseline creatinine, volume of ascites removed, and history of hypotensive symptoms after prior procedures.

Similarly, the role of albumin for improving outcomes in patients with spontaneous bacterial peritonitis is unclear. The trial data specific to this patient population are limited.^{78,79} The two largest RCTs failed to provide an explicit fluid resuscitation protocol for the patients randomized to no albumin, raising the concern for underresuscitation in the control arms of both studies. When similar albumin dosing strategies were used in trials examining patients with cirrhosis and extraperitoneal infections, no benefit was seen and concern for harm was expressed.⁸¹ The panel suggested the use of albumin for spontaneous bacterial peritonitis

(conditional recommendation), but raised concerns regarding the dosing protocol used in two of the four trials and the risk of fluid overload (1.5 g/kg on day 1 and 1.0 g/kg on day 3) and the lack of data suggesting this specific regimen is beneficial compared with alternative dosing (eg, lower dose daily for 3 days). The panel also considered the lack of clarity on whether albumin is necessary for all patients with spontaneous bacterial peritonitis or whether it could be used selectively (ie, patients at high risk of kidney failure or death: serum bilirubin > 4 mg/dL or serum creatinine >1 mg/dL). Additional studies are necessary to address dosing, to address the benefit for patients with and without kidney impairment, and to clarify the risks of adverse events. The panel also noted that not all physicians currently adhere to the trial dosing strategy,^{99,100} although it continues to be recommended in current guidelines.^{93,94} A careful assessment of the patient's volume status, cardiovascular status, and degree of kidney impairment before transfusion is advised and the dose, frequency, or both being modified accordingly. In contrast, the RCTs find no support for the use of albumin in patients with cirrhosis and extraperitoneal infections.⁸¹

In the setting of patients admitted with decompensated cirrhosis and hypoalbuminemia, this guideline is informed by an RCT involving 777 patients¹⁰ that found no improvement in patient important outcomes and a concern for increased adverse events. This led the panel to suggest conditionally against the use of albumin in this setting.

Although a 2021 systematic review of two small RCTs suggested a benefit for facilitating resolution of hepatic encephalopathy and reducing mortality,⁸⁵ the subgroup of patients in the Albumin to Prevent Infection in Chronic Liver Failure study admitted with hepatic encephalopathy did not show improvements in mortality.¹⁰ The panel had uncertainty regarding the benefit of albumin in this patient population and few data on the risks of the treatment, and therefore abstained from making a statement on the role of albumin in this setting until further adequately powered RCTs are conducted.

In nonhospitalized patients with cirrhosis and persistent ascites despite optimized medical management, the role of weekly or biweekly albumin infusions remains unclear. One unmasked study of weekly albumin infusions found improvements in outcomes,⁹² but this was not replicated in a placebo-controlled trial that

examined biweekly albumin infusions.⁹¹ The latter trial enrolled a smaller number of patients and used a lower dose, and therefore may have failed to detect a difference in outcomes. The panel reported residual uncertainty regarding the benefit of this treatment and given this, suggested against its routine use until additional RCTs have been conducted. The use of weekly albumin in this patient population would have considerable impacts on patients, would require chronic IV access, would have considerable impacts on outpatient infusion clinics, and would require a dependable supply of albumin. Although the unmasked trial reported cost-effectiveness,⁹² additional masked trials with cost-effectiveness analyses are necessary to improve precision and generalizability and to inform future guidelines.

A 2020¹⁰¹ and a 2019¹⁰² systematic review on the treatment of hepatorenal syndrome did not identify any randomized trials examining albumin for these patients as compared with placebo or no treatment. Rather, all trials examining this patient population uniformly have administered albumin in both treatment and control arms and have compared vasoconstrictor agents (eg, terlipressin, midodrine) with placebo infusions. Hence, no recommendations regarding the use of albumin for patients with cirrhosis and hepatorenal syndrome could be made.

Discussion

The evidence-base guiding the use of intravenous albumin was largely instigated by the Cochrane Injuries Group Albumin systematic review in 1998,¹⁰³ which raised the concern for harm from albumin. Subsequent to this publication, RCTs comparing albumin with other fluid treatments in multiple patient populations were completed. These trials failed to confirm the concerns for higher mortality rates in albumin-treated patients. The ICTMG undertook these evidence-based albumin guidelines because no comprehensive evidence-based guidelines had been published yet. The goal of the guidelines is to provide clinicians with recommendations and evidence summaries for common indications for albumin, information on ongoing clinical trials, and areas in need of additional research. The ICTMG guidelines group suggested that albumin should not be used routinely for neonatal, pediatric, and adult patients in critical care; for patients experiencing intradialytic hypotension; for patients undergoing cardiovascular surgery; for admitted patients with cirrhosis for treatment (or correction) of hypoalbuminemia or extraperitoneal infections; or for

TABLE 2] Ongoing, Large Randomized Clinical Trials Comparing IV Albumin With Alternative Treatments

