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

Main editor
Morten Hylander Møller

Publishing Info
v0.5 published on 23.05.2016

The Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI)

Contact

Morten Hylander Møller
Dept. of Intensive Care 4131, Copenhagen University Hospital Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark
mortenhylander@gmail.com
+45 22555343

Language

en

Start Date

18.02.2016

Last Edited

23.05.2016

Disclaimer

Sections

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. Perner[1], E. Junttila[2], M. Haney[3], K. Hreinsson[4], R. Kvåle[5], P. O. Vandvik[6] and M. H. Møller[1]

1. Department of Intensive Care, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. **2** Department of Anaesthesiology, Division of Intensive Care, Oulu University Hospital and Department of Anaesthesiology, Tampere University Hospital, Tampere, Finland. **3** Anaesthesiology and Intensive Care Medicine, Umeå University, Umeå, Sweden. **4** Department of Anaesthesiology and Intensive Care Medicine, Landspitali University Hospital, Reykjavik, Iceland. **5** Department of Intensive Care, Haukeland University Hospital, Bergen, Norway. **6** Department of Medicine, Innlandet Hospital Trust-Division Gjøvik, Norway and Norwegian Knowledge Centre for the Health Services, Oslo, Norway

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.

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. Perner[1], E. Junttila[2], M. Haney[3], K. Hreinsson[4], R. Kvåle[5], P. O. Vandvik[6] and M. H. Møller[1]

1. Department of Intensive Care, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. **2** Department of Anaesthesiology, Division of Intensive Care, Oulu University Hospital and Department of Anaesthesiology, Tampere University Hospital, Tampere, Finland. **3** Anaesthesiology and Intensive Care Medicine, Umeå University, Umeå, Sweden. **4** Department of Anaesthesiology and Intensive Care Medicine, Landspitali University Hospital, Reykjavik, Iceland. **5** Department of Intensive Care, Haukeland University Hospital, Bergen, Norway. **6** Department of Medicine, Innlandet Hospital Trust-Division Gjøvik, Norway and Norwegian Knowledge Centre for the Health Services, Oslo, Norway

2 - GENERAL ICU: Fluid resuscitation in adult critically ill 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 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

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

Outcome Timeframe	Study results and measurements	Absolute effect estimates Crystalloid solutions	 HES	Certainty in effect estimates (Quality of evidence)	Summary
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	221 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	91 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	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	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)	19.3 (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

	reference: Control arm of reference used for intervention	**Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Renal replacement therapy	**Intervention reference: Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: Serious** Lack of blinding and allocation concealment showIt **Inconsistency: No serious** Lack of blinding and allocation concealment showIt **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Acute kidney injury	**Intervention reference: Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: Serious** Lack of blinding and allocation concealment showIt **Inconsistency: No serious** Lack of blinding and allocation concealment showIt **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Serious adverse events	**Intervention reference: Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Wide confidence interval showIt **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**

References

[2] Perel P, Roberts I, Ker K Colloids versus crystalloids for fluid resuscitation in critically ill patients.. Pubmed Journal

[3] Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SAR, , Hydroxyethyl starch or saline for fluid resuscitation in intensive care.. Pubmed Journal

[6] Mutter TC, Ruth CA, Dart AB Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function.. Pubmed Journal

[7] Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S, Fluid resuscitation with 6 % hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy.. Pubmed Journal

[12] Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, Fergusson DA Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis.. Pubmed Journal

[15] Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declère AD, Preiser JC, Outin H, Troché G, Charpentier C, Trouillet JL, Kimmoun A, Forceville X, Darmon M, Lesur O, Reignier J, Régnier J, Abroug F, Berger P, Clec'h C, Cle'h C, Cousson J, Thibault L, Chevret S, Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial.. Pubmed Journal

[16] Perner A, Haase N, Wetterslev J Mortality in patients with hypovolemic shock treated with colloids or crystalloids.. Pubmed Journal

[17] Seymour CW, Angus DC Making a pragmatic choice for fluid resuscitation in critically ill patients.. Pubmed Journal

