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2 - GENERAL ICU: Fluid resuscitation in adult critically ill patients with acute circulatory failure
3 - SEPSIS: Fluid resuscitation in adult critically ill septic patients with acute circulatory failure
4 - TRAUMA: Fluid resuscitation in adult critically ill trauma patients with acute circulatory failure
5 - BURNS: Fluid resuscitation in adult critically ill burn patients with acute circulatory failure
Summary of recommendations

1 - About this guideline from the Scandinavian Society for Anesthesiology and Intensive Care (SSAI)

Info Box

This clinical practice guideline -available here with recommendations in multilayered formats available on all devices - was initially published December 2014 in Acta Anaesthesiologica Scandinavica (available in full text through reference nr.34) as part of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine's (SSAI) efforts to improve perioperative and intensive care. The guideline was produced by the SSAI Acute Circulatory Failure task force. The work was initiated by the Clinical Practice Committee of SSAI. See Background text for description of background and methods set up to adhere to standards for trustworthy guidelines (reference nr.xx).

Authors and affiliations: A. Perner¹, E. Junttila², M. Haney³, K. Hreinsson⁴, R. Kvåle⁵, P. O. Vandvik⁶ and M. H. Møller¹

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2 - GENERAL ICU: Fluid resuscitation in adult critically ill patients with acute circulatory failure

Hydroxyethyl starch (HES)

Strong Recommendation

We recommend that crystalloids are used for resuscitation in general ICU patients rather than HES

Albumin

Weak Recommendation

We suggest that crystalloids are used for resuscitation in general ICU patients rather than albumin
Gelatin

Weak Recommendation

We suggest that crystalloids are used for resuscitation in general ICU patients rather than gelatin.

3 - SEPSIS: Fluid resuscitation in adult critically ill septic patients with acute circulatory failure

Hydroxyethyl starch (HES)

Strong Recommendation

We recommend that crystalloids are used for resuscitation in patients with sepsis rather than HES.

Albumin

Weak Recommendation

We suggest that crystalloids are used for resuscitation in patients with sepsis rather than albumin.

Gelatin

Weak Recommendation

We suggest that crystalloids are used for resuscitation in patients with sepsis rather than gelatin.

4 - TRAUMA: Fluid resuscitation in adult critically ill trauma patients with acute circulatory failure

Colloids

Strong Recommendation

We recommend that crystalloids are used for resuscitation in patients with trauma rather than colloids.

5 - BURNS: Fluid resuscitation in adult critically ill burn patients with acute circulatory failure
Colloids

Practice Statement

Clinicians should be aware of the existing very low quality evidence to guide decisions about what fluid to use in patients with burns. We have refrained from making distinct recommendations for either crystalloid solutions, albumin or gelatin whereas use of HES generally is discouraged also in patients with burns. We encourage clinicians to take part in high quality trials to improve best current evidence for patients with burns.
1 - About this guideline from the Scandinavian Society for Anesthesiology and Intensive Care (SSAI)

Background for the development of this guideline

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 (Dellinger 2013). 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 routine 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 (Gattas 2013). This clinical practice guideline is among the first to be produced from our group meeting the new standards for trustworthy guidelines, using the GRADE methodology (www.gradeworkinggroup.org) (Laine 2011; Qaseem 2012; Guyatt 2008).

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). A colleague with focused methodological experience in systematic reviews and the GRADE system (MHM) was invited 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 resuscitation.

GRADE

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for formulating clinical questions, assessing the quality of evidence, generating anticipated absolute effects and for moving from evidence to recommendations (Guyatt 2008). 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 versus colloid resuscitation in critical care by answering the combination of populations / interventions / comparators / outcomes (PICO) questions amounting to 60 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 comparators were hydroxyethyl starch (HES) 130/0.38-0.45 (molecular weight/substitution ratio), gelatin or albumin. 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 trauma and burn, 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 (Gattas 2013; Zarychanski 2013; Perel 2013; Roberts 2011).

The target populations were adult 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 (Finfer 2010).

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://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 down-graded the quality of evidence for an intervention (our confidence in the effect-estimates) for identified risks of bias (due to 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. 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 in GradePro v. 3.5 (downloaded at www.gradeworkinggroup.org). Accordingly, the quality of evidence was rated from “high” to “very low”.

When moving from evidence to recommendations 4 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 (Guyatt 2008; Guyatt 2012).

The recommendations were agreed upon by the group. We specified prospectively 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.

Conflicts of interests (COI)

Guideline authors all declared COI according to requirements for the publication in Acta Anaesthesiologic Scandinavica. 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.

Values and preferences

The guideline panel considered anticipated patient values and preferences when moving from evidence to recommendations, according to the GRADE system. In the absence of patient representation in the guideline panel - and available systematic reviews to inform judgements about values and preferences - these assumptions were based on a high value of avoiding deaths in critically ill patients with acute circulatory failure weighed against other outcomes such as adverse events.

Peer-review

This guideline underwent internal peer-review by the SSAI practice committee before submission to the journal for publication. The journal performed academic peer-review according to their standards. Changes were made based on external peer-review resulting in the final guideline published.