Trial	Trial Details
Effect of Albumin Administration in Hypoalbuminemic Hospitalized Patients With Community-Acquired Pneumonia (ClinicalTrials.gov Identifier: NCT04071041)	Three hundred sixty patients with community-acquired pneumonia. Will compare the outcomes of patients treated with albumin (100 mL of 20% every 12 h for 4 d) compared with standard of care. The primary outcome is the proportion of patients with clinical stability at day 5 of hospitalization.
Albumin Replacement Therapy in Septic Shock (ClinicalTrials.gov Identifier: NCT03869385)	One thousand six hundred sixty-two patients with septic shock randomized to 20% albumin or usual care fluids. The primary outcome is 90-d all-cause mortality.
Albumin in Cardiac Surgery Australian (Postoperative 20% Albumin vs Standard Care and Acute Kidney Injury After High-Risk Cardiac Surgery) (Australian New Zealand Clinical Trials Registry Identifier: ACTRN1261900135516703)	Five hundred ninety patients undergoing high-risk cardiac surgery (combined procedure or eGFR < 60 mL/min/1.73 m ²) and will compare 20% albumin infusion with standard care. The study fluid will be administered on arrival in the ICU and continued for 15 h. The primary outcome is the proportion of patients who demonstrate acute kidney injury in both groups.
Effects of Long-Term Administration of Human Albumin in Subjects With Decompensated Cirrhosis and Ascites (ClinicalTrials.gov Identifier: NCT03451292)	Four hundred ten outpatients with decompensated cirrhosis and ascites will evaluate open-label hyperoncotic albumin as compared with standard medical management (dose of 1.5 g/kg every 10 d for up to 12 mo). The primary outcome is the time to liver transplantation or death at 12 mo.
Albumin to Enhance Recovery After Acute Kidney Injury (ClinicalTrials.gov Identifier: NCT04705896)	Eight hundred fifty-six critically ill patients with acute kidney injury requiring kidney replacement therapy will be randomized to hyperoncotic albumin (25%; 100 mL × two doses) compared with normal saline placebo doses, given with all kidney replacement therapy treatments in the ICU for up to 14 d. The primary outcome is organ support-free days at 28 d after initiation of kidney replacement therapy.

eGFR = estimated glomerular filtration rate.

outpatients with ascites. The ICTMG guidelines conditionally recommended the use of albumin for patients with cirrhosis undergoing large-volume paracentesis or with spontaneous bacterial peritonitis. One of 14 recommendations was a strong recommendation based on more definitive clinical trial evidence, but most of the recommendations were conditional based on low- or very low-quality evidence because of the paucity or conflicting RCT evidence, highlighting the need for ongoing research. The implementation of the guidelines will help to reduce the unnecessary transfusion of albumin and the variability between hospitals.

Guidelines for select patient populations have been published in some jurisdictions, particularly in patients with cirrhosis. The British Society for Gastroenterology published guidelines on the management of patients with cirrhosis and ascites.⁹⁴ They recommend albumin for patients undergoing large-volume paracentesis or with spontaneous bacterial peritonitis. The French Society of

Anesthesiology and Critical Care Medicine and the French Association for the Study of the Liver jointly released guidelines for the management of liver failure in critical care.¹⁰⁴ They recommend the use of albumin for hepatorenal syndrome (with terlipressin), large-volume paracentesis (> 5 L), and spontaneous bacterial peritonitis. The American Association for the Study of Liver Disease guidelines from 2021⁹³ recommend the use of albumin for large-volume paracentesis, severe muscle cramps, severe hyponatremia (sodium < 120 mEq/L), spontaneous bacterial peritonitis, and hepatorenal syndrome. The Italian Association for the Study of Liver Disease and the Italian Society for Transfusion Medicine and Immunohematology guidelines update from 2020 include the use of albumin for ascites requiring moderate doses of diuretics as an outpatient treatment.¹⁰⁵ This was an update from their 2016 guidelines that also recommended the use of albumin in patients requiring large-volume paracentesis, with spontaneous bacterial peritonitis, or with hepatorenal syndrome.¹⁰⁶ Similarly, the European Association for the Study of the Liver 2018 guidelines detailing the

management of patients with decompensated cirrhosis recommended albumin for patients undergoing large-volume paracentesis, with spontaneous bacterial peritonitis, with acute kidney injury without known cause, or with hepatorenal syndrome.⁹⁵ The ICTMG guidelines are concordant with these guidelines for recommending albumin for large-volume paracentesis and spontaneous bacterial peritonitis, but report insufficient evidence to support its use in other settings. The use of albumin for hepatorenal syndrome, in conjunction with terlipressin, was recommended commonly in prior guidelines, likely based on both expert opinion and the fact that randomized trials used albumin in both treatment arms (albumin vs albumin plus terlipressin). We elected to refrain from making a recommendation without clinical trial evidence to support its use and highlight that this indication needs further study.

Guidelines from the Association of the Scientific Medical Societies in Germany published perioperative fluid guidelines for children in 2017.¹⁰⁷ They recommended that colloids, including albumin, be used during surgery where crystalloids alone are not sufficiently effective and blood products are not indicated. In 2021, the Surviving Sepsis Campaign guidelines recommended the use of albumin in the fluid resuscitation of severe sepsis and septic shock when patients required large volumes of crystalloids.⁴⁴

Five RCTs that will enroll an additional 4,864 patients are ongoing and are expected to provide additional clarity on the role of albumin (Table 2). These trials will add clarity to the ICTMG recommendations for intensive care patients with infection, high-risk adult cardiac surgery, patients with acute kidney injury receiving kidney replacement therapy, and outpatients with decompensated cirrhosis.

