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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	6
OBJECTIVES	7
METHODS	7
RESULTS	10
Figure 1.	11
Figure 2.	13
Figure 3.	14
Figure 4.	16
Figure 5.	17
DISCUSSION	19
Figure 6.	20
AUTHORS' CONCLUSIONS	21
ACKNOWLEDGEMENTS	22
REFERENCES	23
CHARACTERISTICS OF STUDIES	28
DATA AND ANALYSES	70
Analysis 1.1. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 1 Mortality.	72
Analysis 1.2. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 2 Mortality (by age).	73
Analysis 1.3. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 3 Acute kidney injury.	74
Analysis 1.4. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 4 Organ system dysfunction.	75
Analysis 1.5. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 5 Sodium.	75
Analysis 1.6. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 6 Potassium.	76
Analysis 1.7. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 7 Chloride.	76
Analysis 1.8. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 8 pH.	77
Analysis 1.9. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 9 Bicarbonate.	78
Analysis 1.10. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 10 Blood products.	78
ADDITIONAL TABLES	78
APPENDICES	80
HISTORY	99
CONTRIBUTIONS OF AUTHORS	99
DECLARATIONS OF INTEREST	100
SOURCES OF SUPPORT	100
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	100
INDEX TERMS	101

[Intervention Review]

Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children

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ABSTRACT

Background

Fluid therapy is one of the main interventions provided for critically ill patients, although there is no general consensus regarding the type of solution. Among crystalloid solutions, 0.9% saline is the most commonly administered. Buffered solutions may offer some theoretical advantages (less metabolic acidosis, less electrolyte disturbance), but the clinical relevance of these remains unknown.

Objectives

To assess the effects of buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children.

Search methods

We searched the following databases to July 2018: CENTRAL, MEDLINE, Embase, CINAHL, and four trials registers. We checked references, conducted backward and forward citation searching of relevant articles, and contacted study authors to identify additional studies. We imposed no language restrictions.

Selection criteria

We included randomized controlled trials (RCTs) with parallel or cross-over design examining buffered solutions versus intravenous 0.9% saline in a critical care setting (resuscitation or maintenance). We included studies on participants with critical illness (including trauma and burns) or undergoing emergency surgery during critical illness who required intravenous fluid therapy. We included studies of adults and children. We included studies with more than two arms if they fulfilled all of our inclusion criteria. We excluded studies performed in persons undergoing elective surgery and studies with multiple interventions in the same arm.

Data collection and analysis

We used Cochrane's standard methodological procedures. We assessed our intervention effects using random-effects models, but when one or two trials contributed to 75% of randomized participants, we used fixed-effect models. We reported outcomes with 95% confidence intervals (CIs).

Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children (Review)

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Main results

We included 21 RCTs (20,213 participants) and identified three ongoing studies. Three RCTs contributed 19,054 participants (94.2%). Four RCTs (402 participants) were conducted among children with severe dehydration and dengue shock syndrome. Fourteen trials reported results on mortality, and nine reported on acute renal injury. Sixteen included trials were conducted in adults, four in the paediatric population, and one trial limited neither minimum or maximum age as an inclusion criterion. Eight studies involving 19,218 participants were rated as high methodological quality (trials with overall low risk of bias according to the domains: allocation concealment, blinding of participants/assessors, incomplete outcome data, and selective reporting), and in the remaining trials, some form of bias was introduced or could not be ruled out.

We found no evidence of an effect of buffered solutions on in-hospital mortality (odds ratio (OR) 0.91, 95% CI 0.83 to 1.01; 19,664 participants; 14 studies; high-certainty evidence). Based on a mortality rate of 119 per 1000, buffered solutions could reduce mortality by 21 per 1000 or could increase mortality by 1 per 1000. Similarly, we found no evidence of an effect of buffered solutions on acute renal injury (OR 0.92, 95% CI 0.84 to 1.00; 18,701 participants; 9 studies; low-certainty evidence). Based on a rate of 121 per 1000, buffered solutions could reduce the rate of acute renal injury by 19 per 1000, or result in no difference in the rate of acute renal injury. Buffered solutions did not show an effect on organ system dysfunction (OR 0.80, 95% CI 0.40 to 1.61; 266 participants; 5 studies; very low-certainty evidence). Evidence on the effects of buffered solutions on electrolyte disturbances varied: potassium (mean difference (MD) 0.09, 95% CI -0.10 to 0.27; 158 participants; 4 studies; very low-certainty evidence); chloride (MD -3.02, 95% CI -5.24 to -0.80; 351 participants; 7 studies; very low-certainty evidence); pH (MD 0.04, 95% CI 0.02 to 0.06; 200 participants; 3 studies; very low-certainty evidence); and bicarbonate (MD 2.26, 95% CI 1.25 to 3.27; 344 participants; 6 studies; very low-certainty evidence).