Strategy for updating

SSAI will update this guideline according to their strategy for “living guidelines” where new evidence that might potentially change the strength or direction of recommendations will lead to dynamic updates of recommendations in the guidelines. These updates will be published in MAGICapp and followed by updates in the journal. The work with dynamic updating of recommendations will commence March 2016.
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### Hydroxyethyl starch (HES)

<table>
<thead>
<tr>
<th>Strong Recommendation</th>
</tr>
</thead>
</table>

We recommend that crystalloids are used for resuscitation in general ICU patients rather than HES

**Key Info**

**Benefits and harms**

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.

**Quality of evidence**

Moderate due to risk of bias

**Rationale**

The rationale is that the updated meta-analysis of crystalloid vs. HES showed clear benefit of crystalloids when balancing all patient-important outcomes, including mortality, in critically ill patients (Perel 2013). The results are supported by the meta-analyses comparing HES to any other comparators (Gatas 2013; Zarychanski 2013) and those of a large, high-quality RCT which compared 0.9% NaCl with 6% HES 130/0.4 in 7,000 ICU patients with signs of hypovolaemia (Myburgh 2012). 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 (Annane 2013) 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; Perner 2014) 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 (Seymour 2013). Given the high risk of bias in CRISTAL, we recommend that crystalloid solutions are used for resuscitation in general ICU patients. The final recommendation from
European Medicines Agency (EMA)’s Pharmacovigilance Risk Assessment Committee (PRAC) also states that HES should not be used in critically ill patients.

**PICO (2.1)**

**Population:** General ICU patients  
**Intervention:** HES  
**Comparator:** Crystalloid solutions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates</th>
<th>Summary</th>
</tr>
</thead>
</table>
| All-cause mortality | Relative risk 1.1  
(CI 95% 1.02 - 1.19)  
Based on data from 9,147 patients in 25 RCTs studies.  
(Randomized controlled) | 201 per 1000  
Difference: 20 more per 1000  
(CI 95% 4 more - 38 more) | Moderate  
Due to risk of bias | HES probably increases all-cause mortality |
| Renal replacement therapy | Relative risk 1.26  
(CI 95% 1.09 - 1.45)  
Based on data from 8,353 patients in 10 RCTs studies.  
(Randomized controlled) | 72 per 1000  
Difference: 19 more per 1000  
(CI 95% 6 more - 32 more) | Moderate | HES probably increases renal replacement therapy |
| Acute kidney injury | Relative risk 1  
(CI 95% 0.84 - 1.2)  
Based on data from 7,993 patients in 15 RCTs studies.  
(Randomized controlled) | 258 per 1000  
Difference: 0 fewer per 1000  
(CI 95% 41 fewer - 52 more) | Moderate | HES probably has little or no difference on acute kidney injury |
| Bleeding | | | | No studies were found that looked at bleeding |
| Serious adverse events | Relative risk 0.98  
(CI 95% 0.14 - 6.98)  
Based on data from 6,774 patients in 1 RCT studies.  
(Randomized controlled) | 1 per 1000  
Difference: 0 fewer per 1000  
(CI 95% 1 fewer - 6 more) | Moderate | HES probably has little or no difference on serious adverse events |
| Length of hospital stay | Based on data from: 7,000 patients in 1 studies.  
(Randomized controlled) | 19.1 (Mean)  
Difference: MD 0.2 more  
(CI 95% 0.8 fewer - 1.1 more) | High | HES has little or no difference on length of hospital stay |

Details about studies used and certainty down- and upgrading

| All-cause mortality | Intervention reference: Baseline/comparator | Risk of bias: Serious Unclear allocation concealment and blinding showit  
Inconsistency: No serious Unclear allocation concealment and blinding showit |
### References


### Summary

The rationale is that the updated meta-analysis of crystalloid vs. HES showed clear benefit of crystalloids when balancing all patient-important outcomes, including mortality, in critically ill patients (Perel 2013). The results are supported by the meta-analyses.
comparing HES to any other comparators (Gatas 2013; Zarychanski 2013) and those of a large, high-quality RCT which compared 0.9% NaCl with 6% HES 130/0.4 in 7,000 ICU patients with signs of hypovolaemia (Myburgh 2012). 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 (Annane 2013) 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; Perner 2014) 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 (Seymour 2013). Given the high risk of bias in CRISTAL, we recommend that crystalloid solutions are used for resuscitation in general ICU patients. The final recommendation from European Medicines Agency (EMA)’s Pharmacovigilance Risk Assessment Committee (PRAC) also states that HES should not be used in critically ill patients.

**Albumin**

*Weak Recommendation*

We suggest that crystalloids are used for resuscitation in general ICU patients rather than albumin

**Key Info**

**Benefits and harms**
An updated meta-analysis of albumin vs. crystalloids in critically ill patients showed no difference in mortality or in other outcomes.

**Quality of evidence**
Moderate due to risk of bias

**Resources and other considerations**
Albumin is a blood product and as such a limited and costly resource.

**Rationale**
The rationale is that the updated meta-analysis of albumin vs. crystalloids in critically ill patients showed no difference in mortality or in other outcomes (Perel 2013). The results are supported by those of a large, high-quality RCT, the SAFE trial, which compared 0.9% NaCl with 4% albumin in 7,000 ICU patients with signs of hypovolaemia (Finfer 2004). In that trial none of the outcome measures differed between the two intervention groups, including mortality, use of RRT and hospital length of stay. 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.

