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GUIDELINES

European Society of Intensive Care Medicine clinical practice guideline on fluid therapy in adult critically ill patients. Part 1: the choice of resuscitation fluids

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Abstract

Purpose: This is the first of three parts of the clinical practice guideline from the European Society of Intensive Care Medicine (ESICM) on resuscitation fluids in adult critically ill patients. This part addresses fluid choice and the other two will separately address fluid amount and fluid removal.

Methods: This guideline was formulated by an international panel of clinical experts and methodologists. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was applied to evaluate the certainty of evidence and to move from evidence to decision.

Results: For volume expansion, the guideline provides conditional recommendations for using crystalloids rather than albumin in critically ill patients in general (moderate certainty of evidence), in patients with sepsis (moderate certainty of evidence), in patients with acute respiratory failure (very low certainty of evidence) and in patients in the perioperative period and patients at risk for bleeding (very low certainty of evidence). There is a conditional recommendation for using isotonic saline rather than albumin in patients with traumatic brain injury (very low certainty of evidence). There is a conditional recommendation for using albumin rather than crystalloids in patients with cirrhosis (very low certainty of evidence). The guideline provides conditional recommendations for using balanced crystalloids rather than isotonic saline in critically ill patients in general (low certainty of evidence), in patients with sepsis (low certainty of evidence) and in patients with kidney injury (very low certainty of evidence). There is a conditional recommendation for using isotonic saline rather than balanced crystalloids in patients with traumatic brain injury (very low certainty of evidence). There is a conditional recommendation for using isotonic crystalloids rather than small-volume hypertonic crystalloids in critically ill patients in general (very low certainty of evidence).

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Conclusions: This guideline provides eleven recommendations to inform clinicians on resuscitation fluid choice in critically ill patients.

Keywords: Albumin, Crystalloid solutions, Colloid solutions, Practice guidelines, Critical care, Fluid therapy

Introduction

Administration of resuscitation fluids is common in the management of critically ill patients [1]. The European Society of Intensive Care Medicine (ESICM) convened a group of content and method experts to issue a clinical practice guideline (CPG) on fluid management in adult critically ill patients. This CPG was divided into three parts: the choice of resuscitation fluids (part 1), the amount of resuscitation fluids (part 2), and fluid removal in the de-escalation phase (part 3). The full list of contributors is presented in the online electronic supplementary material (ESM). In this manuscript, the guideline on the choice of resuscitation fluid will be presented.

Resuscitation fluids are categorized into crystalloids, including isotonic saline and balanced crystalloids, and colloids, with albumin as the reference colloid solution [2]. In clinical practice, the choice of resuscitation fluids varies according to fluid availability, understanding of the physiologic characteristics of different fluids, clinician preferences, practice setting and region [3].

The aim of this CPG from ESICM was to provide evidence-based guidance regarding the choice of resuscitation fluid in adult critically ill patients supported by a critical analysis of the literature.

Methods

Guideline scope and target audience

The scope of this guideline was to provide evidence-based guidance regarding the choice of early resuscitation fluid in adult critically ill patients due to various etiologies. The target audience for this guideline is front-line clinicians (medical and nursing), allied healthcare workers and policymakers in both high- and low-to-middle-income contexts.

Panel selection and organization

Panel members were appointed with consideration of diversity and inclusivity as previously described [4]. The panel consisted of two ESICM Guidelines Co-chairs, one Clinical Chair, two Methods Co-Chairs from ESICM and Guidelines in Intensive Care, Development and Evaluation (GUIDE) group, the Chairperson of the Methodology Group of ESICM, and 11 experts, including clinicians specialized in critical care, anesthesia, infectious diseases and emergency medicine as well as critical care nursing.

Take-home message

For volume expansion, the guideline provides conditional recommendations for using crystalloids rather than albumin in critically ill patients in general, in patients with sepsis, in patients with acute respiratory failure and in patients in the perioperative period and patients at risk for bleeding. There are conditional recommendations for using isotonic saline rather than albumin in patients with traumatic brain injury and for using albumin rather than crystalloids in patients with cirrhosis. The guideline provides conditional recommendations for using balanced crystalloids rather than isotonic saline in critically ill patients in general, in patients with sepsis and in patients with kidney injury. There are conditional recommendations for using isotonic saline rather than balanced crystalloids in patients with traumatic brain injury and for using isotonic crystalloids rather than small-volume hypertonic crystalloids in critically ill patients in general.

The roles of the panel members are outlined in the online electronic supplementary material (ESM).

Conflict of interest management

We applied the principles of management of conflict of interest (COI) as previously described [5]. Panelists were requested to declare any intellectual or financial COI that may influence their participation in the guideline by completing a special form per the ESICM procedures. A summary of individual declarations is provided at the end of the document under the COI section. Panelists received no financial incentives for their participation. In addition, no funding or input from the industry was incorporated into the guideline.

Development of questions and outcomes selection

This guideline addressed the use of commonly used resuscitation fluids in adult critically ill patients: crystalloids (isotonic saline and balanced crystalloids) and albumin. One question addressed small-volume hypertonic or isotonic crystalloids. This guideline did not address other colloids, such as hydroxyethyl starch (HES) or gelatin. In addition, these guidelines did not address fluid choice for managing burns, the use of hypertonic solutions for the management of increased intracranial pressure or the use of albumin solutions to increase serum albumin levels [6, 7].

At the beginning of the process of the guideline development, the panel proposed several questions according to the Population, Intervention, Comparison,

and Outcomes (PICO) format. After deliberations, the panel prioritized eleven questions, which were approved by the guideline leadership. These questions included the following areas: (A) albumin vs. crystalloids (six questions; in critically ill patients in general, patients with sepsis, patients with acute respiratory failure, patients with traumatic brain injury (TBI), patients in the perioperative period and in patients with bleeding or at risk for bleeding and patients with cirrhosis); (B) balanced crystalloids vs. isotonic saline (four questions; in critically ill patients in general, patients with sepsis, patients with TBI, and patients with acute kidney injury); (C) one question for small-volume hypertonic vs. isotonic crystalloids.

Panelists selected and prioritized outcomes for each PICO on a scale from 1 to 9 (ranging from unimportant to critical) [8]. The following outcomes judged as being critical were included: short-term mortality, need for renal replacement therapy, ventilator-free days/duration of mechanical ventilation, intensive care unit (ICU)-free days/ICU length of stay, hospital-free days/hospital length of stay, quality of life and functional outcomes. For the questions regarding patients with TBI, the additional critical outcome of the extended Glasgow Outcome Scale (GOSE) was used.

Literature search

Methodologists searched for relevant systematic reviews and meta-analyses and updated them when needed. When neither was available, we searched for randomized controlled trials in MEDLINE & EMBASE from inception to April 2022, and any relevant trials published subsequently were also included. We used and updated the search, as relevant, from the reviews by Lewis et al., Tseng et al. and Bai et al. for the questions related to albumin vs. crystalloids [9–11], by Hammond et al., Zampieri et al. and Wan et al. for the questions related to balanced crystalloids vs. isotonic saline [12–14] and by Orbegozo et al. for small-volume hypertonic vs. isotonic crystalloids [15]. Although not included in the grading process, data from observational studies were deliberated in panel meetings, as applicable.

Data analysis

The DerSimonian and Laird random-effects model was used when pooling results of effect sizes across randomized controlled trials (RCTs) [16, 17]. Relative risks (RRs) with corresponding 95% confidence intervals (CIs) were used for binary outcomes, while mean differences (MDs) and 95% CIs were used for continuous outcomes. The I^2 statistic was used for descriptive and not inferential purposes, and heterogeneity was assessed mainly on a clinical basis. All analyses were performed using Review Manager (RevMan) [Version 5.4, The Cochrane Collaboration, 2020] [18]. Updated RevMan data from Lewis et al were used [9]. In addition, published results from Bayesian meta-analysis or individual patient data meta-analysis were also included when evaluating the evidence. The results of systematic reviews were reported according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidance, considering the size of effect and certainty of evidence [19].

