REVIEW ARTICLE

Scandinavian clinical practice guideline on choice of fluid in resuscitation of critically ill patients with acute circulatory failure

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Conflict of interests
E. J., M. H., K. H., R. K., P. O. V. and M. H. M. have declared no conflict of interest. A. P. was the sponsor-investigator of the 6S trial, which was supported by B. Braun, and he has received honoraria from Ferring Pharmaceuticals (SC work in a sepsis trial) and LFB S.A. (speakers fee). The Department of Intensive Care, Rigshospitalet receives support for research from CLS Behring, Fresenius Kabi, BioPorto and Cosmed.

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Background: The task force on Acute Circulatory Failure of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine produced this guideline with recommendations concerning the use of crystalloid vs. colloid solutions in adult critically ill patients with acute circulatory failure.
Methods: Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to grade the quality of evidence and to determine the strengths of the recommendations. As efficacy and harm may vary in different subpopulations of patients with acute circulatory failure, we produced recommendations for general intensive care unit (ICU) patients and those with sepsis, trauma and burn injury.
Results: For general ICU patients and those with sepsis, we recommend using crystalloids for resuscitation rather than hydroxyethyl starch and we suggest using crystalloids rather than gelatin and albumin. For patients with trauma we recommend to use crystalloids for resuscitation rather than colloid solutions. For patients with burn injury we provide no recommendations as there are very limited data from randomised trials on fluid resuscitation in this patient population.
Conclusions: We recommend using crystalloid solutions rather than colloid solutions for resuscitation in the majority of critically ill patients with acute circulatory failure.

Practice Guidelines:
• There are other guidelines on fluid therapy for critically ill patients, e.g. from the European Society of Intensive Care Medicine.
• This guideline was developed in line with new standards and systems for trustworthy guidelines by the Clinical Practice Committee of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine to facilitate evidence-based fluid therapy for patients with acute circulatory failure.
• This guideline differs from the previous ones on fluid therapy because it includes recommendations based on the recently updated systematic reviews and meta-analyses of high-quality trials comparing crystalloids with colloids.
• Recommendations based on a higher quality of evidence can be given because substantial amounts of high-quality data have been published in the last years.
[Correction added on 28 January 2015, after first online publication: The Practice Guidelines were added].

As part of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine's (SSAI) efforts to improve perioperative and intensive care, this clinical practice guideline was produced by the SSAI Acute Circulatory Failure task force. The work was initiated by the Clinical Practice Committee of SSAI.

Acute circulatory failure or circulatory shock is a frequent and life-threatening condition that needs prompt and appropriate care.[1] With either cardiac and/or non-cardiac aetiologies, inadequate cardiac output, altered peripheral vascular tone and/or loss or imbalance in intravascular volume can contribute to limited delivery and uptake of substrates in vital organs. If left untreated, hypotension, hypoperfusion and cellular hypoxia may progress to organ failure and death.

Fluid resuscitation is a mainstay therapy for the non-cardiac causes of acute circulatory failure for patients with sepsis, trauma and burn injury, and in support of the circulation in critically ill patients in general. There is a need for clinical practice guidelines to reflect new evidence concerning the choice of fluid for therapy of acute circulatory failure.[2] This clinical practice guideline is among the first to be produced from our group meeting the new standards for trustworthy guidelines, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (http://www.gradeworkinggroup.org).[3–5]

Methods

Process

The Clinical Practice Committee of SSAI appointed national members of the guideline task force for Acute Circulatory Failure (the authors of this paper). We invited two colleagues with focused methodological experience in systematic reviews and the GRADE system (P. O. V. and M. H. M.) to help facilitate the work.

The task force identified key clinical questions for fluid resuscitation, vasopressor therapy, inotropic therapy and diagnostics and monitoring to fully cover the management of acute circulatory failure. This is the report of the work on choice of fluid type for critical care resuscitation.

GRADE

We used the GRADE system for formulating clinical questions, assessing the quality of evidence, generating anticipated absolute effects and for moving from evidence to recommendations.[5] Briefly, clinical questions were formulated in a specific format, which identified the relevant patient population and/or clinical problem (P), the intervention (I) under scrutiny as well as the comparator (C), and patient-important outcomes (O). It is likely that the efficacy and harm of fluids may be context dependent; that is, they can be different for different patient populations, comparator fluids and outcomes. Therefore, we aimed to identify benefits and harms of crystalloid vs. colloid resuscitation in critical care by answering the combination of populations/interventions/comparators/outcomes (PICO) questions outlined in Table 1 amounting to 12 different specific questions in total.