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

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

Outcome Timeframe	Study results and measurements	Absolute effect estimates Crystalloid solutions	 Albumin	Certainty in effect estimates (Quality of evidence)	Summary

References

[2] Perel P, Roberts I, Ker K Colloids versus crystalloids for fluid resuscitation in critically ill patients.. Pubmed Journal

All-cause mortality	Relative risk 1.01 (CI 95% 0.93 - 1.1) Based on data from 9,920 patients in 24 RCTs studies. (Randomized controlled)	184 per 1000 / 186 per 1000 Difference: 2 more per 1000 (CI 95% 13 fewer - 18 more)	Moderate	Albumin probably has little or no difference on all-cause mortality
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	Based on data from: 6,997 patients in 1 RCT studies. (Randomized controlled)	15.6 (Mean) / 15.4 (Mean) Difference: MD 0.2 fewer (CI 95% 0.7 fewer - 0.2 more)	High	Albumin 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 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**

[18] Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, A comparison of albumin and saline for fluid resuscitation in the intensive care unit.. Pubmed

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 Low

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

Outcome Timeframe	Study results and measurements	Absolute effect estimates Crystalloid solutions	 Gelatin	Certainty in effect estimates (Quality of evidence)	Summary
All-cause mortality	Relative risk 0.91 (CI 95% 0.49 - 1.72) Based on data from 506 patients in 11 RCTs studies. (Randomized controlled)	53 per 1000	48 per 1000 Difference: 5 fewer per 1000 (CI 95% 27 fewer - 38 more)	Very Low	We are uncertain whether gelatin increases or decreases all-cause mortality

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		(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 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

[2] Perel P, Roberts I, Ker K Colloids versus crystalloids for fluid resuscitation in critically ill patients.. Pubmed Journal

[19] Bayer O, Reinhart K, Kohl M, Kabisch B, Marshall J, Sakr Y, Bauer M, Hartog C, Schwarzkopf D, Riedemann N Effects of fluid resuscitation with synthetic colloids or crystalloids alone on shock reversal, fluid balance, and patient outcomes in patients with severe sepsis: a prospective sequential analysis.. Pubmed

[20] Mittermayr M, Streif W, Haas T, Fries D, Velik-Salchner C, Klingler A, Oswald E, Bach C, Schnapka-Koepf M, Innerhofer P Hemostatic changes after crystalloid or colloid fluid administration during major orthopedic surgery: the role of fibrinogen administration.. Pubmed

[21] Thomas-Rueddel DO, Vlasakov V, Reinhart K, Jaeschke R, Rueddel H, Hutagalung R, Stacke A, Hartog CS Safety of gelatin for volume resuscitation--a systematic review and meta-analysis.. Pubmed Journal

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

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

Outcome Timeframe	Study results and measurements	Absolute effect estimates Crystalloid solutions	 HES	Certainty in effect estimates (Quality of evidence)	Summary
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:** **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**

Renal replacement therapy	**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**
Acute kidney injury	**Intervention reference: Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** The definition of AKI showIt **Imprecision: No serious** **Publication bias: No serious**
Bleeding	**Intervention reference: Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** No universally agreed definition of the outcome of interest showIt **Imprecision: Serious** Large confidence interval showIt **Publication bias: No serious**
Serious adverse events	**Intervention reference: Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Confidence interval close to 1.00 showIt **Publication bias: No serious**

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

[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

[23] Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard A-L, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J, , Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis.. Pubmed Journal

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.