Authors' conclusions

We found no effect of buffered solutions on preventing in-hospital mortality compared to 0.9% saline solutions in critically ill patients. The certainty of evidence for this finding was high, indicating that further research would detect little or no difference in mortality. The effects of buffered solutions and 0.9% saline solutions on preventing acute kidney injury were similar in this setting. The certainty of evidence for this finding was low, and further research could change this conclusion. Patients treated with buffered solutions showed lower chloride levels, higher levels of bicarbonate, and higher pH. The certainty of evidence for these findings was very low. Future research should further examine patient-centred outcomes such as quality of life. The three ongoing studies once published and assessed may alter the conclusions of the review.

PLAIN LANGUAGE SUMMARY

Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children

Background

Intravenous fluid therapy serves as the cornerstone of treatment for a wide spectrum of severe illnesses. Knowing its impact in terms of clinical outcomes is an important issue. There are some doubts as to whether the use of 0.9% saline may cause higher mortality among inpatients or a relevant worsening of their kidney function.

The aim of this Cochrane Review was to find out if fluid therapy with buffered solutions (water-based salt (saline) solution with a buffer to maintain a constant pH) resulted in fewer hospital deaths and less damage to the kidneys for critically ill adults and children, when compared to 0.9% saline.

Study characteristics

We found 21 studies conducted in both children and adults, with a total of 20,213 participants. These studies compared buffered solutions with 0.9% saline solutions for critically ill adults and children (including those with sepsis, trauma, burns, or shock) who had not had planned surgery. We excluded trials where participants underwent planned (elective) surgery. These studies took place in 13 countries.

Study funding sources

Twelve of the included studies were funded by governments or non-profit organizations, two received mixed funding, one was funded by a company whose role was not clarified, and six provided no details about trial funding.

Key results

Buffered solutions did not seem to reduce hospital deaths or worsening of renal (kidney) function in critically ill adults and children when compared to 0.9% saline.

The review shows that when critically ill patients received buffered solutions compared to 0.9% saline solutions:

1. buffered solutions made little or no difference to overall mortality (19,664 participants; 14 studies; high-certainty evidence);
2. buffered solutions probably may make little or no difference in reducing the number of patients with worsening kidney function (18,701 participants; 9 studies; low-certainty evidence); and

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3. we are uncertain whether buffered solutions reduce impairment of other organs (e.g., lung, liver, or brain function), electrolyte disturbances (increasing or decreasing chloride or sodium or other salts), and the need to receive blood transfusions because evidence certainty has been assessed as very low.

None of the studies looked at blood loss, clotting disturbances (concerning risk of bleeding or clots), and quality of life.

Results varied in terms of the time points at which they were reported, the unit of measurement used, and the measures reported. The total amount of fluid given as fluid therapy was not recorded. Only four studies involved children. These children were less sick than participants included in the adult trials, and kidney damage was not reported. The three ongoing studies once published and assessed may alter the conclusions of this review.

How up-to-date is this review?

We searched for studies that had been published up to July 2018.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Buffered solutions compared to 0.9% saline for resuscitation in critically ill adults and children

Patient or population: critically ill adults and children

Setting: intensive care units in Africa (South Africa), Asia, Europe, Middle East, and North America

Intervention: buffered solutions

Comparison: 0.9% saline

Outcomes	Anticipated absolute effects* (95% CI)		Odds ratio (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Risk with saline 0.9%	Risk with buffered solutions			
Overall mortality (in-hospital death)	Study population ^a		OR 0.91 (0.83 to 1.01)	19,664 (14 RCTs)	⊕⊕⊕⊕ High ^b
	119 per 1000	108 per 1000 (98 to 120)			
Acute renal Injury (defined as RIFLE or AKIN criteria by study authors)	Study population		OR 0.92 (0.84 to 1.00)	18,701 (9 RCTs)	⊕⊕⊕⊖ Low ^{c,d}
	121 per 1000	111 per 1000 (102 to 121)			
Organ system dysfunction (during admission)	Study population		OR 0.80 (0.40 to 1.61)	266 (5 RCTs)	⊕⊖⊖⊖ Very low ^{d-g}
	156 per 1000	137 per 1000 (81 to 235)			
Electrolyte disturbances					
Plasma potassium, mmol/L (during admission)	Median potassium in control groups was 3.55	MD 0.09 (-0.10 to 0.27)	-	158 (4 RCTs)	⊕⊖⊖⊖ Very low ^{d-g}
Plasma chloride, mmol/L (during admission)	Median chloride in control groups was 109.75	MD -3.02 (-5.24 to -0.80)	-	351 (7 RCTs)	⊕⊖⊖⊖ Very low ^{d-g}

Plasma pH (during admission)	Median pH in control groups was 7.36	MD 0.04 (0.02 to 0.06)	-	200 (3 RCTs)	⊕○○○ Very low ^{d-g}
Plasma bicarbonate, mmol/L (during admission)	Median bicarbonate in control groups was 19.75	MD 2.26 (1.25 to 3.27)	-	344 (6 RCTs)	⊕○○○ Very low ^{d-g}

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

* The basis for the basal risk assumption in continuous outcomes is the median control group response across studies.