The populations were general intensive care unit (ICU) patients, patients with sepsis, patients with trauma and patients with burn injury. The standard intervention was crystalloid solution for resuscitation fluid. Relevant com-

Table 1 Clinical and PICO questions used to assess evidence relevant to this guideline statement.

	PICO question			
Clinical question	Population (P)	Intervention (I)	Comparator (C)	Outcomes (O)
1. Should crystalloid or colloid solutions be used for resuscitation of acutely ill patients with circulatory failure?	Adult acutely ill patients: • General ICU patients • Sepsis • Trauma • Burn injury	Crystalloid solutions*	Colloid solutions • HES • Albumin • Gelatin	Mortality at longest follow-up Use of renal replacement therapy Acute kidney injury Bleeding Serious adverse events Length of hospital stay

*Including isotonic saline or balanced salt solutions including Ringer's or Hartman's.

parators were hydroxyethyl starch (HES), gelatin or albumin. For the starch solutions, we assessed when possible HES 130/0.38–0.45 (molecular weight/substitution ratio) rather than the older products with higher molecular weight and substitution ratio. The patient outcomes of interest were mortality, use of renal replacement therapy (RRT), acute kidney injury (AKI), bleeding, serious adverse events (SAEs) and length of hospital stay.

We systematically searched PubMed and the Cochrane Library for recently updated systematic reviews of randomised clinical trials (RCTs) comparing crystalloid solutions with colloid solutions. We updated the searches of the identified reviews in April 2014 using the search strategies of these reviews. If we found no systematic review or subgroup analysis in reviews answering specific PICOs, as it was the case for patients with trauma and burn injury, we searched for RCTs in PubMed [free text: 'random* and (colloid/HES/starch/gelatin/albumin) and (trauma/injur*/burn/thermal)], and in the recently updated systematic reviews on fluid resuscitation in critically ill patients in general.[2,6–8]

The target populations were adult critically ill patients with acute circulatory failure/shock resuscitated with crystalloid or colloid in a high-dependency setting in hospital, including the emergency department, ICU, operating room or recovery room. We excluded systematic reviews and trials done in patients aged less than 18 years, done in elective surgery, those not comparing crystalloids with colloids (e.g. colloid vs. colloid) and those comparing hypertonic crystalloid solution(s) with colloid. Reviews and trials comparing a crystalloid solution to dextrans or HES with molecular weight or substitution ratio above 130 or 0.45, respectively, were excluded because these colloid solutions are less used.[9]

If we identified trials not included in the systematic reviews we updated the meta-analyses with data from the identified RCTs using Revman 5 (http://www.tech.cochrane.org/Revman). If the identified systematic reviews did not provide relevant meta-analyses for our PICOs, we extracted data from relevant RCTs and performed meta-analyses using Revman 5 to obtain pooled effect-estimates for as many of the PICOs as possible.

In keeping with the GRADE methodology, we downgraded the quality of evidence for an intervention (our confidence in the effect-estimates) for identified risks of bias (lack of blinding, or early termination of studies), inconsistency (unexplained heterogeneity), indirectness (e.g. other patient populations or use of surrogate outcomes), imprecision (wide confidence interval around the effect estimate) or publication bias (if identified in the systematic review). The results were presented in summary of finding tables with anticipated relative and absolute effects for the outcomes, together with our confidence in the effect-estimates using GradePro v. 3.5 (downloaded at http://www.gradeworkinggroup.org). Accordingly, the quality of evidence was rated from 'high' to 'very low'.

When moving from evidence to recommendations four factors were considered and integrated: benefits and harms, quality of evidence, values and preferences (of patients or their proxies) and cost considerations. GRADE classifies recommendations as strong when virtually all informed patients would choose the recommended management strategy. Weak recommendations, which

reflect a close call between benefits and harms, uncertainty regarding treatment effects, questionable cost-effectiveness, or variability in values and preferences, apply when fully informed patients would choose different management strategies.[5,10]

The recommendations were agreed upon by the group. We specified in advance that if total agreement could not be obtained, the group would vote; 2/3 of the votes were needed to issue a strong recommendation. Strong recommendations were given the wording 'we recommend' and weak recommendations 'we suggest'. If dissenting opinions occurred for a specific recommendation, they were included in the text for clarification.