Albumin

Weak Recommendation

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

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

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Crystalloid solutions	Albumin	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Acute kidney injury	Relative risk 0.97 (CI 95% 0.81 - 1.17) Based on data from 1,671 patients in 1 RCT studies. (Randomized controlled)	227 per 1000	220 per 1000 Difference: 7 fewer per 1000 (CI 95% 43 fewer - 39 more)	Low	Albumin may have little or no difference on 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

All-cause mortality	Relative risk 0.92 (CI 95% 0.84 - 1) Based on data from 2,999 patients in 2 RCTs studies. (Randomized controlled)	402 per 1000 370 per 1000 Difference: 32 fewer per 1000 (CI 95% 64 fewer - 0 fewer)	Low	Albumin may have little or no difference on all-cause mortality
Renal replacement therapy	Relative risk 1.11 (CI 95% 0.96 - 1.27) Based on data from 3,028 patients in 2 RCTs studies. (Randomized controlled)	201 per 1000 223 per 1000 Difference: 22 more per 1000 (CI 95% 8 fewer - 54 more)	Low	Albumin may have little or no difference on renal replacement therapy
Length of hospital stay	Based on data from: 1,218 patients in 1 RCT studies. (Randomized controlled)	15.6 (Mean) 15.1 (Mean) Difference: MD 0.5 fewer (CI 95% 1.6 fewer - 0.6 more)	Moderate	Albumin probably has little or no difference on length of hospital stay

Details about studies used and certainty down- and upgrading

Acute kidney injury	**Intervention reference:** **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: Very Serious** ALBIOS trial underpowered and open-label showIt **Inconsistency: No serious** ALBIOS trial underpowered and open-label showIt **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
All-cause mortality	**Intervention reference:** **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: Very Serious** ALBIOS trial underpowered and open-label showIt **Inconsistency: No serious** ALBIOS trial underpowered and open-label showIt **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Renal replacement therapy	**Intervention reference:** **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: Very Serious** ALBIOS trial underpowered and open-label showIt **Inconsistency: No serious** ALBIOS trial underpowered and open-label 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: Serious** Subgroup analysis showIt **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

References

[4] Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, A comparison of albumin and saline for fluid resuscitation in the intensive care unit.. Pubmed

[24] Delaney AP, Dan A, McCaffrey J, Finfer S The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis.. Pubmed Journal

[25] Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, Fanizza C, Caspani L, Faenza S, Grasselli G, Iapichino G, Antonelli M, Parrini V, Fiore G, Latini R, Gattinoni L, Albumin replacement in patients with severe sepsis or septic shock.. Pubmed Journal

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

Weak Recommendation

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 Low

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

Outcome Timeframe	Study results and measurements	Absolute effect estimates Crystalloid solutions	 Gelatin	Certainty in effect estimates (Quality of evidence)	Summary

All-cause mortality				No studies were found that looked at all-cause mortality
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		(Mean) (Mean)		No studies were found that looked at length of hospital stay

Details about studies used and certainty down- and upgrading

References

[19] Bayer O, Reinhart K, Kohl M, Kabisch B, Marshall J, Sakr Y, Bauer M, Hartog C, Schwarzkopf D, Riedemann N Effects of fluid resuscitation with synthetic colloids or crystalloids alone on shock reversal, fluid balance, and patient outcomes in patients with severe sepsis: a prospective sequential analysis.. Pubmed

[20] Mittermayr M, Streif W, Haas T, Fries D, Velik-Salchner C, Klingler A, Oswald E, Bach C, Schnapka-Koepf M, Innerhofer P Hemostatic changes after crystalloid or colloid fluid administration during major orthopedic surgery: the role of fibrinogen administration.. Pubmed

[21] Thomas-Rueddel DO, Vlasakov V, Reinhart K, Jaeschke R, Rueddel H, Hutagalung R, Stacke A, Hartog CS Safety of gelatin for volume resuscitation--a systematic review and meta-analysis.. Pubmed Journal

[23] Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard A-L, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J, , Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis.. Pubmed Journal

[26] , Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis.. Pubmed Journal

[27] Reinhart K, Perner A, Sprung CL, Jaeschke R, Schortgen F, Johan Groeneveld AB, Beale R, Hartog CS, Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients.. Pubmed Journal

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 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).

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

Low

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 t other outcome measures.