This guideline is limited by the uncertainty in the evidence identified in the literature search for many different patient populations and the limitation of the search to the English language. The lack of comparative dosing strategies leaves uncertainty on the choice between 4% to 5% and 20% to 25% albumin formulations, the dose for each indication, the risk of fluid overload, and the dosing schedules. The guidelines are limited to common uses of albumin and cannot address every possible patient scenario where albumin has been used in RCTs. The published studies often did not collect or did report adverse reactions from IV albumin, or both, limiting the conclusions regarding the potential risks of albumin. These guidelines improve on those previously published

because of the rigorous methodology, broad scope of the recommendations, inclusion of a patient representative in the guideline process, and broad community consultation process. The guidelines will be supported by tools developed by the ICTMG Dissemination and Implementation Committee to assist hospitals with aligning practice with the evidence.

Future research is needed in multiple clinical settings including: (1) the role and timing of albumin in patients with sepsis or other conditions with insufficient response to crystalloids, (2) the role of albumin in patients undergoing surgery, (3) the role of albumin for intradialytic hypotension, and (4) the role of albumin in all indications for patients with cirrhosis. Research also is needed to understand therapeutic targets of albumin resuscitation (hemodynamic, urinary output, laboratory), the optimal formulation, and the dosing strategy. The risk of IV albumin infusions needs further investigation to allow clinicians to weigh the risk to benefit profile appropriately. Studies should include patient-important outcomes, rather than focusing on short-term physiologic outcomes.

Funding/Support

Funded by the Ontario Regional Blood Coordinating Network and the International Collaboration for Transfusion Medicine Guidelines. The ICTMG receives funding from Canadian Blood Services (funded by the federal government [Health Canada] and the provincial and territorial ministries of health).

Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: J. C. receives research support from Canadian Blood Services and Octapharma and serves on the board of directors of the Canadian Hematology Society. N. J. S. is a director of the National Board of Echocardiography and receives royalties from Wolters Kluwer. A. B. is an employee of Canadian Blood Services. H. K. is an employee of Canadian Blood Services. E. G. C. receives research funding (related to albumin) from Department of Medicine, The Ottawa Hospital and University of Ottawa, The Ottawa Hospital Academic Medical Organization, Kidney Foundation of Canada, and Physician Services Incorporated Foundation; is an editorial board member of the *Canadian Journal of Kidney Health and Disease*; and is a member of the Contrast-Associated Acute Kidney Injury guideline panel for the Canadian Association of Radiologists. B. R. is a guideline methodologist for American Thoracic Society, the Society of Critical Care Medicine, and Canadian Blood Services; is the Knowledge

Translation director for Canadian Critical Care Society; is the grants and manuscripts chair for Canadian Critical Care Trials Group, and in a guideline group member for multiple guidelines. S. R. B. is the chair of the Clinical Pharmacy and Pharmacology section for the Society of Critical Care Medicine (not albumin use related), is a paid consultant for Wolters Kluwer (Lexicomp), is a Society of Critical Care Medicine Social Media Committee member, is a Surviving Sepsis Campaign Research Committee member, and has received a research grant from the National Institute of General Medicine Sciences. L. C. is a guideline group member for the British Society of Gastroenterology (management of ascites in liver cirrhosis), is involved in peer-reviewed publications (multiple topics including relevant to albumin use), received lecturer honoraria for the Canadian Liver Conference 2022, is a hepatology consultant for the Royal Free Hospital London, and is a Liver Committee member of the British Society of Gastroenterology. M. F. receives consultant fees from Cerus Corporation and Biocogniv, Inc.; has received honoraria from Grifols (none were albumin related); is a board member for Project Santa Fe Foundation and the American Board of Pathology; is the Histocompatibility and Identity Testing Committee Chair for College of American Pathologists; is co-team leader for the Biomedical Excellence for Safer Transfusion (BEST) Collaborative; and is the Editorial Committee co-chair for the ICTMG. R. J. has received fellowship funding from Canadian Blood Services, is an employee of William Osler Health System and the University of Cincinnati Medical Center, and is a panel member for ICTMG Platelet Utilization guideline development group. K. P. serves on the board of directors in North America for International Society for Blood Transfusion (ISBT), is a 2023 Association for the Advancement of Blood and Biotherapies (AABB) Red Blood Cells (RBC) guideline panel member, and is a member of the National Advisory Committee of Blood and Blood Products. P. S. S. is director of the Canadian Neonatal Network, director of the Canadian Preterm Birth Network, director of the International Network to Evaluate Outcomes of Neonates, and an external advisory board member for the Canadian Perinatal Surveillance system (none related to albumin manufacturers). H. S. is a consultant for Terumo and Cerus (not albumin related). Z. M. S. is a consultant and advisory board member of Grifols, Fresenius Kabi, and Novartis; receives research funding from Erydel and Fresenius Kabi; serves on the board of directors for the BEST Collaborative and International Council for Commonality in Blood Banking Automation (ICCBBA), Inc.; is the AABB Committee Chair; is vice chair, treasurer,