Results

The results and recommendations based on the PICOs are presented below, in Table 2 and in the summary of finding tables given in the Supporting information. All members of the guideline group agreed upon all of the recommendations.

A. Fluid resuscitation of general ICU patients

1. We recommend that crystalloids are used for resuscitation in general ICU patients rather than HES (strong recommendation and moderate quality of the evidence).

The rationale is that an updated meta-analysis of crystalloid vs. HES showed clear benefit of crystalloids when balancing all patient-important outcomes, including mortality, in critically ill patients (Table S1A).[7] The results are supported by the meta-analyses comparing HES to any other comparators[2,6] and those of a large, high-quality RCT that compared 0.9% NaCl with 6% HES 130/0.4 in 7000 general ICU patients with signs of hypovolaemia.[11] The results of the latter trial indicated no differences in survival or hospital length of stay between the intervention groups, but the HES group had increased use of RRT and increased adverse events, mainly pruritus. Another recently published large RCT, the CRISTAL trial,[12] compared any crystalloid to any colloid solution in ICU patients with shock. The results indicated that colloids (mainly HES) vs. crystalloids (mainly saline) improved 90-day mortality, which was a secondary outcome measure. However, the trial had high risk of bias in several domains (unblinded, uncertain allocation concealment and baseline imbalance)[13] and the results differed from those of the high-quality trials mentioned above. In an accompanying editorial, the editor argued for cautious interpretation of these findings and that crystalloid should be the first line fluid in patients with shock.[14] Given the high risk of bias in CRISTAL, we did not take these data into consideration. Based on the included data we recommend that crystalloid solutions rather than HES are used for resuscitation in general ICU patients. The binding decision from European Commission also states that HES should not be used in critically ill patients.*

2. We suggest that crystalloids are used for resuscitation in general ICU patients rather than albumin (weak recommendation and moderate quality of the evidence).

The rationale is that an updated meta-analysis of albumin vs. crystalloids in critically ill patients showed no difference in mortality or in other outcomes (Table S1B).[7] The results are supported by those of a large, high-quality RCT, the SAFE trial, which compared 0.9% NaCl with 4% albumin in 7000 general ICU patients with signs of hypovolaemia.[15] In that trial none of the outcome measures differed between the two intervention groups, including mortality, use of RRT and hospital length of stay (Table S1B). No cost minimisation analysis was made in SAFE, but albumin is a blood product and as such a limited resource and its cost is much higher than that of crystalloids. Therefore, we suggest using the latter in general ICU patients.

3. We suggest that crystalloids are used for resuscitation in general ICU patients rather than gelatin (weak recommendation and very low quality of the evidence).

The rationale is that the updated meta-analysis of gelatin vs. crystalloids in critically ill patients showed no difference in mortality (Table S1C).[7] However, there were few events in the trials included and the pooled effect-estimate was imprecise. Therefore the benefits and harms of gelatin are largely unknown in these patients, but they have been associated with increased risk of AKI and bleeding.[16,17] These observations are

*http://www.ec.europa.eu/health/documents/community-register/2013/20131219127286/dec_127286_en.pdf

Table 2 Key recommendations and quality of evidence.