CI: confidence interval; MD: mean difference; OR: odds ratio; RCT: randomized controlled trial.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aFew included studies were rated as high risk of bias, and the weight of them was 1%. Relevant heterogeneity was not detected. Several studies did not report mortality but publication bias was not suspected upon the funnel plot. Certainty of the outcome was not downgraded.

^bWe estimated a serious limitation of risk of bias because several studies were not blinded. Certainty of the outcome was downgraded two levels because of risk of bias and publication bias.

^cThe possibility of publication bias is not excluded because several studies did not report this outcome.

^dSeveral studies included in this outcome have high or unclear risk of bias for blinding or incomplete reporting.

^eStudies included few participants and few events.

^fCertainty was downgraded by three levels because risk of bias, imprecision, and publication bias.

^gOnly four studies with a total of 258 participants involved children.

BACKGROUND

Description of the condition

Intravenous fluid therapy is the intervention that is probably provided most frequently for critically ill patients (Myburgh 2015). More than a third of all hospitalized patients are given intravenous fluid therapy (Finfer 2010). It is estimated that every year, 200 million litres of intravenous fluids are used in the USA (Young 2014), as well as 10 million litres of 0.9% saline in the UK (Awad 2008). Intravenous fluid preparations differ in their physiochemical properties. The ideal intravenous fluid should keep electrolytes and pH at physiological levels and should have the ability to expand intravascular volume (Myburgh 2013). For many clinical scenarios, such as sepsis, acute pancreatitis, and severe trauma, intravenous fluid therapy serves as the cornerstone of treatment.

Available options for fluid therapy vary widely in terms of fluid volume, timing, and choice of solution. However, no standard care intravenous fluid therapy has been universally accepted (Finfer 2010; Singer 2012). The cost of different intravenous solutions has been estimated at three to a hundred times greater than the cost of 0.9% saline (Lyu 2014). Several medical societies and authors have developed consensus papers and have presented evidence-based guidelines intended to improve decisions about fluids and related outcomes (Garnacho-Montero 2015; NICE 2013; Raghunathan 2014b; Reinhart 2012). Other guidelines have focused more on critical illness and have provided recommendations concerning fluid therapy (Dellinger 2013; Maravi 2014).

Fluid therapy solutions are classified as colloid or crystalloid solutions. Colloids are solutions composed of large molecules dispersed throughout fluid. In theory, they cannot cross the healthy semi-permeable endothelial layer owing to their large molecular size, but this is not a criterion to be considered for colloids. Colloids have been described as more effective than crystalloids in increasing intravascular volume (Trof 2010).

However, according to two Cochrane Reviews, colloids offer no benefit over crystalloids and may even increase risks of renal failure and death (Lewis 2018; Mutter 2013). Further, studies addressing glycocalyx function during critical illness have provided some explanation for possible detrimental effects of colloids. New insight into the Starling principle suggests that the glycocalyx is the main determining factor in transcapillary flow (Starling 1896). In disease states, the integrity of the glycocalyx may be compromised, which translates to greater permeability and a greater rise in the oncotic pressure gradient, causing interstitial oedema (Levick 2010; Woodcock 2012). Accordingly, recent evidence does not support the use of colloids for resuscitation in critically ill patients (Hartog 2014; Reinhart 2012).

Although 0.9% saline is a widely used crystalloid solution, it causes hyperchloraemic acidosis with significant consequences for patients identified in several observational studies (Raghunathan 2014a; Shaw 2014; Yunos 2014). As safer crystalloids, buffered solutions have been assessed for their resuscitation capacity. According to a Cochrane Review of the safety and efficacy of buffered fluids in adult patients undergoing elective surgery, those who received buffered solutions did not develop hyperchloraemic acidosis (Bampoe 2017). In another systematic review of elective surgery and critical care, high-chloride fluids were associated with greater risk of acute kidney; this particular review provided little

evidence of effects on mortality (Krajewski 2015). Characteristics of elective surgical patients are different from those of critically ill patients. Fluid therapy prescribed for non-surgical patients is more targeted at multiple organ dysfunction syndrome. This means that conclusions of reviews that have examined intravenous fluid therapy in elective surgical patients cannot necessarily be transferred to critically ill patients (Bampoe 2017).

In summary, according to recent evidence, use of colloid solutions in critically ill patients for resuscitation purposes generally is not recommended, and the benefits of buffered solutions versus 0.9% saline in this patient subset remain unclear.

Description of the intervention

Crystalloids are aqueous solutions of ions that show different properties according to their ion concentrations (Appendix 1). Because of its low cost, wide user experience, and general availability, 0.9% saline is the most commonly used intravenous fluid (Awad 2008). Use of terms such as *normal* or *physiological saline* is not recommended by the authors of this Review because, although 0.9% saline contains sodium and chloride in equal concentrations, it contains higher than physiological levels. The terms *normal* and *physiological* reflect historical issues rather than chemical properties (Awad 2008). Hence, in this current review, we used the term *0.9% saline*.