**PICO (2.2)**

**Population:** General ICU patients

**Intervention:** Albumin

**Comparator:** Crystalloid solutions

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Crystalloid solutions</td>
<td>Albumin</td>
<td></td>
</tr>
</tbody>
</table>

**References**

<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th>Relative risk 1.01 (CI 95% 0.93 - 1.1) Based on data from 9,920 patients in 24 RCTs studies. (Randomized controlled)</th>
<th>184 per 1000 Difference: 2 more per 1000 (CI 95% 13 fewer - 18 more )</th>
<th>Moderate</th>
<th>Albumin probably has little or no difference on all-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal replacement therapy</td>
<td></td>
<td></td>
<td></td>
<td>No studies were found that looked at renal replacement therapy</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td></td>
<td></td>
<td></td>
<td>No studies were found that looked at acute kidney injury</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
<td>No studies were found that looked at bleeding</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
<td>No studies were found that looked at serious adverse events</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>Based on data from: 6,997 patients in 1 RCT studies. (Randomized controlled)</td>
<td>15.6 (Mean) Difference: MD 0.2 fewer (CI 95% 0.7 fewer - 0.2 more )</td>
<td>High</td>
<td>Albumin has little or no difference on length of hospital stay</td>
</tr>
</tbody>
</table>

Details about studies used and certainty down- and upgrading

| All-cause mortality | Intervention reference: Baseline/comparator reference: Control arm of reference used for intervention | Risk of bias: Serious Unclear allocation concealment and blinding showit Inconsistency: No serious Unclear allocation concealment and blinding showit Indirectness: No serious Imprecision: No serious Publication bias: No serious |
|---------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|---------|---------------------------------------------------------------|
| Length of hospital stay | Intervention reference: Baseline/comparator reference: Control arm of reference used for intervention | Risk of bias: No serious Inconsistency: No serious Indirectness: No serious Imprecision: No serious Publication bias: No serious |

Summary
The rationale is that the updated meta-analysis of albumin vs. crystalloids in critically ill patients showed no difference in mortality or in other outcomes (Perel 2013). The results are supported by those of a large, high-quality RCT, the SAFE trial, which compared 0.9% NaCl with 4% albumin in 7,000 ICU patients with signs of hypovolaemia (Finfer 2004). In that trial none of the outcome measures differed between the two intervention groups, including mortality, use of RRT and hospital length of stay. 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.

Gelatin
Weak Recommendation

We suggest that crystalloids are used for resuscitation in general ICU patients rather than gelatin

Key Info

Benefits and harms
An updated meta-analysis of gelatin vs. crystalloids in critically ill patients showed no difference in mortality.

Quality of evidence
Very low due to risk of bias and imprecision

Resources and other considerations
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.

Rationale
The rationale is that the updated meta-analysis of gelatin vs. crystalloids in critically ill patients showed no difference in mortality (Perel 2013). 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 acute kidney injury and bleeding (Bayer 2012; Mittermayr 2007). These observations are supported by data from an updated meta-analysis of gelatin vs. albumin/crystalloid (Thomas-Rueddel 2012). 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.

PICO (2.3)
Population: General ICU patients
Intervention: Gelatin
Comparator: Crystalloid solutions

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.91 (CI 95% 0.49 - 1.72) Based on data from 506 patients in 11 RCTs studies. (Randomized controlled)</td>
<td>53 per 1000 48 per 1000 Difference: 5 fewer per 1000 (CI 95% 27 fewer - 38 more)</td>
<td>Very Low</td>
<td>We are uncertain whether gelatin increases or decreases all-cause mortality</td>
</tr>
</tbody>
</table>
## Renal replacement therapy
No studies were found that looked at renal replacement therapy

## Acute kidney injury
No studies were found that looked at acute kidney injury

## Bleeding
No studies were found that looked at bleeding

## Serious adverse events
No studies were found that looked at serious adverse events

## Length of hospital stay
<table>
<thead>
<tr>
<th>(Mean)</th>
<th>(Mean)</th>
</tr>
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</table>

### Details about studies used and certainty down- and upgrading

| All-cause mortality | Intervention reference: Baseline/comparator reference: Control arm of reference used for intervention | Risk of bias: Very Serious Unclear allocation concealement and blinding; low number of patients and events showIt Inconsistency: No serious Unclear allocation concealement and blinding; low number of patients and events showIt Indirectness: No serious Imprecision: Serious Wide confidence interval showIt Publication bias: No serious |

### References


Summary
The rationale is that the updated meta-analysis of gelatin vs. crystalloids in critically ill patients showed no difference in mortality (Perel 2013). 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 acute kidney injury and bleeding (Bayer 2012; Mittermayr 2007). These observations are supported by data from an updated meta-analysis of gelatin vs. albumin/crystalloid (Thomas-Rueddel 2012). 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.
3 - SEPSIS: Fluid resuscitation in adult critically ill septic patients with acute circulatory failure

Background

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 (Dellinger 2013). 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 routine 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 (Gattas 2013). This clinical practice guideline is among the first to be produced from our group meeting the new standards for trustworthy guidelines, using the GRADE methodology (www.gradeworkinggroup.org) (Laine 2011; Qaseem 2012; Guyatt 2008).