	Strength of the recommendation	Benefits and harms	Quality of evidence Reason(s) for downgrading	Comments
Fluid resuscitation of general ICU patients				
1. We recommend that crystalloids are used for resuscitation in general ICU patients rather than HES	Strong	An updated meta-analysis of crystalloid vs. HES in critically ill patients showed clear benefit of crystalloids when balancing all patient-important outcomes, including mortality	Moderate due to risk of bias	
2. We suggest that crystalloids are used for resuscitation in general ICU patients rather than albumin	Weak	An updated meta-analysis of crystalloids vs. albumin in critically ill patients showed no difference in mortality or in other important outcomes	Moderate due to risk of bias	Albumin is a blood product and a limited and costly resource
3. We suggest that crystalloids are used for resuscitation in general ICU patients rather than gelatin	Weak	An updated meta-analysis of crystalloids vs. gelatin in critically ill patients showed no difference in mortality	Very low due to risk of bias and imprecision	Benefits and harms of gelatin are largely unknown, but they have been associated with increased risk of acute kidney injury and bleeding in observational studies
Fluid resuscitation of patients with sepsis				
1. We recommend that crystalloids are used for resuscitation in patients with sepsis rather than HES.	Strong	In two recently updated systematic meta-analyses of crystalloid vs. HES in critically ill septic patients, HES increased long-term (> 28 days) mortality, use of RRT and rates SAEs compared to crystalloids	Moderate due to imprecision	
2. We suggest that crystalloids are used for resuscitation in patients with sepsis rather than albumin.	Weak	A meta-analysis of data from the SAFE and ALBIOS trials showed no benefit or harm from albumin compared to saline	Low due to risk of bias	Albumin is a blood product and a limited and costly resource
3. We suggest that crystalloids are used for resuscitation in patients with sepsis rather than gelatin.	Weak	No meta-analyses or RCTs exist of crystalloids vs. gelatin in patients with sepsis	Very low due to lack of RCTs and meta-analyses	Benefits and harms of gelatin are largely unknown, and they have been associated with increased risk of acute kidney injury and bleeding in observational studies
Fluid resuscitation of patients with trauma				
We recommend that crystalloids are used for resuscitation in patients with trauma rather than colloids.	Strong	A meta-analysis of data of existing RCTs in patients with trauma showed that colloid resuscitation was associated with increased risk of death	Very low due to risk of bias and imprecision	
Fluid resuscitation of patients with burn				
	No recommendation	Very limited data from RCTs	Very low due to risk of bias and imprecision	We refrain from giving any recommendations because of the very low level of evidence

supported by data from an updated meta-analysis of gelatin vs. albumin/crystalloid.[18] As mentioned above, there appears to be no benefit of other colloid solutions in critically ill patients in general, and therefore we suggest that gelatin is not used in these patients. However, the quality of the evidence is very low for this suggestion.

B. Fluid resuscitation of patients with sepsis

1. We recommend that crystalloids are used for resuscitation in patients with sepsis rather than HES (strong recommendation and moderate quality of the evidence).

The rationale is based on two recently updated systematic reviews on patients with sepsis,[19,20] which included most of the same RCTs (we chose to use data from the one including most trials – nine trials with 3456 patients also including SAEs as an outcome vs. six trials with 3033 patients) (Table S2A). The systematic review we report included two RCTs that used albumin as comparator,[19] however few patients received albumin and these contributed with few events and only in the outcomes mortality and SAEs. There was overall heterogeneity among trial results, but this was balanced by the pre-defined subgroup analysis of trials with low risk of bias. These trials also had follow-up for mortality for more than 28 days, which is important because the difference in mortality between patients assigned to HES vs. crystalloid was observed beyond day 28 in one trial.[21] In patients with sepsis, HES 130/0.38–0.45 increased long-term (> 28 days) mortality compared to crystalloids (Table S2A). In addition, the use of RRT was increased and more patients had SAEs with HES compared to crystalloids (Table S2A). The binding decision from the European Commission also states that HES should not be used in patients with sepsis.*

2. We suggest that crystalloids are used for resuscitation in patients with sepsis rather than albumin (weak recommendation and moderate quality of the evidence).

We identified a recently updated systematic review including 17 RCTs.[22] In 12 of the trials included in that review, the comparator was a synthetic colloid, three trials were in children, and one in ARDS patients. As the SAFE trial was the only RCT comparing albumin to crystalloid that included adults with sepsis, we base our suggestion on data from SAFE[15] and the recently published ALBIOS trial.[23] In SAFE, the 1218 included patients with severe sepsis were analysed as predefined subgroup, but sepsis was not a stratification variable at randomisation. In the subgroup analysis of these patients there was a trend towards lower 28-day mortality with albumin vs. saline. In the ALBIOS trial, 1818 patients with severe sepsis were randomised to 20% albumin vs. saline, but there were no differences in 28-day mortality, which was the primary outcome, or in any of the secondary outcome measures.[23] Pooling the data from the SAFE and ALBIOS trials showed no benefit or harm from albumin compared with saline (Fig. 1 and Table S2B). Economic analyses were not made in SAFE or ALBIOS, but albumin is a limited and costly resource. Emerging data from RCTs in adults with sepsis will hopefully clarify the indications for albumin. Until then we suggest not to use albumin for resuscitation in adults with sepsis.