Risk of bias and certainty of evidence

The Cochrane Collaboration Risk of Bias (ROB) 1.0 tool was used to assess the risk of bias of individual RCTs. The GRADE methodology was applied to evaluate the certainty of evidence [20]. Accordingly, the certainty of evidence from randomized controlled trials for each critical outcome started with a high rating, but it could be downgraded by one or two points for each of the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias [21]. If the evidence was primarily based on study subgroups, the validity of the findings was deliberated during the panel discussions. The certainty of evidence for each recommendation was determined considering the totality of evidence across all outcomes including the critical outcome with the lowest certainty [22]. In addition and in line with the GRADE methodology, the panel also considered the relative importance of each outcome so that the whole body of evidence is not downgraded based on the lower confidence in estimates of the effects of a less critical outcome. For each PICO, we reported the level of certainty for each outcome, the level of certainty for the whole body of evidence and the domains that were involved in downgrading in the corresponding Summary of Evidence section, and provided a more detailed description in the Evidence Profile tables in the ESM. The GRADEpro GDT (GRADEpro Guideline Development Tool [Software], McMaster University and Evidence Prime, 2022. Available from www.gradepro.org) was used to create evidence profiles for each PICO.

Recommendation formulation

The panel met online monthly and used the Evidence-to-Decision (EtD) Framework to formulate recommendations [23]. As described in the GRADE methodology, the panel considered the following factors: magnitude of effect, certainty of evidence, patient values and preferences, resources and cost, equity, acceptability, and feasibility when deciding the direction and strength of recommendations. A strong recommendation in favor of an intervention (reported as "we recommend") implies

that the desirable benefit of the intervention outweighs undesirable effects, that most patients and clinicians would choose the recommendation, and that it can be adopted as a policy. On the other hand, a conditional recommendation in favor of an intervention (reported as "we suggest") implies that the desirable benefit of the intervention outweighs the undesirable effects but with a low confidence. It implies that a majority, but not all, individuals will likely be best served by the recommended course of action [23], and that most patients and clinicians, but not all, would accept the suggested action from a conditional recommendation, and for policymakers, it would not be appropriate to be adopted as a policy. To provide practical guidance to critical practitioners, we presented the recommendations in favor of a particular approach rather than against an alternative [24]. The panel used consensus to formulate recommendations and all members approved the final recommendations. A family member of a critically ill patient reviewed the recommendations, provided feedback and supported all eleven recommendations. For each PICO, the panel identified unresolved questions and research gaps as relevant.

Results

Albumin vs. crystalloids

Question 1: Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients in general?

Recommendation

We **suggest** using crystalloids rather than albumin for volume expansion in adult critically ill patients in general.
Conditional recommendation, moderate certainty of evidence.

Remark

Questions 2, 3, 4, 5 and 6 address the use of albumin vs. crystalloids in adult critically ill patients with sepsis , adult critically ill patients with acute respiratory failure, adult critically ill patients with TBI, adult critically ill patients in the perioperative period and those with bleeding or at risk for bleeding and adult critically ill patients with cirrhosis, respectively.

Background

Albumin has been advocated as a more effective fluid for expanding intravascular volume than crystalloids because it is believed to be more effectively retained within the intravascular space and that it maintains the intravascular oncotic pressure [3]. Based on early physiologic considerations, albumin has been considered volume-sparing, expanding intravascular volume at a ratio of 1:3 compared to crystalloids [3]. Albumin has been associated with less interstitial edema compared to crystalloids [3]. However, the importance of oncotic pressure in maintaining circulating volume has been challenged by physiologists, pointing toward a possible regulating role for filtration in micro-vessels [25]. Potentially in line with this view, recent RCTs have failed to demonstrate any advantage of albumin over crystalloids on patient-centered outcomes. The volume-sparing effect of albumin is probably less pronounced and shorter-lasting than initially thought. In the SAFE (the Saline versus Albumin Fluid Evaluation) trial, a double-blind RCT, the ratios of the albumin volume to the saline volume ranged from 1:1.2 to 1:1.6 [26].

Summary of the evidence

A pooled analysis of RCTs showed that albumin compared with crystalloids in critically ill patients resulted in little to no difference in mortality [16 trials, $n = 11{,}896$, RR 0.98, 95% CI 0.93, 1.04, I^2 0%, high certainty of evidence, Fig. 1 and ESM]. Albumin versus crystalloids might have not resulted in a difference in renal replacement therapy (5 trials, $n = 3508$, RR 1.04, CI 0.88, 1.24, I^2 29%, low certainty of evidence). In critically ill patients in general, albumin versus crystalloids did not result in a difference in the duration of mechanical ventilation (high certainty of evidence), might have not affected ICU length of stay (low certainty of evidence), and might have had little to no effect on hospital length of stay but the evidence was very uncertain. There was no data on albumin versus crystalloids' impact on quality of life (ESM). The balance of effects did not favor albumin over crystalloids for volume expansion in critically ill patients, and the certainty of the whole body of evidence across all outcomes was moderate (downgraded for imprecision).

The panel considered additional issues when formulating recommendations for using albumin versus crystalloid solutions (EtD framework, ESM). First, the cost of albumin is higher than that of crystalloids [27, 28]. In an international survey, albumin was approximately 27 times more costly than an equivalent dose of isotonic saline, with 1 mL of 4% albumin being considered an equivalent dose to 1.4 mL of saline based on data from the SAFE trial [26, 28]. Data on cost-effectiveness are limited, but some studies have demonstrated that albumin use might be cost-effective in selected populations [29, 30]. Other studies have shown that albumin is not cost-effective, especially in low-resource settings [31, 32]. Second, the widespread use of albumin may negatively impact the equitable use of healthcare resources. Third, albumin is not available in many resource-limited settings. Fourth, albumin is procured from human blood and, as such, is a limited resource. Fifth, regarding patient values and preferences, the panel felt that most patients would likely find albumin administration acceptable. However, some patients who avoid blood products may