and committee chair for ICCBBA, Inc.; is treasurer for BEST Collaborative; and has a family member (child) who is a summer intern with Grifols, Inc. T. T. is a paid consultant for Inter-View Partners France, A+A, Bayer HealthCare SAS, BVA, Axess Research, and All Global; has received honoraria from AbbeVie, Gilead Sciences, Advanz Pharma France, and Ipsen Pharma; in the principal investigator of randomized controlled trial Albumin Administration in Cirrhotic Patients With Bacterial Infection and a Systemic Inflammatory Response Syndrome Unrelated to Spontaneous Bacterial Peritonitis (ALB-CIRINF) (ClinicalTrials.gov Identifier, NCT01359813) published in 2015; and is a member of the Liver Cirrhosis-related Complications (LCC)-International Special Interest Group. B. W. is a resident physician at Loma Linda University Medical Center. S. S. is chair of the ICTMG and is an employee of National Health Service Blood and Transplant (NHSBT), a blood service operator in England. However, NHSBT is not a manufacturer of the intervention. N. S. is an employee of Canadian Blood Services; receives research funding from the Canadian Institutes for Health Research (Transfusion Requirements in Younger Patients Undergoing Cardiac Surgery [TRICS-IV] RBC transfusion in young cardiac patients; not related to albumin); is an advisory board member for Fresenius Kabius and Janssen; has received honoraria from the International Financial Corporation of the World Bank, Canadian Blood Services, and Ferring; and serves on the PKD guideline panel and ICTMG guideline panels (Fetal Neonatal Alloimmune Thrombocytopenia [FNAIT], Hemolytic Disease of the Newborn [HDN], platelet transfusion, RBC specifications). None declared (D. F., S. A., M. N., C. P., S. R.). See [Appendix 8](#) for the ICTMG Conflict of Interest Policy.

Acknowledgments

Author contributions: All authors had access to all the included evidence base for the guideline, took responsibility for the guideline statements, had authority over manuscript preparation, and the decision to submit the manuscript for publication. All authors contributed to study concept and design. All authors contributed to analysis and interpretation of the data. J. C., N. J. S., E. G. C., B. R., and N. S. contributed to drafting the article. All authors contributed to critical revision of the article for important intellectual content. All authors contributed to final approval of the article. H. K. contributed administrative, technical, or logistical support. J. C., N. J. S., and N. S. contributed to collection and assembly of data.

*** International Collaboration for Transfusion Medicine Guidelines Intravenous Albumin Group Collaborators:** Jerome Flores, PharmD, University Health Network, Toronto; Stéfanie Frappier, University of Ottawa, Ottawa; Yvette Hou, Trillium Health Partners; Lilly Jean-Pierre, Carleton University; Danny Jomaa, MSc, MBI, School of Medicine, Queen's University, Kingston; Monisha Kabir, MSc, Bruyère Research Institute, Ottawa; Leo Kadota, MD, Faculty of Medicine, University of British Columbia; Michelle Lam, CHEO ED SUPPORT Program, Carleton University; David A. Ripsman, Department of Neurology, Faculty of Medicine, University of British Columbia; Ryan

Sandarage, Faculty of Medicine, University of British Columbia; Emilian Staykov, BSc, Michael G. DeGroote School of Medicine, Hamilton; Angelica Venes, Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa; and Melissa Wan, MD, Department of Family Medicine, Queen's University, Kingston. None of the authors reports any conflicts of interest.

*** International Collaboration for Transfusion Medicine Guidelines**

Collaborators: Arwa Al Riyami, MD, Sultan Qaboos University Hospital, Oman; Shubha Allard, MD, National Health Service Blood & Transplant, United Kingdom; Melissa Brouwers, PhD, University of Ottawa, Canada; Jeannie Callum, MD, Sunnybrook Health Sciences Centre and University of Toronto, Canada; James Daly, MBBS, Australian Red Cross Lifeblood, Australia; Gregory A. Denomme, PhD, Versiti Blood Centre of Wisconsin, United States; Lise Estcourt, MB BChir, DLSHTM, DPhil, National Health Services Blood & Transplant, United Kingdom; Dean Fergusson, PhD, MHA, Ottawa Hospital Research Institute, Canada; Mark Fung, MD, PhD, University of Vermont Medical Center, United States; Laura Green, MBBS, MD (Res), National Health Service Blood & Transplant, United Kingdom; Andreas Greinacher, MD, University of Greifswald; Heather Hume, MD, University of Montreal, Canada; Rachel Jug, MD, University of Cincinnati College of Medicine, Cincinnati, OH; Richard Kaufman, MD, Brigham & Women's Hospital Adult Transfusion Service, United States; Hyungsuk Kim, MD, Seoul National University Hospital, Korea; Vernon Louw, PhD, Groote Schuur Hospital, University of Cape Town, South Africa; Tadashi Matsushita, MD, PhD, Nagoya University Hospital, Japan; Michael Murphy, MD, University of Oxford and National Health Service Blood & Transplant, United Kingdom; Joanne Pink, MBBS, Australian Red Cross Lifeblood, Australia; Susan Robinson, MBBS, Guy's and St. Thomas' NHS Foundation Trust, United Kingdom; Cynthia So-Osman, MD, PhD, Sanquin and Erasmus Medical Center, The Netherlands; Simon Stanworth, PhD, NHS Blood and Transplant and Oxford University, United Kingdom; Zbigniew M. Szczepiorkowski, MD, PhD, Dartmouth-Hitchcock Medical Center, United States; Aaron Tobian, MD, PhD, Johns Hopkins University, United States; and Erica Wood, MBBS, Monash University, Australia.