3. We suggest that crystalloids are used for resuscitation in patients with sepsis rather than gelatin (weak recommendation and very low quality of the evidence).

The rationale is based on a recently updated systematic review where no RCTs could be included for adult patients with sepsis.[18] We have updated the search and also found no RCTs in adult patients with sepsis comparing gelatin to crystalloids. Therefore the benefits and harms of gelatin are unknown in patients with sepsis. As noted above, gelatin has been associated with increased risk of kidney failure and bleeding.[16,17] The results from trials assessing other colloids indicate that there are little, if any, differences in fluid volumes and circulatory parameters between patients with sepsis resuscitated with colloid vs. crystalloid solutions.[21,24] Therefore, we recommend that if clinicians want to use gelatin in sepsis, this should only be in the context of an RCT of sufficient size to detect side effects, a notion supported by the European Society of Intensive Care Medicine task force on colloids.[25]

C. Fluid resuscitation of patients with trauma

1. We recommend that crystalloids are used for resuscitation in patients with trauma rather than colloids (strong recommendation and low quality of the evidence).

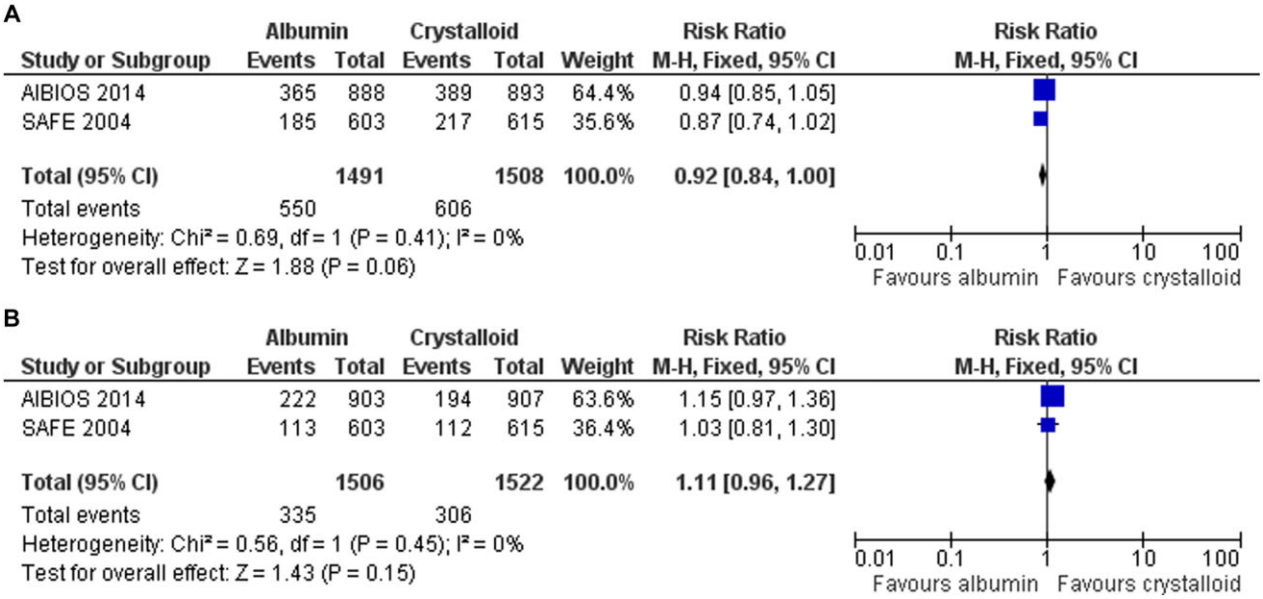

Fig. 1. Forest plot of (A) all-cause mortality and (B) renal replacement therapy in randomised trials of crystalloid vs. albumin for resuscitation of patients with sepsis. Size of squares for risk ratio reflects weight of trial in pooled analyses. Horizontal bars represent 95% confidence intervals.