Other crystalloid formulations, called *balanced* or *buffered solutions*, differ from 0.9% saline in terms of three properties: lower sodium and chloride contents, bringing them closer to normal plasma levels; the presence of other ions such as potassium, calcium, or magnesium, which could have effects on factors such as potassium or lactate levels, or could play a role in liver disease (Orbegozo 2014); and, finally, their contents of anions such as lactate, acetate, and gluconate, which are metabolized to bicarbonate by tissue cells and may exert an additional buffering effect.

How the intervention might work

Data from experimental human and animal studies suggest that an infusion of 0.9% saline may induce greater hyperchloraemic acidosis and interstitial oedema than are associated with the use of intravenous buffered solutions (Chowdhury 2012; Kellum 1998). Experimental studies have shown that hyperchloraemic acidosis increases the risk of worsening renal function through effects such as renal vasoconstriction, low renal perfusion pressure, and low glomerular filtration rate (Schnermann 1976; Wilcox 1983). Effects of acidosis on the immune system have been described in a rat model (Kellum 2006). Further, changes in systemic inflammation response have been linked to acidosis in humans (Wu 2011). In a before-and-after trial, a chloride-restrictive strategy was associated with significant reduction in the incidence of acute kidney injury and in the need for renal replacement therapy (RRT) in adult intensive care patients (Yunos 2012; Yunos 2014). In a recent observational study, hyperchloraemic acidosis was associated with increased mortality among critically ill patients (Raghunathan 2014a). The effect observed could be independent of the fluid volume administered and may be more closely related to the chloride load (Shaw 2014). These data suggest that buffered solutions, with their lower chloride concentrations than 0.9% saline, may reduce the incidence of hyperchloraemic acidosis, thus decreasing the risk of patient-centred outcomes such as renal

failure, need for RRT, and mortality (McCluskey 2013; Raghunathan 2014a).

Why it is important to do this review

Several observational studies in the critical care setting have reported an association between hyperchloraemic acidosis and relevant outcomes such as acute renal injury and mortality (Raghunathan 2014a; Shaw 2014; Yunos 2014).

A recent Cochrane Review concluded that buffered intravenous fluids reduce the incidence of hyperchloraemia and metabolic acidosis in elective surgery (Bampoe 2017). However, the trials reviewed were not adequately powered to permit conclusions about renal failure or mortality, and did not include critically ill patients. Several recent randomized controlled trials (RCTs) have examined the effects of buffered solutions in critically ill patients. In one such study, faster pH normalization was observed among severely dehydrated participants receiving buffered fluid therapy (Cieza 2013). Two RCTs conducted in trauma patients described a reduction in the incidence of hyperchloraemic acidosis without a rise in intracranial pressure (Roquilly 2013; Young 2014). Other trials have explored the potential benefits of buffered solutions in clinical settings such as diabetes (Van Zyl 2012), acute pancreatitis (Wu 2011; Zhao 2013), dengue (Wills 2005), and doxylamine-induced rhabdomyolysis (Cho 2007). However, in the recent (0.9% saline vs Plasma-Lyte 148 for intensive care unit fluid therapy) *SPLIT* study, which included 2278 critical care participants, no differences between 0.9% saline and Plasma-Lyte 148 were reported (Young 2015).

The present systematic review identified and synthesized all available evidence on the efficacy and safety of isotonic buffered solutions versus 0.9% saline when used in critically ill patients. On the basis of wide use of this therapy and the amount of solution administered, minor effects of the intervention may have an impact on clinical outcomes. In addition, possible cost differentials may reduce overall costs.

OBJECTIVES

To assess the effects of buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) with parallel or cross-over design, regardless of language of publication. We excluded studies performed in persons undergoing elective surgery. We considered unpublished studies and abstracts if adequate information on methods and results was provided.

Types of participants

We included studies on participants with critical illness (including trauma, burns, or emergency surgery during critical illness) who require intravenous fluid therapy. We included studies of adults and children, and we explored the effects of age in a subgroup analysis (Subgroup analysis and investigation of heterogeneity).

Types of interventions

We considered interventions that included the use of intravenous buffered solutions containing bicarbonate or its precursors versus intravenous 0.9% saline as control (Appendix 1). We considered all uses of fluids in a critical care setting of resuscitation or maintenance after enrolment. We required that included fluids were isotonic (osmolality 250 to 350 mmol/L). Fluids before enrolment were registered and analysed if they had been reported.

To minimize confounding factors, we did not consider studies with multiple interventions (e.g. colloids plus buffered solutions). Therefore, we excluded studies that compared only crystalloids versus colloids, or those that compared different types of colloids, even if buffered colloids were used. However, we included studies with more than two arms if they fulfilled all of our inclusion criteria and compared buffered solutions versus 0.9% saline.