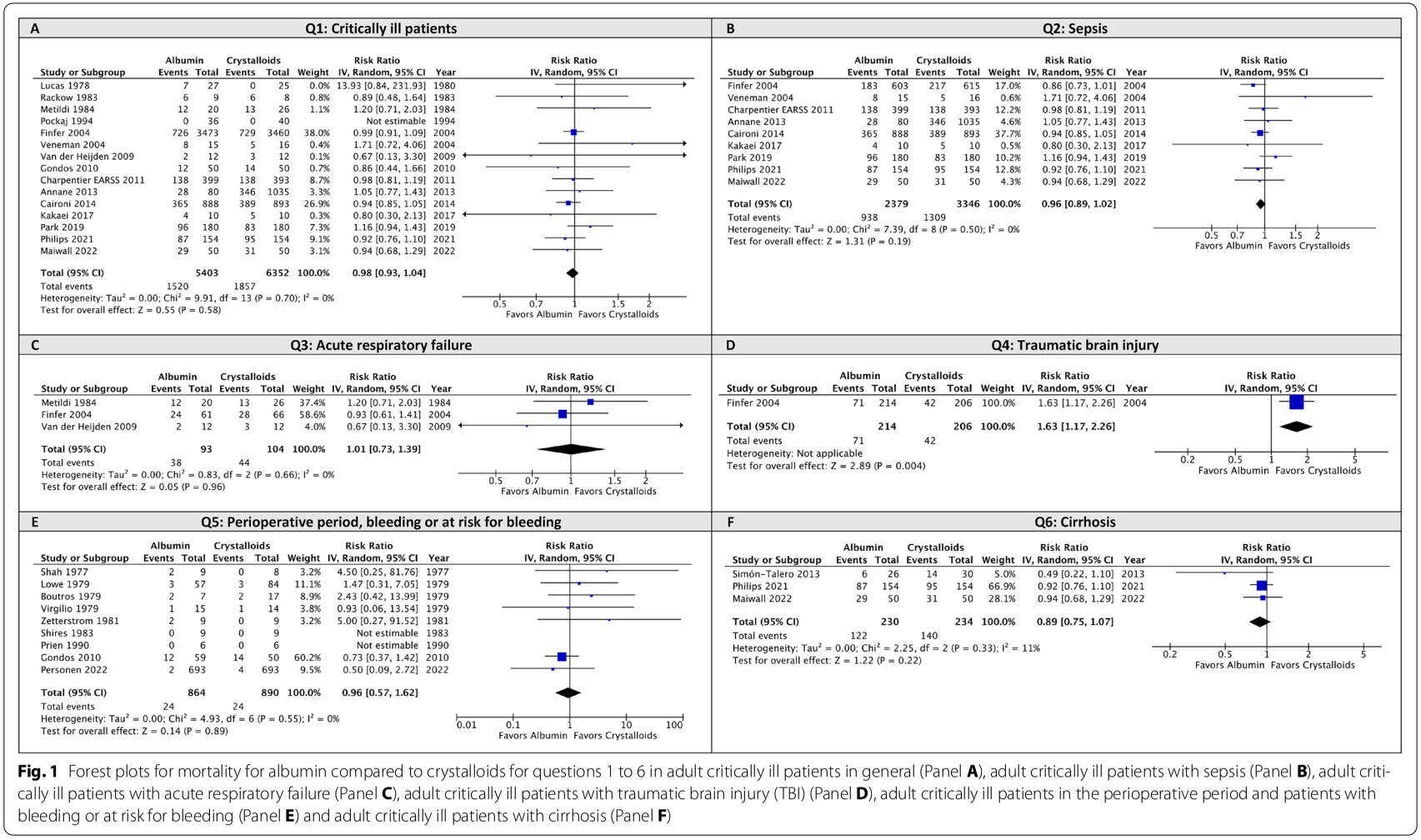
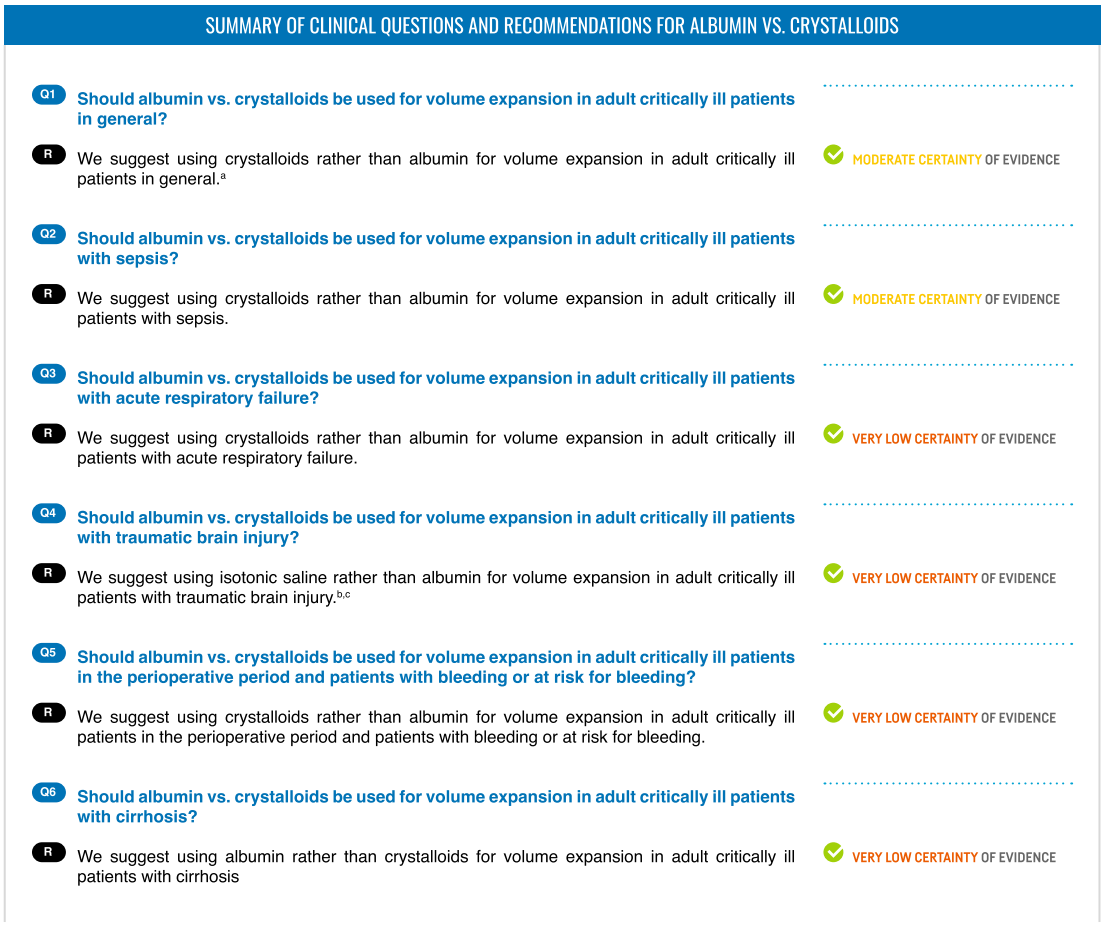


Fig. 1 Forest plots for mortality for albumin compared to crystalloids for questions 1 to 6 in adult critically ill patients in general (Panel **A**), adult critically ill patients with sepsis (Panel **B**), adult critically ill patients with acute respiratory failure (Panel **C**), adult critically ill patients with traumatic brain injury (TBI) (Panel **D**), adult critically ill patients in the perioperative period and patients with bleeding or at risk for bleeding (Panel **E**) and adult critically ill patients with cirrhosis (Panel **F**)

Table 1 Summary of clinical questions and recommendations for albumin vs. crystalloids



[a] Specific recommendations are made for adult critically ill patients with sepsis (Question 2), acute respiratory failure (Question 3), traumatic brain injury (Question 4), patients in the perioperative period and patients with bleeding or at risk for bleeding (Question 5) or cirrhosis (Question 6)

[b] Existing data compares isotonic saline, but not balanced crystalloids, to albumin

[c] A specific recommendation is made for the use of balanced crystalloids vs. isotonic saline in adult critically ill patients with traumatic brain injury (Question 9)

not accept the use of albumin [3]. Rare allergic reactions may also cause some to prefer to avoid albumin [33, 34]. With all these considerations, the panel made a conditional recommendation for using crystalloids rather than albumin for volume expansion in critically ill patients in general (Table 1).

Unresolved questions and research gaps

Studies are needed for albumin solutions in different concentrations, and for the interaction of albumin effect with the volume of crystalloids administered contemporaneously.

Question 2: Should Albumin vs. crystalloids be used for volume expansion in adult critically ill patients with sepsis?

Recommendation

We **suggest** using crystalloids rather than albumin for volume expansion in adult critically ill patients with sepsis.
Conditional recommendation, moderate certainty of evidence.

Background

Patients with sepsis have decreased vascular tone, increased venous capacitance, and capillary leak, and may respond to fluid resuscitation [35]. However,

resuscitation fluids will eventually distribute into the interstitial and intracellular spaces, especially if endothelial integrity is impaired, leading to a gradual loss of effect of fluid administration [35, 36]. In addition, the resulting interstitial edema has been associated with organ dysfunction in sepsis. Albumin may have potential advantages over crystalloids in patients with sepsis and is believed to afford greater plasma-expanding capacity than crystalloids by maintaining the oncotic pressure in the intravascular compartment [3]. In addition, albumin has several pleiotropic properties not related to fluid volume [37–40].