We did not identify an updated systematic review of patients with trauma. In the updated, large systematic reviews of critically ill patients we found RCTs examining crystalloid vs. colloid solutions in trauma. Our own meta-analysis of data of the RCTs in patients with trauma showed that colloid resuscitation was associated with an increased risk of death [Fig. 2 and (Table S3A–C)]. There were not sufficient data to analyse the other outcome measures.

D. Fluid resuscitation of patients with burn injury

For patients with burn injury we could not find updated systematic reviews and we only identified three small RCTs that were relevant for this clinical question.[26–28] Two of these trials were on albumin vs. Ringer's lactate and both were small (total $n = 79$ and $n = 42$) and the larger trial had high risk of bias (lack of allocation concealment and blinding).[26] The third trial assessed 48 patients randomised to HES 130/0.40 vs. Ringer's lactate and showed no benefit or harm of HES,[28] but the interpretation is hampered by the small sample size (imprecision). Based on the very limited amount of data (Fig. 3 and Table S4A–C) we refrain from giving any recommendations or suggestions on choice of resuscitation fluid for burn patients. However, we strongly recommend that clinicians who continue to use colloid solutions in patients with burn injury do so in the context of high quality RCTs given the limited effects and harms observed with colloids in other patient groups (ungraded). And clinicians should be aware of the binding decision from the European Commission, which states that HES should not be used in patients with burn injury.*

Discussion

This guideline on fluid resuscitation has been produced following the recently, updated, high-quality meta-analyses comparing crystalloids with colloids.[2,6,7,19] In addition we meta-analysed data from RCTs in several patient groups to obtain a base for moving from evidence to recommendations or suggestions for as many of the PICO questions as possible. We have issued several strong recommendations favouring crystalloids over colloids in all patient groups. This was based on overall low confidence of benefit from colloid resuscitation, confidence of harm caused by the synthetic colloids (high confidence for HES and low for gelatin) and high cost of albumin, which is also a limited resource. For patients with burn