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). A colleague with focused methodological experience in systematic reviews and the GRADE system (MHM) was invited 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 resuscitation.

GRADE

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for formulating clinical questions, assessing the quality of evidence, generating anticipated absolute effects and for moving from evidence to recommendations (Guyatt 2008). 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 versus colloid resuscitation in critical care by answering the combination of populations / interventions / comparators / outcomes (PICO) questions amounting to 60 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 comparators were hydroxyethyl starch (HES) 130/0.38-0.45 (molecular weight/substitution ratio), gelatin or albumin. 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 trauma and burn, 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 (Gattas 2013; Zarychanski 2013; Perel 2013; Roberts 2011).

The target populations were adult 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 (Finfer 2010).

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://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 down-graded the quality of evidence for an intervention (our confidence in the effect-estimates) for identified risks of bias (due to 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. 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 in GradePro v. 3.5 (downloaded at www.gradeworkinggroup.org). Accordingly, the quality of evidence was rated from “high” to “very low”.

When moving from evidence to recommendations 4 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 (Guyatt 2008; Guyatt 2012).

The recommendations were agreed upon by the group. We specified prospectively 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.

**Hydroxyethyl starch (HES)**

**Strong Recommendation**

We recommend that crystalloids are used for resuscitation in patients with sepsis rather than HES.

**Key Info**

**Benefits and harms**

In two recently updated systematic meta-analyses of crystalloid vs. HES in critically ill septic patients, HES increased long-term (>28 days) mortality compared to crystalloids, and use of RRT was increased and more patients had SAEs with HES compared to crystalloids.

**Quality of evidence**

Moderate due to imprecision

**Rationale**

The rationale is based on two recently updated systematic reviews on patients with sepsis (Haase 2013; Patel 2013), which included most of the same RCTs (we chose to use data from the one including most trials - 9 trials with 3456 patients also including SAEs as an outcome vs. 6 trials with 3033 patients). The systematic review used here (Haase 2013) included two RCTs that used albumin as comparator, though few patients received albumin and these contributed with few events and only in the outcomes mortality and SAEs. In that review, 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 (Perner 2012). In patients with sepsis, HES 130/0.38-0.45 increased long-term (>28 days) mortality compared to crystalloids. In addition, the use of RRT was increased and more patients had SAEs with HES compared to crystalloids. In the revised recommendation from EMA’s PRAC, it is stated that HES should not be used in patients with sepsis.
### PICO (3.1)
**Population:** Septic patients  
**Intervention:** HES  
**Comparator:** Crystalloid solutions

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
</table>
| All-cause mortality | Relative risk 1.11 (CI 95% 1.01 - 1.22)  
Based on data from 3,156 patients in 4 RCTs studies.  
(Randomized controlled) | 305 per 1000  
339 per 1000  
Difference: 34 more per 1000  
(CI 95% 3 more - 67 more) | Moderate | HES probably increases all-cause mortality |
| Renal replacement therapy | Relative risk 1.36 (CI 95% 1.08 - 1.72)  
Based on data from 1,311 patients in 5 RCTs studies.  
(Randomized controlled) | 153 per 1000  
208 per 1000  
Difference: 55 more per 1000  
(CI 95% 12 more - 110 more) | High | HES increases renal replacement therapy |
| Acute kidney injury | Relative risk 1.18 (CI 95% 0.99 - 1.4)  
Based on data from 994 patients in 3 RCTs studies.  
(Randomized controlled) | 295 per 1000  
348 per 1000  
Difference: 53 more per 1000  
(CI 95% 3 fewer - 118 more) | Moderate | HES probably increases acute kidney injury |
| Bleeding | Relative risk 1.34 (CI 95% 0.81 - 2.21)  
Based on data from 994 patients in 3 RCTs studies.  
(Randomized controlled) | 141 per 1000  
189 per 1000  
Difference: 48 more per 1000  
(CI 95% 27 fewer - 171 more) | Low | HES may increase bleeding |
| Serious adverse events | Relative risk 1.3 (CI 95% 1.03 - 1.67)  
Based on data from 1,069 patients in 4 RCTs studies.  
(Randomized controlled) | 142 per 1000  
185 per 1000  
Difference: 43 more per 1000  
(CI 95% 4 more - 95 more) | Moderate | HES probably increases serious adverse events |
| Length of hospital stay | (Mean) | (Mean) | | No studies were found that looked at length of hospital stay |

**Details about studies used and certainty down- and upgrading**

**All-cause mortality**  
**Intervention reference:** Control arm of reference used for intervention  
**Baseline/comparator reference:** Control arm of reference used for intervention  
**Risk of bias:** No serious  
**Inconsistency:** No serious  
**Indirectness:** No serious  
**Imprecision:** Serious 95% confidence interval close to 1.00 showIt  
**Publication bias:** No serious
We suggest that crystalloids are used for resuscitation in patients with sepsis rather than albumin.