Types of outcome measures

Primary outcomes

1. Overall (in-hospital) mortality
2. Acute kidney injury (AKI) during hospitalization as defined by risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage kidney disease (RIFLE), or by Acute Kidney Injury Network (AKIN) criteria

Secondary outcomes

1. Number of participants with organ system dysfunction (respiratory, haemodynamic, central nervous system, and hepatic) as defined in the included studies during admission
2. Electrolyte disturbances during admission (hyperchloraemic acidosis; serum sodium, potassium, calcium, and chloride concentrations; pH; serum bicarbonate; base excess; strong ion difference) measured as serum levels or defined by study authors (e.g. presence or absence of hyperchloraemic acidosis)
3. Blood loss or transfusion requirement during admission
4. Coagulation disturbances (expressed as thrombocytopenia or coagulopathy) during admission
5. Total volume of intravenous fluids needed during resuscitation
6. Quality of life measured with Short Form (SF)-36 and the EuroQOL quality of life questionnaire (EQ-5D) (Angus 2003)
7. Cost

Search methods for identification of studies

Electronic searches

We searched for studies with systematic and sensitive search strategies as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 6 (Higgins 2011). We applied no language, publication year, or publication status restrictions.

We searched the following databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2018 Issue 6).
2. MEDLINE (Ovid SP, 1946 to July 2018).
3. Embase (Embase Elsevier, 1974 to July 2018).
4. CINAHL (Ebsco, 1980 to July 2018).

We developed a subject-specific search strategy in MEDLINE and modified it appropriately for the other databases. Where appropriate, we used the highly sensitive search strategy designed by Cochrane for identifying RCTs and controlled clinical trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 6 (Higgins 2011). Our search strategies can be found in Appendix 2.

Searching other resources

We checked the bibliographic references and citations of relevant studies and reviews for further references to trials. We also searched ClinicalTrials.gov (www.clinicaltrials.gov), as well as the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/), for unpublished and ongoing studies; Open Grey for grey literature (<http://opengrey.eu/>), and Google Scholar for additional trials (July 2018).

We searched abstracts from the most relevant meetings from 2000 to 2018.

1. Society of Critical Care Medicine (SCCM).
2. European Society of Intensive Care Medicine (ESICM).
3. Spanish Society of Intensive Care Medicine (SEMICYUC).
4. American Society of Critical Care Medicine (ASCCM).
5. European Society of Anaesthesiologists (ESA).
6. American Society of Anesthesiologists (ASA).
7. International Anesthesia Research Society (IARS).
8. Spanish Society of Anaesthesia (SEDAR).
9. American Thoracic Society (ATS).
10. American College of Surgeons (ACS).
11. Society of Thoracic Surgeons (STS).

We contacted experts in the field and main investigators to ask for any ongoing, missed, or unreported studies. We checked the reference lists of all included studies and relevant systematic reviews.

Data collection and analysis

Selection of studies

We selected studies according to the methods of the Cochrane Emergency and Critical Care Group. At least two review authors (AMA and JAB) independently screened all relevant abstracts and titles to determine whether they fulfilled the inclusion criteria. We piloted eligibility criteria on a sample of reports (including studies that the review authors deemed definitely eligible, definitely not eligible, and doubtful) to ensure their performance. We classified studies into three categories: 'exclude', 'uncertain', and 'include', according to pre-determined criteria for this review (see [Criteria for considering studies for this review](#)). At that stage, we excluded only papers classified as 'exclude'. During a second stage of the process, the same two review authors (AMA and JAB) independently examined full-text reports to check whether the studies complied with the eligibility criteria of this review. We resolved disagreements by discussion and consulted a third review author (MC) if we could not reach consensus. If appropriate, we contacted study authors to clarify the eligibility of a study. Finally, if we were unable to obtain necessary information, we excluded the study in question. We were not blinded to the names and affiliations of study authors, to journals, nor to study results at any stage of

the review process. We performed the selection of studies and data extraction using [Covidence](#) software.

Data extraction and management

We modified the Cochrane Emergency and Critical Care Group data extraction form and piloted it with five studies to ensure its suitability (Appendix 3). Two review authors (AMA and JAB) independently extracted data. We compared results and resolved discrepancies by discussion or by consultation with a third review author (MC). We extracted the following information from each trial.

1. Study authors, journal and year of publication.
2. Study design.
3. Study hypothesis.
4. Statistical information: estimation of sample size, statistical power, and analysis methods.
5. Participant characteristics: demographics, previous diseases, fulfilment of inclusion criteria, and baseline comparability.
6. Intervention and control groups, outcome measures.
7. Results.
8. Risk of bias domains.
9. Conflicts of interest and funding.

Two review authors (JAB and AMA) entered the data into Review Manager 5 and checked them for accuracy ([Review Manager 2014](#)).