PICO (4.1)

Population: Trauma patients

Intervention: HES

Comparator: Crystalloid solutions

Outcome Timeframe	Study results and measurements	Absolute effect estimates Crystalloid solutions	 HES	Certainty in effect estimates (Quality of evidence)	Summary
All-cause mortality	Relative risk 1.25 (CI 95% 0.76 - 2.06) Based on data from 636 patients in 2 RCTs studies. (Randomized controlled)	78 per 1000	98 per 1000 Difference: 20 more per 1000 (CI 95% 19 fewer - 83 more)	Low	HES may increase all-cause mortality
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		(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 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

[3] Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SAR, , Hydroxyethyl starch or saline for fluid resuscitation in intensive care.. Pubmed Journal

[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 t other outcome measures.

PICO (4.2)

Population: Trauma patients

Intervention: Albumin

Comparator: Crystalloid solutions

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Crystalloid solutions	Albumin	**Certainty in effect estimates** (Quality of evidence)	**Summary**
All-cause mortality	Relative risk 1.35 (CI 95% 1.03 - 1.77) Based on data from 1,522 patients in 5 RCTs studies. (Randomized controlled)	104 per 1000	140 per 1000 Difference: 36 more per 1000 (CI 95% 3 more - 80 more)	Low	Albumin may increase all-cause mortality
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		(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 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

[4] Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, A comparison of albumin and saline for fluid resuscitation in the intensive care unit.. Pubmed

[31] Lowe RJ, Moss GS, Jilek J, Levine HD Crystalloid vs colloid in the etiology of pulmonary failure after trauma: a randomized trial in man.. Pubmed

[32] Lucas CE, Weaver D, Higgins RF, Ledgerwood AM, Johnson SD, Bouwman DL Effects of albumin versus non-albumin resuscitation on plasma volume and renal excretory function.. Pubmed

[33] Metildi LA, Shackford SR, Virgilio RW, Peters RM Crystalloid versus colloid in fluid resuscitation of patients with severe pulmonary insufficiency.. Pubmed

[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

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 t other outcome measures.

PICO (4.3)

Population: Trauma patients

Intervention: Gelatin

Comparator: Crystalloid solutions

Outcome Timeframe	Study results and measurements	Absolute effect estimates Crystalloid solutions	 Gelatin	Certainty in effect estimates (Quality of evidence)	Summary
All-cause mortality	Relative risk 0.59 (CI 95% 0.11 - 3.11) Based on data from 34 patients in 1 RCT studies. (Randomized controlled)	188 per 1000	111 per 1000 Difference: 77 fewer per 1000 (CI 95% 167 fewer - 397 more)	Low	Gelatin may have little or no difference on all-cause mortality
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		(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 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

[36] Wu JJ, Huang MS, Tang GJ, Kao WF, Shih HC, Su CH, Lee CH Hemodynamic response of modified fluid gelatin compared with lactated ringer's solution for volume expansion in emergency resuscitation of hypovolemic shock patients: preliminary report of a prospective, randomized trial.. Pubmed

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 t 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/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

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.

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

Outcome Timeframe	Study results and measurements	Absolute effect estimates Crystalloid solutions	 HES	Certainty in effect estimates (Quality of evidence)	Summary
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	347 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	262 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 showIt

	reference: Control arm of reference used for intervention	**Inconsistency: No serious** Underpowered; long-term mortality (90 day) was a post-hoc analysis; mortality not primary outcome showIt **Indirectness: No serious** **Imprecision: Serious** Wide confidence interval showIt **Publication bias: No serious**
Renal replacement therapy	**Intervention reference: Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: Serious** Underpowered showIt **Inconsistency: No serious** Underpowered showIt **Indirectness: No serious** **Imprecision: Serious** Wide confidence interval showIt **Publication bias: No serious**

References

[28] Goodwin CW, Dorethy J, Lam V, Pruitt BA Randomized trial of efficacy of crystalloid and colloid resuscitation on hemodynamic response and lung water following thermal injury.. Pubmed