**Summary**

The rationale is based on two recently updated systematic reviews on patients with sepsis (Haase 2013; Patel 2013), which included most of the same RCTs (we chose to use data from the one including most trials - 9 trials with 3456 patients also including SAEs as an outcome vs. 6 trials with 3033 patients). The systematic review used here (Haase 2013) included two RCTs that used albumin as comparator, though few patients received albumin and these contributed with few events and only in the outcomes mortality and SAEs. In that review, 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 (Perner 2012). In patients with sepsis, HES 130/0.38-0.45 increased long-term (>28 days) mortality compared to crystalloids. In addition, the use of RRT was increased and more patients had SAEs with HES compared to crystalloids. In the revised recommendation from EMA's PRAC, it is stated that HES should not be used in patients with sepsis.

**References**


[22] Patel A, Waheed U, Brett SJ Randomised trials of 6% tetrastarch (hydroxyethyl starch 130/0.4 or 0.42) for severe sepsis reporting mortality: systematic review and meta-analysis.. PubMed Journal

We identified a recently updated systematic review including 17 RCTs (Delaney 2011). In 12 of the trials included in that review, the comparator was a synthetic colloid, 3 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 (Finfer 2004) and the recently published ALBIOS trial (Caironi 2014).

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 any of the secondary outcome measures (Caironi 2014). Pooling the data from the SAFE and ALBIOS trials showed no benefit or harm from albumin compared to saline. 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.

### Key Info

**Benefits and harms**
A meta-analysis of data from the SAFE and ALBIOS trials showed no benefit or harm from albumin compared to saline.

**Quality of evidence**
Low due to risk of bias

**Resources and other considerations**
Albumin is a blood product and as such a limited and costly resource

### Rationale

We identified a recently updated systematic review including 17 RCTs (Delaney 2011). In 12 of the trials included in that review, the comparator was a synthetic colloid, 3 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 (Finfer 2004) and the recently published ALBIOS trial (Caironi 2014). 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 any of the secondary outcome measures (Caironi 2014). Pooling the data from the SAFE and ALBIOS trials showed no benefit or harm from albumin compared to saline. 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.

### PICO (3.2)

**Population:** Septic patients

**Intervention:** Albumin

**Comparator:** Crystalloid solutions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute kidney injury</strong></td>
<td>Relative risk 0.97 (CI 95% 0.81 - 1.17) Based on data from 1,671 patients in 1 RCT studies. (Randomized controlled)</td>
<td>227 per 1000 220 per 1000</td>
<td>Low</td>
<td>Albumin may have little or no difference on acute kidney injury</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td>No studies were found that looked at bleeding</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td>No studies were found that looked at serious adverse events</td>
</tr>
<tr>
<td></td>
<td>Relative risk</td>
<td>CI 95%</td>
<td>Based on data from</td>
<td>Patients in</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------</td>
<td>--------</td>
<td>-------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.92</td>
<td>0.84 - 1</td>
<td>2,999</td>
<td>2 RCTs</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>1.11</td>
<td>0.96 - 1.27</td>
<td>3,028</td>
<td>2 RCTs</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>1.11</td>
<td>1.04 - 1.17</td>
<td>1,218</td>
<td>1 RCT</td>
</tr>
</tbody>
</table>

**Details about studies used and certainty down- and upgrading**

<table>
<thead>
<tr>
<th>Acute kidney injury</th>
<th>Intervention reference: Baseline/comparator reference: Control arm of reference used for intervention</th>
<th>Risk of bias: Very Serious ALBIOS trial underpowered and open-label showlt Indirectness: No serious Imprecision: No serious Publication bias: No serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Intervention reference: Baseline/comparator reference: Control arm of reference used for intervention</td>
<td>Risk of bias: Very Serious ALBIOS trial underpowered and open-label showlt Indirectness: No serious Imprecision: No serious Publication bias: No serious</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>Intervention reference: Baseline/comparator reference: Control arm of reference used for intervention</td>
<td>Risk of bias: Very Serious ALBIOS trial underpowered and open-label showlt Indirectness: No serious Imprecision: No serious Publication bias: No serious</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>Intervention reference: Baseline/comparator reference: Control arm of reference used for intervention</td>
<td>Risk of bias: Serious Subgroup analysis showlt Indirectness: No serious Imprecision: No serious Publication bias: No serious</td>
</tr>
</tbody>
</table>

**References**


Summary
We identified a recently updated systematic review including 17 RCTs (Delaney 2011). In 12 of the trials included in that review, the comparator was a synthetic colloid, 3 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 (Finfer 2004) and the recently published ALBIOS trial (Caironi 2014). 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 any of the secondary outcome measures (Caironi 2014). Pooling the data from the SAFE and ALBIOS trials showed no benefit or harm from albumin compared to saline. 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.

Gelatin
We suggest that crystalloids are used for resuscitation in patients with sepsis rather than gelatin

Key Info

Benefits and harms
No meta-analyses or RCTs of gelatin vs. crystalloids in critically ill septic patients exists.

Quality of evidence
Very low due to lack of RCTs and meta-analyses

Resources and other considerations
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.

Rationale
The rationale is based on a recently updated systematic review where no RCTs could be included for adult patients with sepsis (Thomas-Rueddel 2012). We have up-dated 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 (Bayer 2012; Mittermayr 2007). 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 (Perner 2012; Finfer 2011). 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 (Reinhart 2012).