Role of sponsors: The Ontario Regional Blood Coordinating Network did not have any role in the design, analysis, and interpretation of the data or preparation, review, and approval of the manuscript.

Disclaimer: The views herein do not necessarily reflect the views of the Ontario Regional Blood Coordinating Network, Canadian Blood Services or the federal, provincial, or territorial governments of Canada.

Other contributions: The authors thank Kimberly Figures and Sophie Chargé for administrative support and Rouhi Fazalzad and Thomasin Adams Webber for assistance with the library searches.

Additional information: The e-Appendixes are available online under "Supplementary Data."

References

- Horowitz IN, Tai K. Hypoalbuminemia in critically ill children. *Arch Pediatr Adolesc Med.* 2007;161(11):1048-1052.
- Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med.* 2006;34(5):1297-1310.
- Hubner M, Mantziari S, Demartines N, Pralong F, Coti-Bertrand P, Schafer M. Postoperative albumin drop is a marker for surgical stress and a predictor for clinical outcome: a pilot study. *Gastroenterol Res Pract.* 2016;2016:8743187.
- Kaysen GA, Dubin JA, Muller HG, et al. Inflammation and reduced albumin synthesis associated with stable decline in serum albumin in hemodialysis patients. *Kidney Int.* 2004;65(4):1408-1415.
- Fleck A, Raines G, Hawker F, et al. Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. *Lancet.* 1985;1(8432):781-784.
- Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology.* 2008;109(4):723-740.
- Tarin Remohi MJ, Sanchez Arcos A, Santos Ramos B, Bautista Paloma J, Guerrero Aznar MD. Costs related to inappropriate use of albumin in Spain. *Ann Pharmacother.* 2000;34(10):1198-1205.
- Buckley MS, Knutson KD, Agarwal SK, et al. Clinical pharmacist-led impact on inappropriate albumin use and costs in the critically ill. *Ann Pharmacother.* 2020;54(2):105-112.
- Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR. Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion.* 2010;50(4):753-765.
- China L, Freemantle N, Forrest E, et al. A randomized trial of albumin infusions in hospitalized patients with cirrhosis. *N Engl J Med.* 2021;384(9):808-817.
- Thevenot T, Bureau C, Oberti F, et al. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. *J Hepatol.* 2015;62(4):822-830.
- Howard G, Downward G, Bowie D. Human serum albumin induced hypotension in the postoperative phase of cardiac surgery. *Anaesth Intensive Care.* 2001;29(6):591-594.
- Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med.* 2004;350(22):2247-2256.
- Shimode N, Yasuoka H, Kinoshita M, et al. Severe anaphylaxis after albumin infusion in a patient with abaptoglobulinemia. *Anesthesiology.* 2006;105(2):425-426.
- Warkentin TE, Ning S, Lim W. Colloid transfusion, natural anticoagulant depletion, and symmetric peripheral gangrene. *N Engl J Med.* 2020;383(16):1592-1594.
- Connelly-Smith L, Alquist CR, Aqui NA, et al. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Writing Committee of the American Society for Apheresis: the ninth special issue. *J Clin Apher.* 2023;38(2):77-278.
- Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
- Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008.
- Skubas NJ, Callum J, Bathla A, et al. International Collaboration for Transfusion Medicine Guidelines. Intravenous albumin in cardiac and vascular surgery: a systematic review and meta-analysis. *Br J Anaesth.* 2024;132(2):237-250.
- Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011;64(4):383-394.
- Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ.* 2004;328(7454):1490.
- Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *BMJ.* 2008;336(7652):1049-1051.
- Lewis SR, Pritchard MW, Evans DJ, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane Database Syst Rev.* 2018;8:CD000567.
- Perner A, Junttila E, Haney M, et al. Scandinavian clinical practice guideline on choice of fluid in resuscitation of critically ill patients with acute circulatory failure. *Acta Anaesthesiol Scand.* 2015;59(3):274-285.
- Patel A, Laffan MA, Waheed U, Brett SJ. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. *BMJ.* 2014;349:g4561.
- Jiang L, Jiang S, Zhang M, Zheng Z, Ma Y. Albumin versus other fluids for fluid resuscitation in patients with sepsis: a meta-analysis. *PLoS One.* 2014;9(12):e114666.
- Leitch A, Craig G, Sadler P. Human albumin solution resuscitation in severe sepsis and septic shock. *J Intensive Care Soc.* 2013;14(1):45-52.
- Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. *Crit Care Med.* 2011;39(2):386-391.