Summary of the evidence

For patients with sepsis, the pooled analysis demonstrated that albumin versus crystalloids in patients with sepsis did not result in a difference in mortality (9 trials, $n = 5725$, RR 0.96, 95% CI 0.89–1.02, I^2 0%, high certainty of evidence, Fig. 1 and ESM). In the CRISTAL (Colloids Versus Crystalloids for the Resuscitation of the Critically Ill) trial, patients were randomized to receive colloids (gelatines, dextrans, hydroxyethyl starches, or 4% or 20% of albumin) or crystalloids [41]. Because randomization was not stratified according to the type of colloid, we conducted a sensitivity analysis excluding the patients from this trial, and the results did not change. Albumin versus crystalloids probably did not result in a difference in renal replacement therapy (5 trials, $n = 3508$, RR 1.04, CI 0.88, 1.24, I^2 29%, moderate certainty of evidence). In patients with sepsis, albumin versus crystalloids probably did not affect ICU length of stay (moderate certainty of evidence), might not have resulted in a difference in ventilator-free days (low certainty of evidence), and might have had little to no effect on mechanical ventilation duration and hospital length of stay but the evidence was very uncertain. The balance of effects did not favor albumin over crystalloids for volume expansion in patients with sepsis. The certainty of the whole body of evidence was moderate (downgraded for imprecision).

Considering the increased cost and limited availability of albumin and the additional considerations listed earlier (under question 1), the panel made a conditional recommendation for using crystalloids rather than albumin for volume expansion in patients with sepsis (Table 1).

Does albumin have a role in selected groups of patients with sepsis? The panel discussed thoroughly the potential role of albumin in the following selected groups: patients with hypo-albuminemia, patients who received large volumes of crystalloids and patients with septic shock. Trials in these specific patient groups have been limited; hence, the role of albumin in these groups remains an area of uncertainty. A sub-study from the SAFE trial evaluated whether outcomes of resuscitation with albumin or isotonic saline in critically ill patients depend on patients' baseline serum albumin concentration [42]. In this sub-study, which included 6045 patients, 25% of whom had sepsis on admission, the odds ratios for death for albumin compared with saline for patients with a baseline serum albumin concentration of 25 g/l or less and more than 25 g/l were 0.87 and 1.09, respectively (ratio of odds ratios 0.80, 95% CI 0.63–1.02, P value = 0.08 for heterogeneity) [42]. Given the limited existing data, there were different views among the panelists about using albumin for volume expansion for patients with hypo-albuminemia, patients who received large volumes of crystalloids and patients with septic shock. Therefore, no recommendations for or against using albumin in these groups were issued.

Unresolved questions and research gaps

The choice of fluid in different phases of sepsis therapy (resuscitation, optimization, stabilization, and evacuation) is still largely unclear and requires further study [43]. The role of concentrated albumin as a resuscitation fluid in patients with sepsis is unclear. Further studies need to evaluate whether there are specific groups of patients with sepsis in which albumin improves outcomes. Fluid choice in resource-limited settings needs to be evaluated. Cost-effective analyses of using albumin in patients with sepsis are required across different settings and patient populations, including those with hypoalbuminemia.

Question 3: Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients with acute respiratory failure?

Recommendation

We **suggest** using crystalloids rather than albumin for volume expansion in adult critically ill patients with acute respiratory failure.
Conditional recommendation, very low certainty of evidence.

Background

Acute respiratory distress syndrome (ARDS) is a major cause of acute respiratory failure [44, 45]. One of the hallmark features of ARDS is the increased alveolar-capillary permeability resulting in the accumulation of fluids into the alveolar space [46]. Fluid filtration across the alveolar-capillary barrier has traditionally been viewed according to the classic Starling model

[47]. In this model, fluid filtration is mainly determined by the hydrostatic gradient and oncotic gradient, and the interstitial space is considered to have a low protein concentration. It is now recognized that the interstitial space has a high protein concentration, limiting the oncotic gradient and reducing fluid return to the plasma compartment and that much of the residual fluid in the interstitial space is removed through the lymphatic system [47].

The optimal fluid for patients with acute respiratory failure (including ARDS) is a fluid that corrects hemodynamic instability and improves tissue perfusion without inducing pulmonary interstitial edema and compromising pulmonary function. There are data suggesting that albumin used concurrently with furosemide improves oxygenation in patients with ARDS compared to crystalloids [48].

Summary of the evidence

The literature search identified 3 RCTs, with a total of 197 participants randomized to receive either albumin or crystalloids in acute respiratory failure (ARF). This included data from a subgroup in the SAFE trial [26], comprised of only 123 of 6997 randomized patients (1.8%, not stratified by ARF) and two other small studies (46 and 24 patients randomized) [49, 50]. The pooled analysis demonstrated that albumin, compared to crystalloids, in patients with acute respiratory failure had no effect on mortality, but the evidence was very uncertain (RR 1.01, 95% CI 0.73–1.39, I^2 0%, very low certainty of evidence, Fig. 1 and ESM). No other outcomes were reported for this population (ESM). The balance of benefits and harms of either strategy did not favor albumin or crystalloids, and the certainty of the whole body of evidence was very low (downgraded for risk of bias and imprecision, ESM).

Considering the factors discussed earlier, including the cost, equity, availability, and patient preferences, the panel made a conditional recommendation for using crystalloids rather than albumin for volume expansion in patients with ARF (Table 1).

Unresolved questions and research gaps

There are no published clinical trials that have evaluated the effect of albumin or other types of fluids on patient-centered outcomes in ARDS. There is also a need to investigate the cost-effectiveness of albumin and its effects on long-term outcomes in patients with ARDS.

Question 4: Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients with traumatic brain injury (TBI)?

Recommendation

We **suggest** using isotonic saline rather than albumin for volume expansion in adult critically ill patients with TBI.
Conditional recommendation, very low certainty of evidence.

Remark

Existing RCT data compares isotonic saline, but not balanced crystalloids, to albumin.

Question 9 addresses the use of balanced crystalloids vs isotonic saline in adult critically ill patients with TBI.

Background

Current management of severe TBI is centered on maintaining adequate cerebral perfusion pressure, necessitating treatment with intravenous fluids and vasopressors [51]. Concerns about the safety of 4% albumin were raised based on the subgroup analysis from the SAFE trial [26].

Summary of the evidence

In the literature review of RCTs comparing albumin with crystalloids in patients with TBI, we identified only the subgroup analysis from the SAFE trial [10, 52]. The analysis demonstrated that using 4% albumin compared to isotonic saline for volume expansion in the subgroup of patients with TBI might have increased mortality at day 28, but the evidence was very uncertain (26.1% vs. 15.7%, RR 1.68, 95% CI 1.16–2.43, P value = 0.005, very low certainty of evidence Fig. 1 and ESM). A long-term follow-up study demonstrated that mortality at two years might have remained higher in the albumin group, but the evidence was very uncertain (420 patients, 33.2% vs. 20.4%, RR 1.63, 95% CI 1.17–2.26, P value = 0.003, very low certainty of evidence, Fig. 1 and ESM) [52]. Patients in the albumin group might less likely have had favorable neurologic outcomes as measured by the GOSE, but the evidence was very uncertain (ESM) [52]. This effect was driven by patients with severe TBI (Glasgow Coma Scale (GCS) score < 9) [52]. A mechanistic study [53] ascribed the excess mortality observed in SAFE-TBI to cerebral edema based on observed higher intracranial pressure in patients in the albumin group compared to the isotonic saline group at the end the first week (19.2 ± 1.07 versus 15.4 ± 1.06 mmHg, P value = 0.01). The balance of benefits and harms favored isotonic saline over albumin, the certainty of the whole body of evidence

across all outcomes was very low (downgraded for the risk of bias and imprecision).