[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

[30] Béchir M, Puhan MA, Fasshauer M, Schuepbach RA, Stocker R, Neff TA Early fluid resuscitation with hydroxyethyl starch 130/0.4 (6%) in severe burn injury: a randomized, controlled, double-blind clinical trial.. Pubmed Journal

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

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Crystalloid solutions	Albumin	**Certainty in effect estimates** (Quality of evidence)	**Summary**
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	233 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

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 reference:** Control arm of reference used for intervention	**Risk of bias: Very Serious** Low number of patients; lack of allocation concealment and blinding showIt **Inconsistency: No serious** Low number of patients; lack of allocation concealment and blinding showIt **Indirectness: No serious** **Imprecision: Serious** Wide confidence interval showIt **Publication bias: No serious**

References

[28] Goodwin CW, Dorethy J, Lam V, Pruitt BA Randomized trial of efficacy of crystalloid and colloid resuscitation on hemodynamic response and lung water following thermal injury.. Pubmed

[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

[30] Béchir M, Puhan MA, Fasshauer M, Schuepbach RA, Stocker R, Neff TA Early fluid resuscitation with hydroxyethyl starch 130/0.4 (6%) in severe burn injury: a randomized, controlled, double-blind clinical trial.. Pubmed Journal

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 (5.3)

Population: Burn patients

Intervention: Gelatin

Comparator: Crystalloid solutions

Outcome Timeframe	Study results and measurements	Absolute effect estimates Crystalloid solutions	 Gelatin	Certainty in effect estimates (Quality of evidence)	Summary
All-cause mortality					No studies were found that looked at all-cause mortality
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		(Mean)	(Mean)		No studies were found that looked at length of hospital stay

Details about studies used and certainty down- and upgrading

References

[28] Goodwin CW, Dorethy J, Lam V, Pruitt BA Randomized trial of efficacy of crystalloid and colloid resuscitation on hemodynamic response and lung water following thermal injury.. Pubmed

[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

[30] Béchir M, Puhan MA, Fasshauer M, Schuepbach RA, Stocker R, Neff TA Early fluid resuscitation with hydroxyethyl starch 130/0.4 (6%) in severe burn injury: a randomized, controlled, double-blind clinical trial.. Pubmed Journal

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

[1] Roberts I, Blackhall K, Alderson P, Bunn F, Schierhout G Human albumin solution for resuscitation and volume expansion in critically ill patients.. Pubmed Journal

[2] Perel P, Roberts I, Ker K Colloids versus crystalloids for fluid resuscitation in critically ill patients.. Pubmed Journal

[3] Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SAR, , Hydroxyethyl starch or saline for fluid resuscitation in intensive care.. Pubmed Journal

[4] Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, A comparison of albumin and saline for fluid resuscitation in the intensive care unit.. Pubmed

[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

[6] Mutter TC, Ruth CA, Dart AB Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function.. Pubmed Journal

[7] Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S, Fluid resuscitation with 6 % hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy.. Pubmed Journal

[8] Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent J-L, Moreno R, Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012.. Pubmed Journal

[9] Laine C, Taichman DB, Mulrow C Trustworthy clinical guidelines.. Pubmed Journal

[10] Qaseem A, Forland F, Macbeth F, Ollenschläger G, Phillips S, van der Wees P, Guidelines International Network: toward international standards for clinical practice guidelines.. Pubmed Journal

[11] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.. Pubmed Journal

[12] Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, Fergusson DA Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis.. Pubmed Journal

[13] Guyatt GH, Norris SL, Schulman S, Hirsh J, Eckman MH, Akl EA, Crowther M, Vandvik PO, Eikelboom JW, McDonagh MS, Lewis SZ, Gutterman DD, Cook DJ, Schünemann HJ, Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.. Pubmed Journal

[14] Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, Du B, McArthur C, Myburgh J, Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units.. Pubmed Journal