29. Rochwerg B, Alhazzani W, Sindi A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. *Ann Intern Med.* 2014;161(5):347-355.
30. Bansal M, Farrugia A, Balboni S, Martin G. Relative survival benefit and morbidity with fluids in severe sepsis—a network meta-analysis of alternative therapies. *Curr Drug Saf.* 2013;8(4):236-245.
31. Rochwerg B, Alhazzani W, Gibson A, et al. Fluid type and the use of renal replacement therapy in sepsis: a systematic review and network meta-analysis. *Intensive Care Med.* 2015;41(9):1561-1571.
32. Navickis RJ, Greenhalgh DG, Wilkes MM. Albumin in burn shock resuscitation: a meta-analysis of controlled clinical studies. *J Burn Care Res.* 2016;37(3):e268-e278.
33. Uhlig C, Silva PL, Deckert S, Schmitt J, de Abreu MG. Albumin versus crystalloid solutions in patients with the acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care.* 2014;18(1):R10.
34. Oczkowski SJ, Mazzetti I. Colloids to improve diuresis in critically ill patients: a systematic review. *J Intensive Care.* 2014;2:37.
35. Martin GS, Bassett P. Crystalloids vs. colloids for fluid resuscitation in the intensive care unit: a systematic review and meta-analysis. *J Crit Care.* 2019;50:144-154.
36. Tseng CH, Chen TT, Wu MY, Chan MC, Shih MC, Tu YK. Resuscitation fluid types in sepsis, surgical, and trauma patients: a systematic review and sequential network meta-analyses. *Crit Care.* 2020;24(1):693.
37. Kitsios GD, Mascari P, Ettunsi R, Gray AW. Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: a meta-analysis. *J Crit Care.* 2014;29(2):253-259.
38. Itagaki Y, Yoshida N, Banno M, Momosaki R, Yamada K, Hayakawa M. Efficacy of albumin with diuretics in mechanically ventilated patients with hypoalbuminemia: a systematic review and meta-analysis. *Medicine (Baltimore).* 2022;101(37):e30276.
39. Saw MM, Chandler B, Ho KM. Benefits and risks of using gelatin solution as a plasma expander for perioperative and critically ill patients: a meta-analysis. *Anaesth Intensive Care.* 2012;40(1):17-32.
40. Heshmati SM, Rasouli HR. Fluid resuscitation, which fluid is the best for each patient? A systematic review and meta analysis. *Iran Red Crescent Med J.* 2017;19(3):e41729.
41. Park CHL, de Almeida JP, de Oliveira GQ, et al. Lactated Ringer's versus 4% albumin on lactated Ringer's in early sepsis therapy in cancer patients: a pilot single-center randomized trial. *Crit Care Med.* 2019;47(10):e798-e805.
42. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med.* 2014;370(15):1412-1421.
43. Mahmoodpoor A, Zahedi S, Pourakbar A, et al. Efficacy of furosemide-albumin compared with furosemide in critically ill hypoalbuminemia patients admitted to intensive care unit: a prospective randomized clinical trial. *Daru.* 2020;28(1):263-269.
44. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med.* 2021;49(11):e1063-e1143.
45. Ford N, Hargreaves S, Shanks L. Mortality after fluid bolus in children with shock due to sepsis or severe infection: a systematic review and meta-analysis. *PLoS One.* 2012;7(8):e43953.
46. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med.* 2011;364(26):2483-2495.
47. Maitland K, Pamba A, English M, et al. Pre-transfusion management of children with severe malarial anaemia: a randomised controlled trial of intravascular volume expansion. *Br J Haematol.* 2005;128(3):393-400.
48. Maitland K, Pamba A, English M, et al. Randomized trial of volume expansion with albumin or saline in children with severe malaria: preliminary evidence of albumin benefit. *Clin Infect Dis.* 2005;40(4):538-545.
49. Levin M, Cunningham AJ, Wilson C, et al. Effects of saline or albumin fluid bolus in resuscitation: evidence from re-analysis of the FEAST trial. *Lancet Respir Med.* 2019;7(7):581-593.