PICO (3.3)

Population: Septic patients
Intervention: Gelatin
Comparator: Crystalloid solutions
<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th>No studies were found that looked at all-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal replacement therapy</td>
<td>No studies were found that looked at renal replacement therapy</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>No studies were found that looked at acute kidney injury</td>
</tr>
<tr>
<td>Bleeding</td>
<td>No studies were found that looked at bleeding</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>No studies were found that looked at serious adverse events</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>No studies were found that looked at length of hospital stay</td>
</tr>
</tbody>
</table>

Details about studies used and certainty down- and upgrading

References


Summary

The rationale is based on a recently updated systematic review where no RCTs could be included for adult patients with sepsis (Thomas-Rueddel 2012). 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 (Bayer 2012; Mittermayr 2007). 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 (Perner 2012; Finfer 2011). 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 (Reinhart 2012).
4 - TRAUMA: Fluid resuscitation in adult critically ill trauma patients with acute circulatory failure

Background

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 (Dellinger 2013). 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 routine 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 (Gattas 2013). This clinical practice guideline is among the first to be produced from our group meeting the new standards for trustworthy guidelines, using the GRADE methodology (www.gradeworkinggroup.org) (Laine 2011; Qaseem 2012; Guyatt 2008).

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). A colleague with focused methodological experience in systematic reviews and the GRADE system (MHM) was invited 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 resuscitation.

GRADE

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for formulating clinical questions, assessing the quality of evidence, generating anticipated absolute effects and for moving from evidence to recommendations (Guyatt 2008). 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 versus colloid resuscitation in critical care by answering the combination of populations / interventions / comparators / outcomes (PICO) questions amounting to 60 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 comparators were hydroxyethyl starch (HES) 130/0.38-0.45 (molecular weight/substitution ratio), gelatin or albumin. 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 trauma and burn, 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 (Gattas 2013; Zarychanski 2013; Perel 2013; Roberts 2011).

The target populations were adult 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 (Finfer 2010).

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://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 down-graded the quality of evidence for an intervention (our confidence in the effect-estimates) for identified risks of bias (due to 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. 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 in GradePro v. 3.5 (downloaded at www.gradeworkinggroup.org). Accordingly, the quality of evidence was rated from "high" to "very low".

When moving from evidence to recommendations 4 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 (Guyatt 2008; Guyatt 2012).

The recommendations were agreed upon by the group. We specified prospectively 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.

**Colloids**

**Strong Recommendation**

We recommend that crystalloids are used for resuscitation in patients with trauma rather than colloids.

**Key Info**

**Benefits and harms**

A meta-analysis of data of existing RCTs in patients with trauma showed that colloid resuscitation was associated with an increased risk of mortality.

**Quality of evidence**

Very low due to risk of bias and imprecision

**Rationale**

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 versus 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. There were not sufficient data to analyse other outcome measures.

**PICO (4.1)**

**Population:** Trauma patients  
**Intervention:** HES  
**Comparator:** Crystalloid solutions
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 1.25 (CI 95% 0.76 - 2.06) Based on data from 636 patients in 2 RCTs studies. (Randomized controlled)</td>
<td>78 per 1000 Difference: 20 more per 1000 (CI 95% 19 fewer - 83 more)</td>
<td>Low</td>
<td>HES may increase all-cause mortality</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td></td>
<td></td>
<td></td>
<td>No studies were found that looked at renal replacement therapy</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td></td>
<td></td>
<td></td>
<td>No studies were found that looked at acute kidney injury</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
<td>No studies were found that looked at bleeding</td>
</tr>
<tr>
<td>Serious adverse events</td>
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<td>No studies were found that looked at serious adverse events</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>(Mean)</td>
<td>(Mean)</td>
<td></td>
<td>No studies were found that looked at length of hospital stay</td>
</tr>
</tbody>
</table>

Details about studies used and certainty down- and upgrading

| All-cause mortality | Intervention reference: Baseline/comparator reference: Control arm of reference used for intervention | Risk of bias: Serious Limitations in reporting and follow-up showit Inconsistency: No serious Limitations in reporting and follow-up showit Indirectness: No serious Imprecision: Serious Wide confidence interval showit Publication bias: No serious |

References


[35] James MFM, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma) .. Pubmed Journal
Summary
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 versus 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. There were not sufficient data to analyse other outcome measures.

PICO (4.2)
Population: Trauma patients
Intervention: Albumin
Comparator: Crystalloid solutions

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 1.35 (CI 95% 1.03 - 1.77) Based on data from 1,522 patients in 5 RCTs studies. (Randomized controlled)</td>
<td>104 per 1000 (CI 95% 3 more - 80 more)</td>
<td>Low</td>
<td>Albumin may increase all-cause mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>140 per 1000</td>
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<tr>
<td>Renal replacement therapy</td>
<td></td>
<td></td>
<td></td>
<td>No studies were found that looked at renal replacement therapy</td>
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<tr>
<td>Acute kidney injury</td>
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<td>No studies were found that looked at acute kidney injury</td>
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<tr>
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<tr>
<td>Serious adverse events</td>
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<td>No studies were found that looked at serious adverse events</td>
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<tr>
<td>Length of hospital stay</td>
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<td>No studies were found that looked at length of hospital stay</td>
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</tr>
</tbody>
</table>
Summary

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 versus 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. There were not sufficient data to analyse other outcome measures.