Dealing with duplicate publications

If we found several publications that referred to the same trial, we included the primary version of the study and referenced all secondary reports. We selected the most complete data among all publications found.

Assessment of risk of bias in included studies

Two review authors (JAB and AMA), independently assessed the methodological quality of each trial that fulfilled the inclusion requirements of our review. We extracted information related to risk of bias from each study according to the following domains: random sequence generation; allocation concealment; blinding of participants/investigators; outcome assessment; incomplete outcome data; and selective reporting, in accordance with the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If any of the above data were not available for the publication of interest, or if it was unclear whether criteria were met, we contacted the study author by email to request further information. If needed, we considered other sources of bias related to the design of the studies, as specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In accordance with recent publications, we considered industry funding as a potential source of bias (Bero 2013; Lundh 2012). We considered funding when work force, materials, or grants were provided for the study. We established the risk of funding bias as defined in Appendix 4. We did not exclude trials on the basis of risk of bias but conducted subgroup analyses to explore the effects of risk of bias in the meta-analysis (see [Subgroup analysis and investigation of heterogeneity](#)). We performed the subgroup analysis to determine if the effect on primary outcome changed when we assessed only studies with low risk of bias for randomization, allocation concealment, and study blinding.

Measures of treatment effect

We performed all analyses according to standards specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We selected measures of treatment effects according to how data were expressed in studies as follows.

1. Dichotomous data (e.g. need for RRT): odds ratio (OR).
2. Continuous data (e.g. potassium levels): mean difference (MD), standard deviation (SD), or standardized mean difference (SMD) when original studies used different scales.

We reported outcomes with 95% confidence intervals (CIs).

Unit of analysis issues

We dealt with trials with cluster or cross-over design and multiple arms as specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Elbourne 2002; Higgins 2011). First, for cluster design, if adjusted data were available, we incorporated them into analyses. Adjusted data for blood products outcomes in Semler 2018 were not available. For this outcome, we reduced the size of the trial to its 'effective sample size', considering an intracluster correlation coefficient of 0.01 (Hannan 1994). Second, for multiple-arms trials, we included each buffered pair-wise comparison separately and divided up the sample size of the 0.9% saline group among the comparisons.

Dealing with missing data

We conducted analyses on an intention-to-treat basis, meaning that:

1. we analysed participants in the intervention groups to which they were randomized, regardless of the intervention they actually received; and
2. we considered outcome data for all participants and included all randomized participants in the analysis.

For missing data, we used this strategy.

1. Contact study authors by email or by letter to request those data.
2. Describe missing outcomes for studies as proportions of participants for whom we had no data with reasons.

We performed sensitivity analysis by using two alternative scenarios for participants with incomplete or missing data for the two primary outcomes considered (overall mortality and acute renal injury during hospitalization) (Jakobsen 2014).

1. 'Best-worst' case scenario analyses: we considered participants with missing outcome data to be successes in the experimental group and failures in the control group. The denominator included all participants in the trial.
2. 'Worst-best' case scenario analyses: we considered participants with missing outcome data to be failures in the experimental group and successes in the control group. The denominator included all participants in the trial.

Assessment of heterogeneity

We checked for heterogeneity by considering:

1. clinical and methodological characteristics of studies;

2. forest plots of study results to visually check for overlaps in confidence intervals; and
3. results of the χ^2 test for statistical heterogeneity (we considered trial results as heterogeneous with $P < 0.10$) and results of the I^2 statistic for quantification of heterogeneity. We judged the importance of the observed value of I^2 according to the magnitude and direction of effects and the strength of evidence of heterogeneity (from 0% to 40% heterogeneity - might not consider important; from 30 to 60% heterogeneity - might be moderate; from 50% to 90% heterogeneity - might be substantial; and from 75% to 100% heterogeneity - might be considerable) (Deeks 2011). We explored the reasons behind substantial or considerable heterogeneity by performing subgroup analyses.

Assessment of reporting biases

We minimized reporting bias by including both published and unpublished studies. We developed a strategy to search for unpublished studies (Searching other resources), and we looked for publication bias in every outcome reported. The pre-defined strategy for assessment of reporting bias consisted of the following.

1. Graphically, if more than 10 studies were included for the considered outcome, we created a funnel plot (a scatter plot of the intervention effect against a measure of study size).
2. We assessed funnel plot asymmetry statistically if 10 or more studies were meta-analysed.

We interpreted results while considering all causes of asymmetry (not only publication bias).

Data synthesis

We performed statistical tests according to the recommendations of the Cochrane Emergency and Critical Care Group using the Review Manager 5 package (Review Manager 2014), provided by Cochrane for data synthesis and analysis.

Assessment of significance

We assessed our intervention effects by using a random-effects meta-analytical model. If one or two trials contributed to 75% of randomized participants, we used a fixed-effect model (Jakobsen 2014). We compared results of both models in a sensitivity analysis (see Sensitivity analysis). We did not calculate trial sequential analyses (TSA) because of the recent position statement published by Cochrane (Schmid 2018).