50. Maitland K, George EC, Evans JA, et al. Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial. *BMC Med.* 2013;11:68.
51. Jardine LA, Jenkins-Manning S, Davies MW. Albumin infusion for low serum albumin in preterm newborn infants. *Cochrane Database Syst Rev.* 2004;(3):CD004208.
52. Osborn DA, Evans N. Early volume expansion for prevention of morbidity and mortality in very preterm infants. *Cochrane Database Syst Rev.* 2004;(2):CD002055.
53. Han JJ, Yim HE, Lee JH, et al. Albumin versus normal saline for dehydrated term infants with metabolic acidosis due to acute diarrhea. *J Perinatol.* 2009;29(6):444-447.
54. Fortin PM, Bassett K, Musini VM. Human albumin for intradialytic hypotension in haemodialysis patients. *Cochrane Database Syst Rev.* 2010;(11):CD006758.
55. Knoll GA, Grabowski JA, Dervin GF, O'Rourke K. A randomized, controlled trial of albumin versus saline for the treatment of intradialytic hypotension. *J Am Soc Nephrol.* 2004;15(2):487-492.
56. Rostoker G, Griuncelli M, Loridon C, Bourlet T, Illouz E, Benmaadi A. A pilot study of routine colloid infusion in hypotension-prone dialysis patients unresponsive to preventive measures. *J Nephrol.* 2011;24(2):208-217.
57. van der Sande FM, Kooman JP, Barendregt JN, Nieman FH, Leunissen KM. Effect of intravenous saline, albumin, or hydroxyethylstarch on blood volume during combined ultrafiltration and hemodialysis. *J Am Soc Nephrol.* 1999;10(6):1303-1308.
58. Macedo E, Karl B, Lee E, Mehta RL. A randomized trial of albumin infusion to prevent intradialytic hypotension in hospitalized hypoalbuminemic patients. *Crit Care.* 2021;25(1):18.
59. Silversides JA, Pinto R, Kuint R, et al. Fluid balance, intradialytic hypotension, and outcomes in critically ill patients undergoing renal replacement therapy: a cohort study. *Crit Care.* 2014;18(6):624.
60. Augustine JJ, Sandy D, Seifert TH, Paganini EP. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. *Am J Kidney Dis.* 2004;44(6):1000-1007.
61. Chou JA, Kalantar-Zadeh K, Mathew AT. A brief review of intradialytic hypotension with a focus on survival. *Semin Dial.* 2017;30(6):473-480.
62. Lim PS, Yang CC, Li HP, Lim YT, Yeh CH. Midodrine for the treatment of intradialytic hypotension. *Nephron.* 1997;77(3):279-283.
63. Alappan R, Cruz D, Abu-Alfa AK, Mahnensmith R, Perazella MA. Treatment of severe intradialytic hypotension with the addition of high dialysate calcium concentration to midodrine and/or cool dialysate. *Am J Kidney Dis.* 2001;37(2):294-299.
64. Douvris A, Malhi G, Hiremath S, et al. Interventions to prevent hemodynamic instability during renal replacement therapy in critically ill patients: a systematic review. *Crit Care.* 2018;22(1):41.
65. Edrees FY, Katari S, Baty JD, Vijayan A. A pilot study evaluating the effect of cooler dialysate temperature on hemodynamic stability during prolonged intermittent renal replacement therapy in acute kidney injury. *Crit Care Med.* 2019;47(2):e74-e80.
66. Selby NM, McIntyre CW. A systematic review of the clinical effects of reducing dialysate fluid temperature. *Nephrol Dial Transplant.* 2006;21(7):1883-1898.
67. Mustafa RA, Bdair F, Akl EA, et al. Effect of lowering the dialysate temperature in chronic hemodialysis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol.* 2016;11(3):442-457.
68. Sars B, van der Sande FM, Kooman JP. Intradialytic hypotension: mechanisms and outcome. *Blood Purif.* 2020;49(1-2):158-167.
69. Buckley MS, Erstad BL, Lansburg JM, Agarwal SK. Hyperoncotic albumin reduces net fluid loss associated with hemodialysis. *Hosp Pharm.* 2020;55(2):130-134.
70. Hecht-Dolnik M, Barkan H, Taharka A, Loftus J. Hetastarch increases the risk of bleeding complications in patients after off-