[15] Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declère AD, Preiser JC, Outin H, Troché G, Charpentier C, Trouillet JL, Kimmoun A, Forceville X, Darmon M, Lesur O, Reignier J, Régnier J, Abroug F, Berger P, Clec'h C, Cle'h C, Cousson J, Thibault L, Chevret S, Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial.. Pubmed Journal

[16] Perner A, Haase N, Wetterslev J Mortality in patients with hypovolemic shock treated with colloids or crystalloids.. Pubmed Journal

[17] Seymour CW, Angus DC Making a pragmatic choice for fluid resuscitation in critically ill patients.. Pubmed Journal

[18] Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, A comparison of albumin and saline for fluid resuscitation in the intensive care unit.. Pubmed

[19] Bayer O, Reinhart K, Kohl M, Kabisch B, Marshall J, Sakr Y, Bauer M, Hartog C, Schwarzkopf D, Riedemann N Effects of fluid resuscitation with synthetic colloids or crystalloids alone on shock reversal, fluid balance, and patient outcomes in patients with severe sepsis: a prospective sequential analysis.. Pubmed

[20] Mittermayr M, Streif W, Haas T, Fries D, Velik-Salchner C, Klingler A, Oswald E, Bach C, Schnapka-Koepf M, Innerhofer P Hemostatic changes after crystalloid or colloid fluid administration during major orthopedic surgery: the role of fibrinogen administration.. Pubmed

[21] Thomas-Rueddel DO, Vlasakov V, Reinhart K, Jaeschke R, Rueddel H, Hutagalung R, Stacke A, Hartog CS Safety of gelatin for volume resuscitation--a systematic review and meta-analysis.. Pubmed Journal

[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

[23] Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard A-L, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J, , Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis.. Pubmed Journal

[24] Delaney AP, Dan A, McCaffrey J, Finfer S The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis.. Pubmed Journal

[25] Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, Fanizza C, Caspani L, Faenza S, Grasselli G, Iapichino G, Antonelli M, Parrini V, Fiore G, Latini R, Gattinoni L, Albumin replacement in patients with severe sepsis or septic shock.. Pubmed Journal

[26] , Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis.. Pubmed Journal

[27] Reinhart K, Perner A, Sprung CL, Jaeschke R, Schortgen F, Johan Groeneveld AB, Beale R, Hartog CS, Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients.. Pubmed Journal

[28] Goodwin CW, Dorethy J, Lam V, Pruitt BA Randomized trial of efficacy of crystalloid and colloid resuscitation on hemodynamic response and lung water following thermal injury.. Pubmed

[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

[30] Béchir M, Puhan MA, Fasshauer M, Schuepbach RA, Stocker R, Neff TA Early fluid resuscitation with hydroxyethyl starch 130/0.4 (6%) in severe burn injury: a randomized, controlled, double-blind clinical trial.. Pubmed Journal

[31] Lowe RJ, Moss GS, Jilek J, Levine HD Crystalloid vs colloid in the etiology of pulmonary failure after trauma: a randomized trial in man.. Pubmed

[32] Lucas CE, Weaver D, Higgins RF, Ledgerwood AM, Johnson SD, Bouwman DL Effects of albumin versus non-albumin resuscitation on plasma volume and renal excretory function.. Pubmed

[33] Metildi LA, Shackford SR, Virgilio RW, Peters RM Crystalloid versus colloid in fluid resuscitation of patients with severe pulmonary insufficiency.. Pubmed

[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

[36] Wu JJ, Huang MS, Tang GJ, Kao WF, Shih HC, Su CH, Lee CH Hemodynamic response of modified fluid gelatin compared with lactated ringer's solution for volume expansion in emergency resuscitation of hypovolemic shock patients: preliminary report of a prospective, randomized trial.. Pubmed

[37] Perner A, Junttila E, Haney M, Hreinsson K, Kvåle R, Vandvik PO, Møller MH, Scandinavian clinical practice guideline on choice of fluid in resuscitation of critically ill patients with acute circulatory failure.. Acta anaesthesiologica Scandinavica 2015;59(3):274-85-null Pubmed Journal