We calculated Bayes factor (ratio between the probability that the meta-analysis result given the null hypothesis is true divided by the probability that the meta-analysis result given the alternative hypothesis is true) for primary outcomes based on a relative risk reduction (RRR) of 20%. We chose a Bayes factor less than 0.1 as the threshold for significance.

Subgroup analysis and investigation of heterogeneity

If the number of studies was appropriate, we conducted subgroup analyses to examine the following.

Participant subsets

1. Neurocritical participants
2. Septic participants

3. Burn or trauma participants
4. Surgical critically ill participants
5. Participants with primary electrolyte imbalance (dehydration or diabetic ketoacidosis)

Intravenous buffered fluid received

1. Fluids containing bicarbonate as buffer
2. Fluids containing a bicarbonate precursor as buffer

Age group

1. Adults ≥ 16 years old
2. Children < 16 years old

Risk of bias

1. Trials with low risk of bias
2. Trials with unclear or high risk of bias

We assessed differences between subgroups by performing the test of interaction (Altman 2003).

Summary of findings and GRADE

We designed a 'Summary of findings' table using GRADE profiler software to summarize the key results of our review (GRADEpro GDT). We indicated in this table the population, intervention, and comparison, along with relevant outcomes. We used the GRADE system to assess the quality of evidence associated with the following outcomes (Guyatt 2008).

1. Overall (in-hospital) mortality.
2. Acute renal injury.
3. Organ system dysfunction.
4. Electrolyte disturbances.

The GRADE approach appraises the quality of evidence according to the extent to which one can be confident that an estimate of

effect or association reflects the item assessed. Two review authors (JAB and AMA) independently assessed the quality of the body of evidence for the design of [Summary of findings for the main comparison](#). Our confidence in the estimate of effect was evaluated in terms of study limitations, inconsistency of effect or unexplained heterogeneity, imprecision of results, indirectness, and publication bias. We used trial sequential analyses as a supplement for a more thorough assessment of imprecision (Guyatt 2011).

Sensitivity analysis

We undertook the following sensitivity analyses.

1. We evaluated the impact of risk of bias from individual trials in the magnitude or direction of overall effect. We excluded studies with high or unclear risk of bias in the following domains: allocation features, levels of missing data, and blinding of outcome assessment.
2. We explored potential differences when the fixed-effect model versus the random-effects model was used.

RESULTS

Description of studies

See [Characteristics of included studies](#), [Characteristics of excluded studies](#), [Characteristics of studies awaiting classification](#), and [Characteristics of ongoing studies](#).

Results of the search

We conducted a search on 7 July 2018 (Figure 1). We retrieved 10,286 records. After reading the abstracts, we excluded 10,251 articles for one of the following reasons: irrelevance, overlap, or design. We identified 35 papers for further examination. We included 21 studies in the review. We excluded 14 studies because they did not fulfil our inclusion criteria. We found three ongoing trials in registries of clinical trials.

Figure 1. Flow diagram.

Included studies

We included 21 studies, with a total of 20,213 participants (Aditjaningsih 2017; Allen 2016; Choosakul 2018; Dung 1999; Hasman 2012; Hassan 2017; Mahajan 2012; Mahler 2011; Ngo 2001; Ratanarat 2017; Reddy 2014; Semler 2016; Semler 2018; Van Zyl 2012; Vasu 2013; Verma 2016; Viaene 2014; Wu 2011; Young 2014; Young 2015; de-Madaira 2018). Three RCTs with 19,054 participants (94.2%) contributed.

The details of the included trials are provided in the [Characteristics of included studies](#) table. All publications were written in English. All 21 included trials were published between 1999 and 2018.

Participants

Sixteen included trials were conducted in adults, four were conducted in the paediatric population, and one trial limited neither minimum nor maximum age as an inclusion criterion (Young 2015). Most participants were males, and the proportion of females ranged between 12% and 63%, in the 19 trials that reported this information. All studies enrolled critically ill

participants - five specifically acute pancreatitis (Choosakul 2018; de-Madaira 2018; Reddy 2014; Vasu 2013; Wu 2011); three severe dehydration (Allen 2016; Hasman 2012; Mahajan 2012); three diabetic ketoacidosis (Aditianingsih 2017; Mahler 2011; Van Zyl 2012); two dengue shock syndrome (Dung 1999; Ngo 2001); two severe trauma (Hassan 2017; Young 2014); and one shock (Ratanarat 2017).