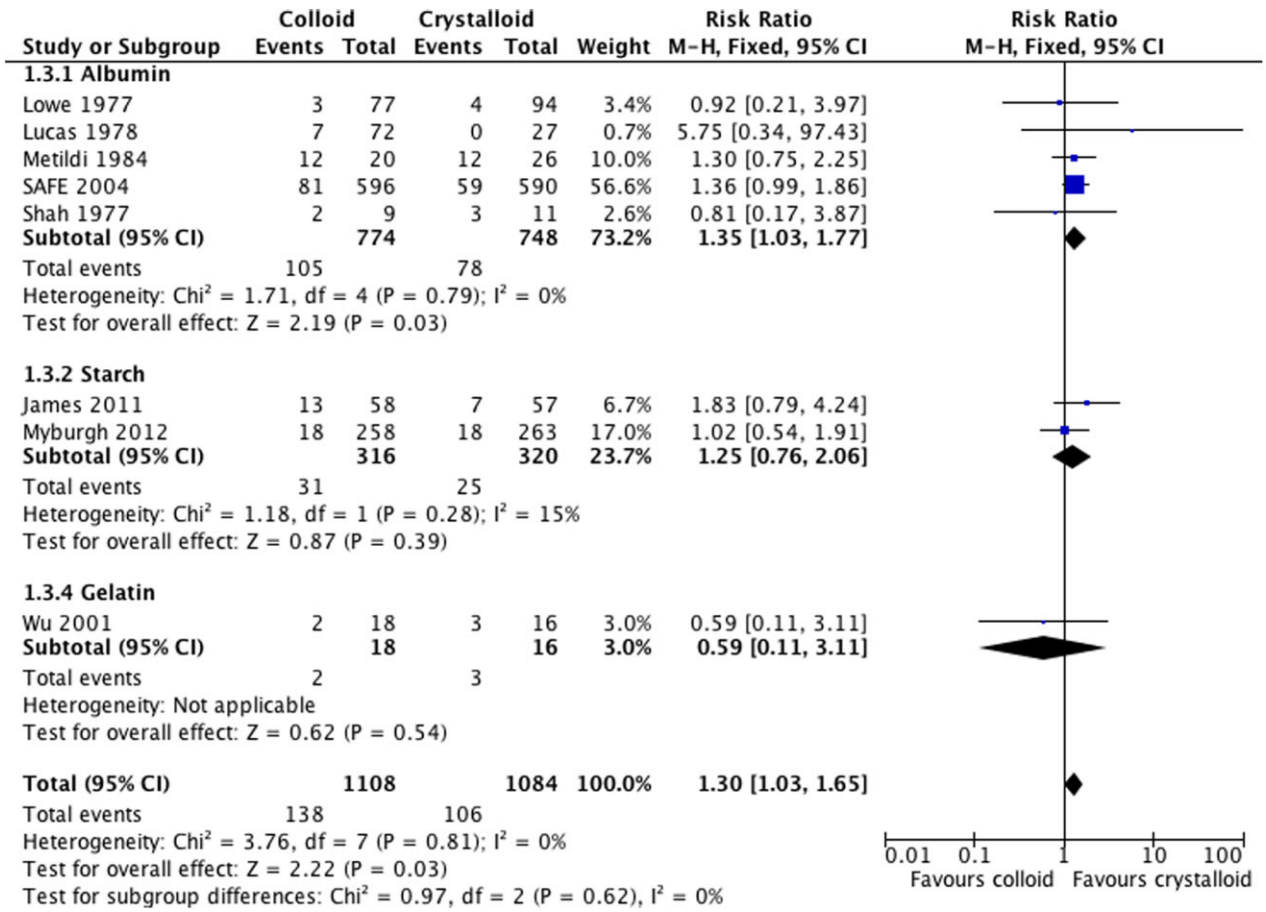

Fig. 2. Forest plot of all-cause mortality in randomised trials of crystalloid vs. colloid solutions for resuscitation of patients with trauma.[11,15,34–39] The trial results were sub-grouped based on the colloid solution (albumin, starch and gelatin) used in the trials. Size of squares for risk ratio reflects weight of trial in pooled analyses. Horizontal bars represent 95% confidence intervals.

injury, we considered the quality of the evidence to be very low and chose not to issue recommendations for these patients. Patients with burn injury likely represent a specific entity because of the massive capillary leak and therefore the results from the other patient categories may be less applicable to these patients. It is our impression that colloid solutions, albumin in particular, are part of burn resuscitation in clinical practice. Therefore, high-quality trials are urgently needed in patients with burn injury to ensure that this practice is cost-effective and without harm. The use of HES, on the other hand, is now restricted in patients with burn injury by EU legislation.

Our recommendation against the three types of colloids, albumin, HES and gelatin, may result in increased use of dextrans[29,30] or the development of new types of colloids. We believe that clinicians who would consider using dextrans or other types of colloids should do so only in the context of RCTs. The likelihood that dextrans or other colloids would benefit critically ill patients is low given the lack of benefit of albumin. In addition the risk of harm by dextrans, in particular, is eminent because they have been associated with AKI and bleeding.[31,32]

The strengths of our guideline include the application of new standards for trustworthy guidelines and the use of the GRADE methodology, which ensured a systematic and transparent process. The limitations include the reliance upon recently updated systematic reviews for the majority of recommendations. In these, there was no subgrouping of patients based on indications for fluid therapy, most likely because no single indications are supported by high-quality data.