The finding was based on a post hoc subgroup analysis. However, subsequent studies suggested the physiologic plausibility of the finding. The 4% albumin solution used in the study was hypotonic (260 mOsm/L), raising the question of whether excess mortality was due to the hypotonic carrier fluid or to the albumin itself. An animal study designed to answer this question suggested that the albumin solution's hypotonicity might have been a contributing factor [54]. The panel noted that the balance of effects, cost and equity considerations all favored using isotonic saline over albumin. Therefore, the panel made a conditional recommendation for using isotonic saline rather than albumin in TBI patients requiring fluid resuscitation (Table 1).

Unresolved questions and research gaps

No robust data are addressing the safety and efficacy of hyperoncotic (20–25%) human albumin solution in patients with severe TBI [55].

Question 5: Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients in the perioperative period and in patients with bleeding or at risk for bleeding?

Recommendation

We **suggest** using crystalloids rather than albumin for volume expansion in critically ill patients in the perioperative period and patients with bleeding or at risk for bleeding.
Conditional recommendation, very low certainty of evidence.

Background

Intravenous infusion of resuscitation fluids not containing coagulation factors impairs coagulation by diluting the plasma [56, 57]. This non-specific dilutional effect on coagulation is determined by the fluid's volume efficacy, which explains why crystalloids, especially when given in large volumes, are more likely than albumin to cause dilutional coagulopathy [56]. In a matched controlled study of trauma patients, low-compared with high-volume crystalloid replacement was associated with reduced coagulopathy, blood transfusion, and mortality, suggesting that the effect is volume-dependent [58]. In addition to the dilutional effect, colloids in general, induce derangements in specific coagulation factors, although these effects are observed the least with albumin compared with other colloids [56].

Summary of the evidence

Based on a recent systematic analysis by Tseng et al., we identified nine trials comparing albumin with crystalloids in adult critically ill patients in the perioperative period and in patients with bleeding or at risk for bleeding [10]. Of these, six trials were performed in patients undergoing major vascular surgery and three were in trauma patients. All studies but one were conducted > 15 years ago. Albumin, compared to crystalloids had no effect on mortality, but the evidence was very uncertain (9 trials, $n = 1754$, RR 0.96, 95% CI 0.57–1.62, I^2 0%, Fig. 1 and ESM). Acute kidney injury was assessed in one study: albumin, compared to crystalloids, had no effect on acute kidney injury, but the evidence was very uncertain. Those receiving albumin had a numerically smaller blood transfusion volume, which was not statistically significant and the evidence was very uncertain (mean difference −224 ml, 95% CI −490, 42, I^2 95%, ESM). The balance of benefits and harms did not favor albumin or crystalloids, and the certainty of the whole body of evidence across all outcomes was very low (downgraded for risk of bias, indirectness, and imprecision).

Given the balance of effect, in addition to the considerations of albumin versus crystalloids discussed earlier about the cost, equity, availability and patient preferences, the panel made a conditional recommendation for using crystalloids rather than albumin for volume expansion in patients with or at risk of bleeding (Table 1).

Unresolved questions and research gaps

The available evidence is mostly based on relatively old RCTs, which had limited evaluation of outcomes of interest. More contemporary RCTs are needed to better understand the effect of fluid choice in this population and evaluate the presence of differential effects across patients' subgroups.

Question 6: Should albumin vs. crystalloids be used for volume expansion in adult critically ill patients with cirrhosis?

Recommendation

We **suggest** using albumin rather than crystalloids for volume expansion in adult critically ill patients with cirrhosis.
Conditional recommendation, very low certainty of evidence.

Background

Advanced cirrhosis is associated with complex hemodynamic changes, characterized by increased splanchnic blood volume and relative central hypovolemia [59].

Infusion of albumin is widely used in cirrhotic patients for intravascular volume expansion. In addition, studies suggest that the administration of albumin may have beneficial effects through its antioxidant and anti-inflammatory effects as well as its binding properties for endogenous and exogenous toxins [59, 60].

In managing patients with cirrhosis, albumin is used for various indications, including decompensated cirrhosis, ascites, encephalopathy, infections, hepatorenal syndrome and hypoalbuminemia [61–63]. Several systematic reviews and CPGs have been published over the years, addressing these indications based on the existing data that varied in settings (mainly hospitalized patients) and comparisons [11, 61–69]. Many of the conducted trials, for example, those evaluating hepatorenal syndrome, included albumin in both study arms, indicating the lack of equipoise in the medical community in some of these indications.

Summary of the evidence

A literature review identified three relevant RCTs based on a recent systematic review by Bai et al., addressing the question of albumin versus crystalloids [11]. One trial was performed on critically ill patients with cirrhosis, while the other two included all hospitalized patients with cirrhosis [70–72]. The studies compared hyper-oncotic albumin in different doses and concentrations. Aggregate data from the three trials on 464 patients showed no statistically significant difference in mortality between albumin and crystalloids, with the point estimate favoring albumin, but the evidence was very uncertain (RR 0.89, 95% CI 0.75–1.07, I^2 11%, very low certainty of evidence, Fig. 1 and ESM). Similar findings were shown when evaluating the need for renal replacement therapy, ICU and hospital lenght of stay (LOS) (all very low certainty of evidence, only one trial included, ESM) [72]. The balance of benefits and harms favored albumin over crystalloids, and the certainty of the whole body of evidence across all outcomes was very low (downgraded for indirectness and imprecision).

Cost-effectiveness data are limited. One study from Germany, Italy, and Spain demonstrated that albumin was cost-effective in the treatment of decompensated cirrhosis [27]. However, data from low-middle-income countries are lacking. Despite increased costs and reduced equity (EtD framework, ESM), the panel made a conditional recommendation for using albumin rather than crystalloids for volume expansion in critically ill patients with cirrhosis (Table 1).

Unresolved questions and research gaps

Given the limited available data, future work is needed to evaluate the question of albumin vs. crystalloids for volume expansion in adult critically ill patients with cirrhosis. The role of albumin 20% vs 5% in this population for volume expansion requires further study.

Balanced crystalloids vs. isotonic saline

Question 7: Should balanced crystalloids vs. isotonic saline be used for volume expansion in adult critically ill patients in general?

Recommendation
We **suggest** using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients. *Conditional recommendation, low certainty of evidence.*
Remarks
In settings with a limited supply of balanced crystalloids, it is advised to prioritize using balanced crystalloids rather than isotonic saline in patients who require large volumes of resuscitation fluids and those with hyperchloremia or acidosis.
In settings where balanced crystalloids are unavailable, isotonic saline is an acceptable alternative.
Conversely, isotonic saline should be considered in patients with hypochloremia or metabolic alkalosis.
Questions 8, 9 and 10 address the use of balanced crystalloids vs isotonic saline in adult critically ill patients with sepsis , traumatic brain injury , and acute kidney injury, respectively.

Background

Isotonic saline (normal saline, 0.9% saline) is traditionally the most commonly used crystalloid solution worldwide [2, 73]. Because isotonic saline contains sodium and chloride in equal concentrations (each 154 mmol/l), the strong ion difference is zero [3, 74]. As a result, rapid administration of a large volume of isotonic saline can cause hyperchloremic metabolic acidosis. It is recognized now that hyperchloremia may be associated with acute kidney injury [3, 74, 75].

The use of balanced crystalloids has risen over the last few years because of concerns about the adverse effects of isotonic saline [2]. Compared to isotonic saline, balanced crystalloids have lower chloride concentrations by substituting some chloride with an organic anion, such as lactate, acetate, gluconate and malate [3, 74]. Additionally, balanced crystalloids contain cations other than sodium (potassium, calcium and magnesium) [3, 74].