PICO (4.3)

Population: Trauma patients

Intervention: Gelatin

Comparator: Crystalloid solutions

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 0.59 (CI 95% 0.11 - 3.11) Based on data from 34 patients in 1 RCT studies. (Randomized controlled)</td>
<td>188 per 1000 Crystalloid solutions</td>
<td>111 per 1000 Gelatin</td>
<td>Low Gelatin may have little or no difference on all-cause mortality</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>167 fewer per 1000 (CI 95% 167 fewer - 397 more)</td>
<td>No studies were found that looked at renal replacement therapy</td>
<td></td>
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<tr>
<td>Aspect</td>
<td>Mean</td>
<td>Mean</td>
<td>Details about studies used and certainty down- and upgrading</td>
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<tr>
<td>Acute kidney injury</td>
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<td></td>
<td>No studies were found that looked at acute kidney injury</td>
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<td>Length of hospital stay</td>
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<td>No studies were found that looked at length of hospital stay</td>
<td></td>
</tr>
</tbody>
</table>

**Details about studies used and certainty down- and upgrading**

- **All-cause mortality**
  - **Intervention reference:** Control arm of reference used for intervention
  - **Baseline/comparator reference:** Control arm of reference used for intervention
  - **Risk of bias:** Serious
  - **Limitations in reporting and follow-up:** Show
  - **Inconsistency:** No serious
  - **Limitations in reporting and follow-up:** Show
  - **Indirectness:** No serious
  - **Wide confidence interval:** Show
  - **Imprecision:** Serious
  - **Publication bias:** No serious

**References**


**Summary**

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 versus 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. There were not sufficient data to analyse other outcome measures.
5 - BURNS: Fluid resuscitation in adult critically ill burn patients with acute circulatory failure

Background

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 (Dellinger 2013). 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 routine 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 (Gattas 2013). This clinical practice guideline is among the first to be produced from our group meeting the new standards for trustworthy guidelines, using the GRADE methodology (www.gradeworkinggroup.org) (Laine 2011; Qaseem 2012; Guyatt 2008).

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). A colleague with focused methodological experience in systematic reviews and the GRADE system (MHM) was invited 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 resuscitation.

GRADE

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for formulating clinical questions, assessing the quality of evidence, generating anticipated absolute effects and for moving from evidence to recommendations (Guyatt 2008). 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 versus colloid resuscitation in critical care by answering the combination of populations / interventions / comparators / outcomes (PICO) questions amounting to 60 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 comparators were hydroxyethyl starch (HES) 130/0.38-0.45 (molecular weight/substitution ratio), gelatin or albumin. 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 trauma and burn, we searched for RCTs in PubMed (free text: “random” and (colloid/HES/starch/gelatin/albumin) and (trauma/injury/burn/thermal)), and in the recently updated systematic reviews on fluid resuscitation in critically ill patients in general (Gattas 2013; Zarychanski 2013; Perel 2013; Roberts 2011).

The target populations were adult 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 dextran or HES...
with molecular weight or substitution ratio above 130 or 0.45, respectively, were excluded because these colloid solutions are less used (Finfer 2010).

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://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 down-graded the quality of evidence for an intervention (our confidence in the effect-estimates) for identified risks of bias (due to 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. 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 in GradePro v. 3.5 (downloaded at www.gradeworkinggroup.org). Accordingly, the quality of evidence was rated from “high” to “very low”.

When moving from evidence to recommendations 4 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 (Guyatt 2008; Guyatt 2012).

The recommendations were agreed upon by the group. We specified prospectively 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.

Colloids

Clinicians should be aware of the existing very low quality evidence to guide decisions about what fluid to use in patients with burns. We have refrained from making distinct recommendations for either crystalloid solutions, albumin or gelatin whereas use of HES generally is discouraged also in patients with burns. We encourage clinicians to take part in high quality trials to improve best current evidence for patients with burns.

Key Info

Benefits and harms
Very limited data from RCTs.

Quality of evidence
Very low due to risk of bias and imprecision

Resources and other considerations
We refrain from giving any recommendations because of the very low level of evidence.

Rationale
For patients with burn injury we could not find updated systematic reviews and we only identified 3 small RCTs that were relevant for this guideline (Goodwin 1983; Cooper 2006; Bechir 2013). Two of these trials were on albumin versus 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) (Goodwin 1983). The third trial assessed 48 patients randomised to HES 130/0.40 versus Ringer’s lactate and showed no benefit or harm of HES (Bechir 2013), but the interpretation is hampered by the small sample size. Based on the very limited amount of data 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).