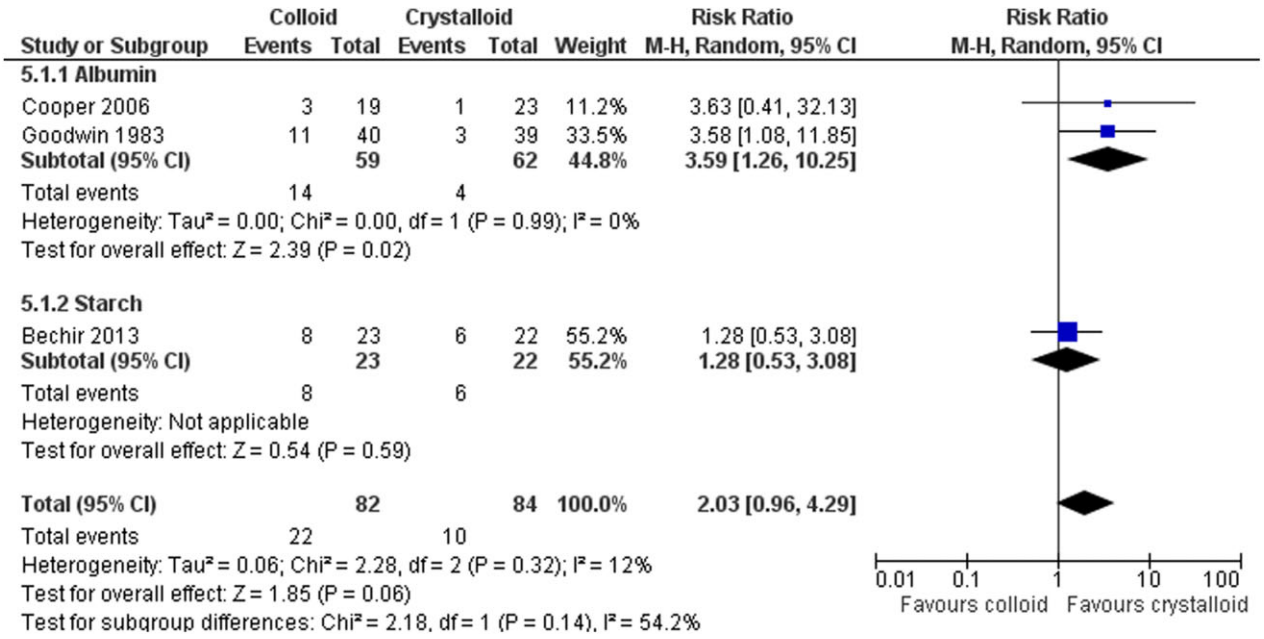

Fig. 3. Forest plot of all-cause mortality in randomised trials of crystalloid vs. colloid solutions for resuscitation of patients with burn injury.[26–28] The trial results were sub-grouped based on the colloid solution (albumin and starch) used in the trials. Size of squares for risk ratio reflects weight of trial in pooled analyses. Horizontal bars represent 95% confidence intervals.

We did several meta-analyses, but the number of included RCTs was small, which is a limitation in the evidence base not the guideline per se. We did not include all patient-important outcome measures (e.g. quality of life), because we, a priori, found it less likely to find data from meta-analyses or RCTs on these outcomes. To our knowledge there is only one report on data on quality of life of patients randomised to different types of fluids.[33] Bias may have influenced the results as the chair of the task force was the principal investigator of the 6S trial,[21] which showed harm from HES in sepsis. However, all members of the group formed and agreed upon all recommendations and suggestions in this guideline, making it less likely that bias influenced the results and recommendations.

In conclusion, we recommend using crystalloids for resuscitation of critically ill adult patients including general ICU patients and those with sepsis or trauma. We refrain from giving any recommendations or suggestions on choice of resuscitation fluid for patients with burn injury, because of the very low quality of evidence in these patients. If resuscitation using colloids is to continue, high-quality trials should be performed to ensure patient safety and overall benefit for patients and society.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. (A) Question: Should crystalloids or HES be used for acute circulatory failure in general ICU patients? (B) Question: Should crystalloids or albumin be used for acute circulatory failure in general ICU patients? (C) Question:

Should crystalloids or gelatin be used for acute circulatory failure in general ICU patients?

Table S2. (A) Question: Should crystalloids or HES be used for acute circulatory failure in patients with sepsis? (B) Question: Should crystalloids or albumin be used for acute circulatory failure in patients with sepsis? (C) Question: Should crystalloids or gelatin be used for acute circulatory failure in patients with sepsis?

Table S3. (A) Question: Should crystalloids or HES be used for acute circulatory failure in patients with trauma? (B) Question: Should crystalloids or albumin be used for acute circulatory failure in patients with trauma? (C) Question: Should crystalloids or gelatin be used for acute circulatory failure in patients with trauma?

Table S4. (A) Question: Should crystalloids or HES be used for acute circulatory failure in patients with burn? (B) Question: Should crystalloids or albumin be used for acute circulatory failure in patients with burn? (C) Question: Should crystalloids or gelatin be used for acute circulatory failure in patients with burn?