Summary of the evidence

Our literature review, including the recent systematic review and meta-analysis on the topic by Hammond et al. [13] identified 11 studies with a total of 35,884 participants, of which 9 RCTs with 35,644 participants reported the mortality outcome. The pooled estimate demonstrated that balanced crystalloids compared with isotonic saline in adult critically ill patients did not result in a statistically significant difference in mortality (RR 0.93, 95% CI 0.76–1.15, I^2 88.44%). In the same systematic review, the risk ratio (RR) for 90-day mortality with balanced crystalloids versus saline in a pooled analysis from six trials (34,450 participants) with a low risk of bias was 0.96 (95% CI 0.91–1.01, I^2 12.1%). In a Bayesian analysis using vague priors, the posterior probability that balanced crystalloids reduced mortality was 91.69% for all trials and 89.5% for low-risk of bias trials [13]. In an individual patient data meta-analysis (six RCTs, 34653 patients) using a Bayesian regression model, the odds ratio for 90-day mortality with balanced crystalloids versus saline was 0.962 (95% credible interval 0.909–1.019), with an absolute difference −0.4 percentage points [−1.5 to 0.2]) and a posterior probability that balanced solutions reduced mortality of 89.5% [14]. These findings were generally aligned with the findings of a systematic review that included observational studies and RCTs [76]. Collectively, the existing data showed that balanced crystalloids compared with isotonic saline probably resulted in a slight reduction in mortality (moderate certainty of evidence). Balanced crystalloids compared with isotonic saline probably did not result in a difference in renal replacement therapy (low certainty of evidence), might not have changed ventilation-free days (moderate certainty of evidence), did not affect vasopressor-free days or ICU LOS (high certainty of evidence for both outcomes) and probably did not change hospital length of stay (moderate certainty of evidence, ESM). The balance of benefits and harms favored balanced crystalloids over isotonic saline, and the certainty of the whole body of evidence across all outcomes was low (downgraded for risk of bias, imprecision and inconsistency).

Because the balance of benefits and harms favored balanced crystalloids over isotonic saline in critically ill patients, the panel issued a conditional recommendation for using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients (Table 2).

In a 2014 study conducted in 426 ICUs from 27 countries, the average cost for crystalloids overall was less than 1 United States Dollars (USD) per 100 mL, with isotonic saline being the least costly [28]. There was an 11-fold variation in the cost of isotonic saline across countries, ranging from 0.09 to 1.04 USD/100 mL [28]. There was a seven-fold variation in the cost of balanced crystalloids across countries, ranging from 0.14 to 1.04 USD/100 mL [28]. The panel acknowledged the unavailability or limited availability and the higher cost of balanced crystalloids compared to isotonic saline in many settings worldwide, especially in low-income countries [28]. In settings where there is a limited supply of balanced crystalloids, the panel advised to prioritize using balanced crystalloids rather than isotonic saline in patients who require large volumes of resuscitation fluids and in those with hyperchloremia or acidosis. A good practice could be to monitor chloride levels and switch from saline to balanced crystalloids if hyperchloremia develops. In situations where balanced crystalloids are unavailable, isotonic saline was considered an acceptable alternative. Conversely, isotonic saline should be considered in patients with hypochloremia or metabolic alkalosis.

Unresolved questions and research gaps

There is a need to compare the effect of different balanced solutions, e.g., PlasmaLyte, Ringer's lactate or acetate and others on patient-centered outcomes. Trials of guided therapy with balanced crystalloids and isotonic saline are an important next step for critically ill patients. Such trials could, for example, include regular chloride measurements, allowing for prompt intervention in case of hyperchloremia. Additionally, such trials could consider cost variations of fluids and laboratory tests across different settings.

Question 8: Should balanced crystalloids vs. isotonic saline be used for volume expansion in adult critically ill patients with sepsis?

Recommendation

We **suggest** using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients with sepsis.
Conditional recommendation, low certainty of evidence.

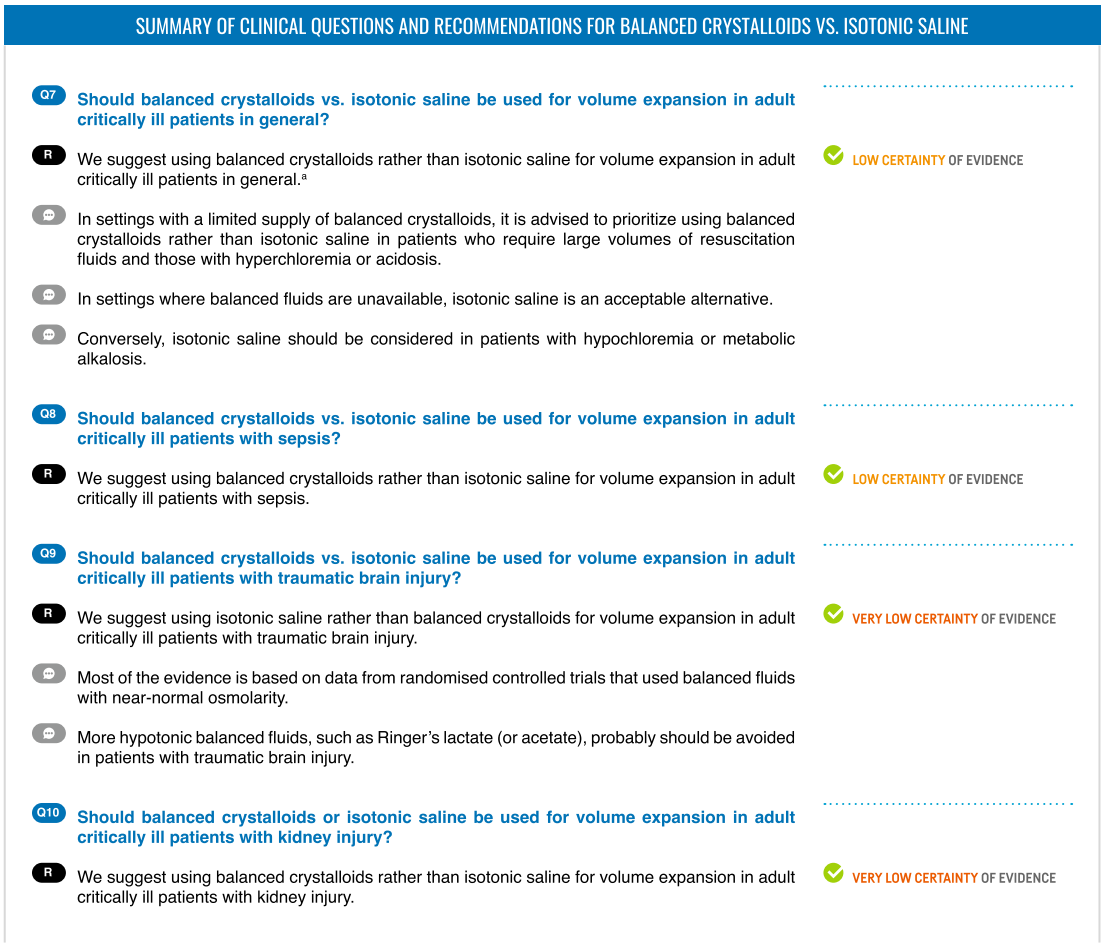
Background

Isotonic saline was globally the most commonly used resuscitation fluid in patients with sepsis until data emerged suggesting that isotonic saline might increase the risk of acute kidney injury due to the high chloride content [77–80]. As a result, balanced crystalloids have gained popularity as the fluid of choice due to their lower chloride content, which mimics human physiologic levels [2].

Summary of the evidence

All recent trials comparing balanced crystalloids to saline evaluated subgroups of patients with sepsis [81–85]. Six

Table 2 Summary of clinical questions and recommendations for balanced crystalloids vs. isotonic saline



[a] Specific recommendations are made for adult critically ill patients with sepsis (Question 8), traumatic brain injury (Question 9), or acute kidney injury (Question 10)

studies contributed to the mortality outcome, including 6914 participants with sepsis [13]. The pooled estimate demonstrated that balanced solutions compared with isotonic saline in adult critically ill patients with sepsis probably did not result in a statistically significant reduction in mortality (RR 0.93, 95% CI 0.85–1.01, I^2 19.26%). In an individual patient data meta-analysis using a Bayesian regression model, the odds ratio for 90-day mortality among patients with sepsis with balanced crystalloids versus isotonic saline was 0.935 (95% credible interval 0.847–1.040) with a posterior probability that balanced solutions reduced mortality of 89.3% [14]. Collectively, the existing data showed that balanced crystalloids compared with isotonic saline probably resulted in a slight reduction in mortality (moderate certainty of evidence). Balanced crystalloids compared with isotonic saline might not have resulted in differences in renal replacement therapy or ventilation-free days (low certainty of evidence for both outcomes) and probably did not affect vasopressor-free days (moderate certainty of evidence) (ESM). The balance of benefits and harms favored balanced crystalloids over isotonic saline, and the certainty of the whole body of evidence across all outcomes was low (downgraded for inconsistency and imprecision).