- pump coronary bypass surgery: a randomized clinical trial. *J Thorac Cardiovasc Surg.* 2009;138(3):703-711.
71. Lee EH, Kim WJ, Kim JY, et al. Effect of exogenous albumin on the incidence of postoperative acute kidney injury in patients undergoing off-pump coronary artery bypass surgery with a preoperative albumin level of less than 4.0 g/dl. *Anesthesiology.* 2016;124(5):1001-1011.
 72. Pesonen E, Vlasov H, Suojaranta R, et al. Effect of 4% albumin solution vs Ringer acetate on major adverse events in patients undergoing cardiac surgery with cardiopulmonary bypass: a randomized clinical trial. *JAMA.* 2022;328(3):251-258.
 73. Hanley C, Callum J, McCluskey S, Karkouti K, Bartoszko J. Albumin use in bleeding cardiac surgical patients and associated patient outcomes. *Can J Anaesth.* 2021;68(10):1514-1526.
 74. Balachandran M, Banneheke P, Pakavakis A, et al. Postoperative 20% albumin vs standard care and acute kidney injury after high-risk cardiac surgery (ALBICS): study protocol for a randomised trial. *Trials.* 2021;22(1):558.
 75. Simonetti RG, Perricone G, Nikolova D, Bjelakovic G, Gluud C. Plasma expanders for people with cirrhosis and large ascites treated with abdominal paracentesis. *Cochrane Database Syst Rev.* 2019;6: CD004039.
 76. Kulkarni AV, Singh S, Sharma M, et al. Prevention of paracentesis-induced circulatory dysfunction—a systematic review and network meta-analysis. *Gastro Hep.* 2020;2(3):92-103.
 77. Zaccherini G, Tufoni M, Bernardi M. Albumin administration is efficacious in the management of patients with cirrhosis: a systematic review of the literature. *Hepat Med.* 2020;12:153-172.
 78. Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. *Clin Gastroenterol Hepatol.* 2013;11(2):123-130 e121.
 79. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med.* 1999;341(6):403-409.
 80. Fernandez J, Angeli P, Trebicka J, et al. Efficacy of albumin treatment for patients with cirrhosis and infections unrelated to spontaneous bacterial peritonitis. *Clin Gastroenterol Hepatol.* 2020;18(4):963-973 e914.
 81. Wong YJ, Qiu TY, Tam YC, Mohan BP, Gallegos-Orozco JF, Adler DG. Efficacy and safety of IV albumin for non-spontaneous bacterial peritonitis infection among patients with cirrhosis: a systematic review and meta-analysis. *Dig Liver Dis.* 2020;52(10): 1137-1142.
 82. Leao GS, John Neto G, Jotz RF, Mattos AA, Mattos AZ. Albumin for cirrhotic patients with extraperitoneal infections: a meta-analysis. *J Gastroenterol Hepatol.* 2019;34(12):2071-2076.
 83. Philips CA, Maiwall R, Sharma MK, et al. Comparison of 5% human albumin and normal saline for fluid resuscitation in sepsis induced hypotension among patients with cirrhosis (FRISC study): a randomized controlled trial. *Hepatol Int.* 2021;15(4): 983-994.
 84. Maiwall R, Kumar A, Pasupuleti SSR, et al. A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]. *J Hepatol.* 2022;77(3):670-682.
 85. Is B, Bombassaro IZ, Tovo CV, et al. Albumin in the management of hepatic encephalopathy: a systematic review and meta-analysis. *Ann Hepatol.* 2021;26:100541.
 86. Sharma BC, Singh J, Srivastava S, et al. Randomized controlled trial comparing lactulose plus albumin versus lactulose alone for treatment of hepatic encephalopathy. *J Gastroenterol Hepatol.* 2017;32(6):1234-1239.
 87. Simon-Talero M, Garcia-Martinez R, Torrens M, et al. Effects of intravenous albumin in patients with cirrhosis and episodic hepatic encephalopathy: a randomized double-blind study. *J Hepatol.* 2013;59(6):1184-1192.
 88. Teh KB, Loo JH, Tam YC, Wong YJ. Efficacy and safety of albumin infusion for overt hepatic encephalopathy: a systematic review and meta-analysis. *Dig Liver Dis.* 2021;53(7):817-823.
 89. Fagan A, Gavis EA, Gallagher ML, et al. A double-blind randomized placebo-controlled trial of albumin in outpatients with hepatic encephalopathy: HEAL study. *J Hepatol.* 2023;78(2): 312-321.
 90. Sandi BB, Leao GS, de Mattos AA, de Mattos AZ. Long-term albumin administration in patients with cirrhosis and ascites: a meta-analysis of randomized controlled trials. *J Gastroenterol Hepatol.* 2021;36(3):609-617.
 91. Sola E, Sole C, Simon-Talero M, et al. Midodrine and albumin for prevention of complications in patients with cirrhosis awaiting liver transplantation. A randomized placebo-controlled trial. *J Hepatol.* 2018;69(6):1250-1259.
 92. Caraceni P, Riggio O, Angeli P, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. *Lancet.* 2018;391(10138):2417-2429.
 93. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology.* 2021;74(2): 1014-1048.
 94. Aithal GP, Palaniyappan N, China L, et al. Guidelines on the management of ascites in cirrhosis. *Gut.* 2021;70(1):9-29.
 95. European Association for the Study of the Liver. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol.* 2018;69(2):406-460.
 96. Osawa L, Nakanishi H, Kurosaki M, et al. Plasma renin activity predicts prognosis and liver disease-related events in liver cirrhosis patients with ascites treated by tolvaptan. *Dig Dis.* 2022;40(4): 479-488.
 97. Paternostro R, Reiberger T, Mandorfer M, et al. Plasma renin concentration represents an independent risk factor for mortality and is associated with liver dysfunction in patients with cirrhosis. *J Gastroenterol Hepatol.* 2017;32(1):184-190.
 98. Hartl L, Jachs M, Desbalmes C, et al. The differential activation of cardiovascular hormones across distinct stages of portal hypertension predicts clinical outcomes. *Hepatol Int.* 2021;15(5): 1160-1173.
 99. Garioud A, Cadranet JF, Pauwels A, et al. Albumin use in patients with cirrhosis in France: results of the “ALBU-LIVE” survey: a case for better EASL guidelines diffusion and/or revision. *J Clin Gastroenterol.* 2017;51(9):831-838.
 100. Caraceni P, Pavesi M, Baldassarre M, Bernardi M, Arroyo V. The use of human albumin in patients with cirrhosis: a European survey. *Expert Rev Gastroenterol Hepatol.* 2018;12(6):625-632.
 101. Thomson MJ, Taylor A, Sharma P, Lok AS, Tapper EB. Limited progress in hepatorenal syndrome (HRS) reversal and survival 2002-2018: a systematic review and meta-analysis. *Dig Dis Sci.* 2020;65(5):1539-1548.
 102. Best LM, Freeman SC, Sutton AJ, et al. Treatment for hepatorenal syndrome in people with decompensated liver cirrhosis: a network meta-analysis. *Cochrane Database Syst Rev.* 2019;9:CD013103.
 103. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ.* 1998;317(7153):235-240.
 104. Paugam-Burtz C, Levesque E, Louvet A, et al. Management of liver failure in general intensive care unit. *Anaesth Crit Care Pain Med.* 2020;39(1):143-161.
 105. Caraceni P, Angeli P, Prati D, et al; Italian Association for the Study of the Liver (AISF); on behalf of the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI). AISF-SIMTI position paper on the appropriate use of albumin in patients with liver cirrhosis: a 2020 update. *Blood Transfus.* 2021;19(1):9-13.
 106. Caraceni P, Angeli P, Prati D, et al. AISF-SIMTI position paper: the appropriate use of albumin in patients with liver cirrhosis. *Blood Transfus.* 2016;14(1):8-22.
 107. Sumpelmann R, Becke K, Brenner S, et al. Perioperative intravenous fluid therapy in children: guidelines from the Association of the Scientific Medical Societies in Germany. *Paediatr Anaesth.* 2017;27(1):10-18.