### PICO (5.1)
**Population:** Burn patients  
**Intervention:** HES  
**Comparator:** Crystalloid solutions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
</table>
| All-cause mortality | Relative risk 1.27  
  (CI 95% 0.51 - 3.26)  
  Based on data from 45 patients in 1 RCT studies.  
  (Randomized controlled) |  
  | 273 per 1000  
  Difference: 74 more per 1000  
  ( CI 95% 134 fewer - 617 more ) | Very Low | There were too few who experienced all-cause mortality, to determine whether HES made a difference |
| Renal replacement therapy | Relative risk 0.96  
  (CI 95% 0.35 - 2.64)  
  Based on data from 45 patients in 1 RCT studies.  
  (Randomized controlled) |  
  | 273 per 1000  
  Difference: 11 fewer per 1000  
  ( CI 95% 177 fewer - 448 more ) | Low | There were too few who experienced renal replacement therapy, to determine whether HES made a difference |
| Acute kidney injury |  |  |  | No studies were found that looked at acute kidney injury |
| Bleeding |  |  |  | No studies were found that looked at bleeding |
| Serious adverse events |  |  |  | No studies were found that looked at serious adverse events |
| Length of hospital stay | (Mean)  
(Mean) |  |  | No studies were found that looked at length of hospital stay |

**Details about studies used and certainty down- and upgrading**

- **All-cause mortality**  
  **Intervention reference:** Baseline/comparator  
  **Risk of bias:** Very Serious Underpowered; long-term mortality (90 day) was a post-hoc analysis; mortality not primary outcome showed
For patients with burn injury we could not find updated systematic reviews and we only identified 3 small RCTs that were relevant for this guideline (Goodwin 1983; Cooper 2006; Bechir 2013). Two of these trials were on albumin versus 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) (Goodwin 1983). The third trial assessed 48 patients randomised to HES 130/0.40 versus Ringer's lactate and showed no benefit or harm of HES (Bechir 2013), but the interpretation is hampered by the small sample size. Based on the very limited amount of data 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).

### References


[29] Cooper AB, Cohn SM, Zhang HS, Hanna K, Stewart TE, Slutsky AS, Five percent albumin for adult burn shock resuscitation: lack of effect on daily multiple organ dysfunction score. Pubmed


### Summary

For patients with burn injury we could not find updated systematic reviews and we only identified 3 small RCTs that were relevant for this guideline (Goodwin 1983; Cooper 2006; Bechir 2013). Two of these trials were on albumin versus 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) (Goodwin 1983). The third trial assessed 48 patients randomised to HES 130/0.40 versus Ringer’s lactate and showed no benefit or harm of HES (Bechir 2013), but the interpretation is hampered by the small sample size. Based on the very limited amount of data 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).

### PICO (5.2)

**Population:** Burn patients  
**Intervention:** Albumin  
**Comparator:** Crystalloid solutions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates</th>
<th>Summary</th>
</tr>
</thead>
</table>
| All-cause mortality | | Relative risk 3.59 (CI 95% 1.26 - 10.25)  
Based on data from 121 patients in 2 RCTs studies. (Randomized controlled) | 65 per 1000  
Difference: 168 more per 1000  
(CI 95% 17 more - 601 more) | Very Low | There were too few who experienced all-cause mortality, to determine whether albumin made a difference |

| Renal replacement therapy | | No studies were found that looked at renal replacement therapy | | | |
Summary

For patients with burn injury we could not find updated systematic reviews and we only identified 3 small RCTs that were relevant for this guideline (Goodwin 1983; Cooper 2006; Bechir 2013). Two of these trials were on albumin versus 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) (Goodwin 1983). The third trial assessed 48 patients randomised to HES 130/0.4 versus Ringer’s lactate and showed no benefit or harm of HES (Bechir 2013), but the interpretation is hampered by the small sample size. Based on the very limited amount of data 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).

### PICO (5.3)
**Population:** Burn patients  
**Intervention:** Gelatin  
**Comparator:** Crystalloid solutions

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td>No studies were found that looked at all-cause mortality</td>
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<tr>
<td>Renal replacement therapy</td>
<td></td>
<td></td>
<td></td>
<td>No studies were found that looked at renal replacement therapy</td>
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<tr>
<td>Acute kidney injury</td>
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<td></td>
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<td>No studies were found that looked at acute kidney injury</td>
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<tr>
<td>Bleeding</td>
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<td>No studies were found that looked at bleeding</td>
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<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
<td>No studies were found that looked at serious adverse events</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td></td>
<td>(Mean)</td>
<td></td>
<td>No studies were found that looked at length of hospital stay</td>
</tr>
</tbody>
</table>

Details about studies used and certainty down- and upgrading
References


[29] Cooper AB, Cohn SM, Zhang HS, Hanna K, Stewart TE, Slutsky AS, Five percent albumin for adult burn shock resuscitation: lack of effect on daily multiple organ dysfunction score. PubMed


Summary

For patients with burn injury we could not find updated systematic reviews and we only identified 3 small RCTs that were relevant for this guideline (Goodwin 1983; Cooper 2006; Bechir 2013). Two of these trials were on albumin versus 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) (Goodwin 1983). The third trial assessed 48 patients randomised to HES 130/0.40 versus Ringer’s lactate and showed no benefit or harm of HES (Bechir 2013), but the interpretation is hampered by the small sample size. Based on the very limited amount of data 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).
References


[5] Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen Bo, Wetterslev M, Wetterslev J Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis.. Pubmed Journal


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[34] Shah DM, Browner BD, Dutton RE, Newell JC, Powers SR Cardiac output and pulmonary wedge pressure. Use for evaluation of fluid replacement in trauma patients. Pubmed

[35] James MFM, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). Pubmed Journal