Based on the available evidence, the panel issued a conditional recommendation for using balanced crystalloids rather than isotonic saline for volume expansion in patients with sepsis (Table 2).

Unresolved questions and research gaps

There is a need for trials comparing the effects of different balanced crystalloids on patient-centered outcomes in patients with sepsis.

Question 9: Should balanced crystalloids vs. isotonic saline be used for volume expansion in adult critically ill patients with traumatic brain injury (TBI)?

Recommendation

We **suggest** using isotonic saline rather than balanced crystalloids for volume expansion in adult critically ill patients with TBI.
Conditional recommendation, very low certainty of evidence.

Remarks

Most of the evidence is based on data from RCTs that used balanced crystalloids with near-normal osmolarity.

More hypotonic balanced crystalloids, such as Ringer's lactate (or acetate), probably should be avoided in patients with TBI.

Background

Fluid osmolarity is an important consideration in patients with TBI, as low fluid osmolality has been linked to the development of cerebral edema [86]. Isotonic saline is considered the reference solution because it has an osmolarity of 308 mOsmol/L, which is slightly higher than that of the plasma. Balanced crystalloids vary in osmolarity, but they have an osmolarity slightly lower than isotonic saline. Ringer's lactate (or acetate) is slightly hypotonic (osmolarity of Ringer's lactate 273 mOsmol/L) [87] and has been associated with higher mortality among patients with TBI compared to isotonic saline in observational data [88]. However, even other balanced crystalloids that have an osmolality near to the serum osmolality, such as Plasma-Lyte 148 (osmolarity of 294 mOsmol/L), have been linked to increased mortality in recent RCTs (see below).

Summary of the evidence

Based on a recent systematic review, we identified subgroup data from 3 RCTs with a low risk of bias that compared balanced crystalloids with isotonic saline and reported data on mortality for patients with TBI [13, 81, 83, 85, 89]. The balanced crystalloid in two trials was Plasma-Lyte, and in one trial Plasma-Lyte or Ringer's lactate [89]. The pooled analysis ($n = 1896$ participants) demonstrated an increase in mortality with balanced crystalloids compared with isotonic saline (RR 1.25, 95% CI 1.01–1.54; $I^2 = 7\%$). In an individual patient data meta-analysis using a Bayesian regression model, the odds ratio for mortality among patients with TBI with balanced crystalloids compared to isotonic saline was 1.424 (95% credible interval 1.1–1.818) with a high posterior probability (97.5%) that balanced crystalloids increased mortality [14]. Collectively, the existing data showed that balanced crystalloids compared with isotonic saline might have resulted in an increase in mortality (low certainty of evidence). Balanced crystalloids, compared to isotonic saline, had little to no effect on renal replacement therapy but the evidence was very uncertain (very low certainty of evidence) (ESM). There were no reported data on neurologic outcomes. However, a secondary analysis of the SMART trial (Isotonic Solutions and Major Adverse Renal Events trial) demonstrated that balanced crystalloids compared with isotonic saline were associated with worse discharge disposition (death or discharge to another medical facility) in critically injured patients with TBI (adjusted odds ratio [aOR] 1.38, 95% CI 1.02–1.86, P value = 0.04) [89]. The balance of benefits and harms favored isotonic saline over balanced crystalloids, and the certainty of the whole body of evidence across all outcomes was very low (downgraded for risk of bias, inconsistency, indirectness, and imprecision).

Based on the available evidence, the panel issued a conditional recommendation for using isotonic saline rather than balanced crystalloids for volume expansion in adult critically ill patients with TBI (Table 2). Because most of the evidence is based on data from RCTs that used balanced crystalloids with near-normal osmolarity and because of observational data demonstrating harm of Ringer's lactate in patients with TBI, the panel advised avoiding Ringer's lactate (or acetate), in patients with TBI.

Question 10: Should balanced crystalloids or isotonic saline be used for volume expansion in adult critically ill patients with kidney injury?

Recommendation

We **suggest** using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients with kidney injury.
Conditional recommendation, very low certainty of evidence.

Background

Volume expansion in patients with acute kidney injury (AKI) aims to improve tissue perfusion and maintain fluid balance without further compromising kidney function.

Summary of the evidence

Our literature review identified only one small relevant RCT ($n = 38$) comparing balanced crystalloids or isotonic saline in prerenal AKI with pre-established chronic kidney disease (CKD) [90]. Administration of Ringer's lactate or isotonic saline did not result in a significant

difference in short or long-term kidney function, and none of the patients required dialysis [90]. We also identified indirect evidence from RCTs on patients with renal transplantation, including the recently published BEST-Fluids (Better Evidence for Selecting Transplant Fluids) trial [12, 91–93]. In this population, pooled data (8 RCTs, $n=1526$ patients) demonstrated that balanced crystalloids compared to isotonic saline might have reduced renal replacement therapy (RR 0.85, 95% CI 0.73–0.99, I^2 0%, low certainty of evidence) and the need for mechanical ventilation (low certainty of evidence) and probably have reduced delayed graft function (moderate certainty of evidence). There were no significant differences in hospital LOS, but the evidence was very uncertain (ESM). The certainty of the whole body of evidence across all outcomes was very low (downgraded for inconsistency, indirectness, and imprecision).

The costs of balanced crystalloids solutions are modest; their availability varies and is probably limited in resource-poor settings. Taking all the above in consideration, the panel issued a conditional recommendation for using balanced crystalloids rather than isotonic saline for volume expansion in adult critically ill patients with acute kidney injury (Table 2).

Unresolved questions and research gaps

There is a need for more data on the choice of balanced crystalloids or isotonic saline for volume expansion in adult critically ill patients with acute kidney injury.

Small-volume hypertonic or isotonic crystalloids

Question 11: Should small-volume hypertonic or isotonic crystalloids be used for volume expansion in adult critically ill patients?

Recommendation

We **suggest** using isotonic crystalloids rather than small-volume hypertonic fluids for volume expansion in adult critically ill patients.
Conditional recommendation, very low certainty of evidence.

Background

Hypertonic saline solution (3%, 5%, 7.5%, 20% or other concentrations) has been investigated in animal models as an alternative to isotonic crystalloids as for the management of hypovolemic, hemorrhagic and septic shock. The hypertonic saline solution provides immediate intravascular volume expansion but with a reduced amount of administered volume [94]. Limited evidence from observational cohorts showed that a positive fluid balance was associated with worse ICU mortality and functional outcomes of TBI patients [95]. It has been shown that hypertonic saline solution, compared to isotonic saline, was associated with improved hemodynamics [96]. Hypertonic saline solution may have favorable anti-inflammatory effects [97]. Because smaller volumes of hypertonic saline are needed to expand intravascular volume, it has an advantage as a resuscitation fluid on the battlefield and in pre-hospital settings [98–100]. However, the high chloride content of hypertonic saline may have adverse effects, including acidosis, coagulopathy, and impaired renal function [101]. Of note, the use of hypertonic saline in patients with traumatic brain injury (TBI) as a bolus in a pre-hospital setting or as a continuous infusion in the ICU has not improved either short-term or long-term outcomes compared to patients who received conventional fluids [100, 102].

Summary of the evidence

Our literature search, including reviewing existing systematic reviews [15, 103–107] identified 17 RCTs comparing hypertonic saline solution to isotonic crystalloids in patients with trauma, hypovolemia, sepsis, and surgery. Pooled analysis suggested that hypertonic saline solution compared to isotonic crystalloids in adult critically ill patients did not reduce mortality (17 trials, $n=2195$, RR 0.99, 95% CI 0.88–1.12, I^2 0%, low certainty of evidence, Fig. 2 and ESM). The analysis also suggested that hypertonic saline solution compared to isotonic crystalloids did not result in a difference in renal replacement therapy, ventilation-free days, ICU length of stay, or functional outcomes (low certainty of evidence for the four outcomes) and the evidence about hospital length of stay was very uncertain (very low certainty of evidence, ESM). The balance of benefits and harms did not favor small-volume hypertonic or isotonic crystalloids, and the certainty of the whole body of evidence across all outcomes was very low (downgraded for risk of bias, inconsistency, and imprecision).

The balance of effects did not favor either hypertonic saline solution to isotonic crystalloids. However, given the variable availability, the additional cost, and the limited acceptability of hypertonic saline among critical care practitioners, the panel issued a conditional recommendation for using isotonic crystalloids rather than small volume hypertonic fluids for volume expansion (Table 3).

Unresolved questions and research gaps

Further research is required to identify if there are subgroups of adult critically ill patients who may benefit from hypertonic saline for volume expansion [108].

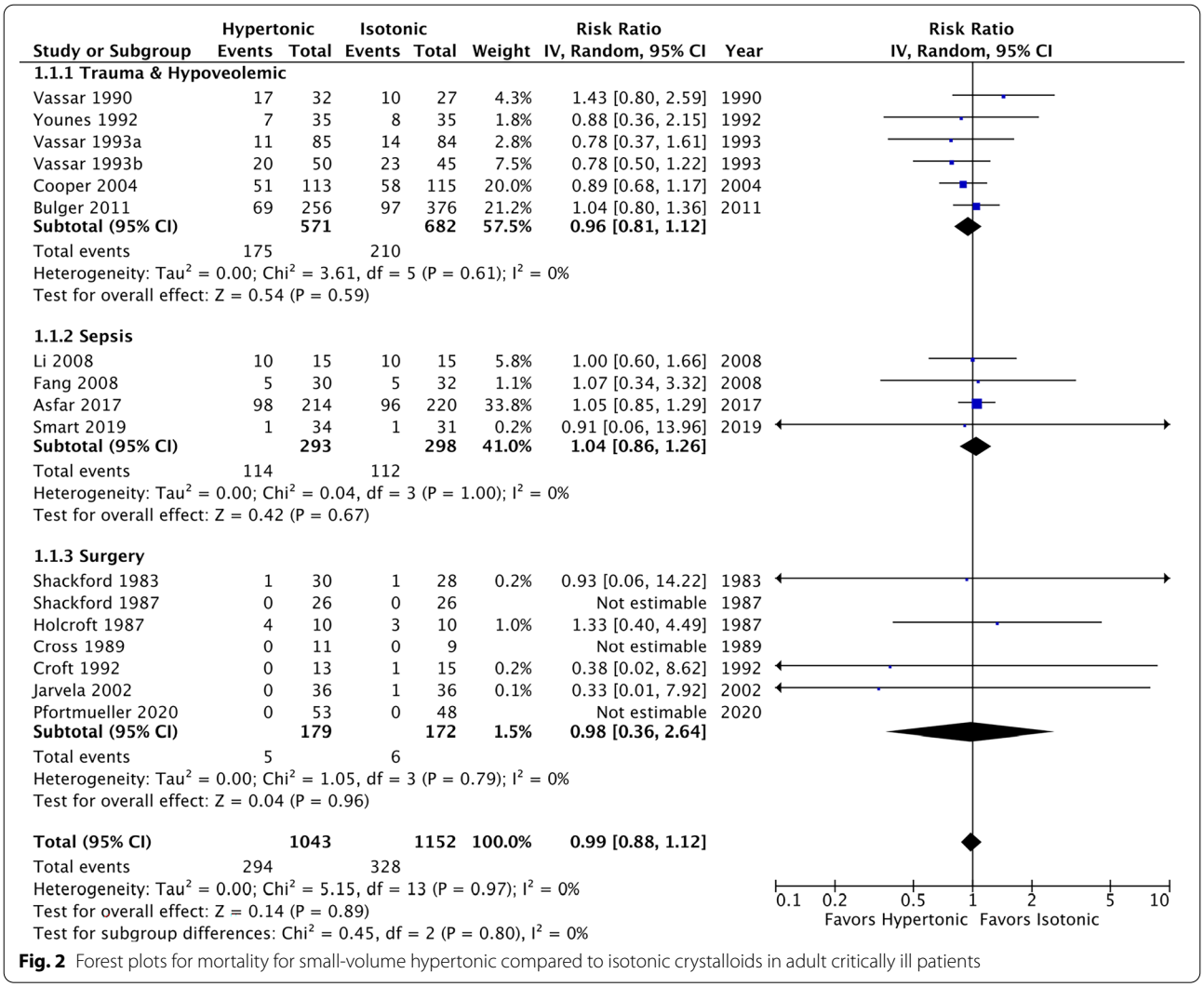


Fig. 2 Forest plots for mortality for small-volume hypertonic compared to isotonic crystalloids in adult critically ill patients

Table 3 Summary of the clinical question and recommendation for small-volume hypertonic or isotonic crystalloids

SUMMARY OF CLINICAL QUESTIONS AND RECOMMENDATIONS FOR SMALL-VOLUME HYPERTONIC OR ISOTONIC CRYSTALLOIDS	
Q11 Should small-volume hypertonic or isotonic crystalloids be used for volume expansion in adult critically ill patients?	
R We suggest using isotonic crystalloids rather than small-volume hypertonic fluids for volume expansion in adult critically ill patients.	VERY LOW CERTAINTY OF EVIDENCE

CERTAINTY OF EVIDENCE:
NO EVIDENCE / VERY LOW / LOW / MODERATE / HIGH

Q QUESTION R RECOMMENDATION REMARK

NO RECOMMENDATION CONDITIONAL RECOMMENDATION STRONG RECOMMENDATION
CONDITIONAL RECOMMENDATION AGAINST STRONG RECOMMENDATION AGAINST

Conclusions

In conclusion, these guidelines present 11 evidence-based recommendations (summarized in Tables 1, 2 and 3) regarding the use of albumin, balanced crystalloids and isotonic saline as resuscitation fluid in adult critically ill patients. In addition, research priorities were identified for future studies.

Supplementary Information

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Declarations

Conflicts of interest

YMA: none. EB-C: None. AC: none. DDB: received remuneration from Fresenius, Baxter, Pfizer, Edwards, Philips, and has published and presented on the topic. KD: none. NPJ received unrestricted funding from Octaphrama for investigator driven research on development of fluids for shock treatment that are associated with reduced vascular permeability, and reported publishing on the topic. NH reported that her institute, the George Institute for Global Health, has received research and travel funding from Baxter, Fresenius Karbi, Grifols and CSL. She has several publications related to the topic including Crystalloid vs Hydroxyethyl Starch Trial (CHEST); Fluid TRIPS; Plasma-Lyte vs saline trial (PLUS) and has presented research findings in relation to fluid therapy at national and international critical care conferences. JHL presented on the topic at national and international meetings, one opinion piece in Acta Anaesthesiologica Scandinavia (regarding the use of starches (HES)). DL: none. KM: none. AM received a lecture fee from Baxter. MHM: none. DP: participated in guidelines focused on fluid management in cerebral injury. RMS: none. JLV: none. FGZ received consulting fees from Baxter International and is the PI of the BaSICS trial that received logistic support and fluid donation from Baxter Hospitalar (Brazil). FA: none.

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