The intervention

1. Nine studies administered Ringer's lactate (Choosakul 2018; de-Madaira 2018; Dung 1999; Mahajan 2012; Ngo 2001; Reddy 2014; Vasu 2013; Van Zyl 2012; Wu 2011)
2. Five trials used Plasma-Lyte A (Allen 2016; Mahler 2011; Verma 2016; Young 2014; Young 2015)
3. Three studies used Sterofundin (Hassan 2017; Ratanarat 2017; Viaene 2014)
4. Two studies used either Ringer's lactate or Plasma-Lyte A in an intervention arm (Semler 2016; Semler 2018)
5. One trial administered both Ringer's lactate and Plasma-Lyte A in different arms of multiple interventions (Hasman 2012)
6. One used Ringerfundin (Aditianingsih 2017)

Setting

There was geographical variability across the included studies. Trials were performed in Belgium (Viaene 2014), Canada (Allen 2016), India (Mahajan 2012; Reddy 2014; Vasu 2013), Indonesia (Aditianingsih 2017), Malaysia (Hassan 2017), New Zealand and Australia (Verma 2016; Young 2015), South Africa (Van Zyl 2012), Spain (de-Madaira 2018), Thailand (Choosakul 2018; Ratanarat 2017), Turkey (Hasman 2012), USA (Allen 2016; Mahler 2011; Semler 2016; Semler 2018; Wu 2011; Young 2014), and Vietnam (Dung 1999; Ngo 2001).

Type of study

Five trials were multi-centric studies (Allen 2016; Semler 2018; Verma 2016; Wu 2011; Young 2015). Most of the included trials had medium sample sizes, enrolling between 22 and 230 participants. The largest study enrolled 15,904 participants (Semler 2018). Most of the included trials were parallel studies, and three were cluster multiple-cross-over (Semler 2016; Semler 2018; Young 2015). Three studies compared multiple interventions, and we considered only their buffered solution and 0.9% saline arms

(Hasman 2012; Dung 1999; Ngo 2001). One study used a four-arm (2×2) factorial design (Wu 2011).

Financial sponsorship

Financial sponsorship was provided by non-industry sources in the majority of included studies. One trial was supported by industry (Allen 2016), and two were supported by mixed funding (Verma 2016; Young 2015). Six studies did not report the sponsorship source in their publications (Aditianingsih 2017; Hasman 2012; Mahler 2011; Reddy 2014; Vasu 2013; Viaene 2014).

Contact with study authors

We contacted study authors for further information. Three authors of included studies responded. Dr. de-Madaira provided a recent full-text publication (de-Madaira 2018), Dr. Semler provided additional methodological details regarding the characteristics of clusters, and Dr. Aditianingsih confirmed the data related to in-hospital mortality. We contacted 13 study authors regarding methodology and outcomes, but they did not respond.

Excluded studies

We excluded 14 studies because they did not fulfil our inclusion criteria (Benoit 2016; Chen 2004; Cho 2007; Crivits 2016; Dybvik 1995; Fang 2008; Galas 2009; Kartha 2017; Martin 2018; Omar 2018; Rainier-Pope 1962; Roquilly 2013; Rowell 2016; Yung 2017). The characteristics of these studies are summarized in the [Characteristics of excluded studies](#) table.

Studies awaiting classification

We identified no studies awaiting classification.

Ongoing studies

We found three ongoing trials in registries of clinical trials (NCT02721654; NCT02835157; NCT02875873). We have summarized the characteristics of these studies in the [Characteristics of ongoing studies](#) table.

Risk of bias in included studies

Details of individual studies are available in the [Characteristics of included studies](#), the risk of bias summary (Figure 2), and the risk of bias graph (Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): Objective outcomes (e.g. mortality)	Blinding of participants and personnel (performance bias): Subjective outcomes (e.g. author defined renal failure)	Blinding of outcome assessment (detection bias): Objective outcomes (e.g. mortality)	Blinding of outcome assessment (detection bias): Subjective outcomes (e.g. author defined renal failure)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aditjaningsih 2017	?	+	?	?	+	?	+	?	?
Allen 2016	+	+	+	+	+	+	-	+	-
Choosakul 2018	+	+	?	?	+	?	+	+	+
de-Madaira 2018	+	+	+	+	+	+	?	?	+
Dung 1999	+	+	+	+	+	+	+	?	+
Hasman 2012	+	+	+	+	+	?	+	?	+
Hassan 2017	+	+	?	?	+	?	-	?	+
Mahajan 2012	+	+	+	+	+	+	+	+	+
Mahler 2011	+	+	+	+	+	?	-	?	?
Ngo 2001	+	+	+	+	+	?	-	?	+

Figure 2. (Continued)

Ngo 2001	+	+	+	+	+	?	-	?	+
Ratanarat 2017	?	?	+	-	?	?	?	?	+
Reddy 2014	?	?	?	?	+	?	?	?	?
Semler 2016	+	+	+	-	+	-	+	+	+
Semler 2018	?	+	+	-	+	-	+	+	+
Van Zyl 2012	+	+	+	+	+	+	-	?	+
Vasu 2013	?	?	?	?	+	?	?	?	?
Verma 2016	+	+	+	+	+	+	-	+	+
Viaene 2014	?	?	?	?	+	?	?	?	?
Wu 2011	+	+	+	-	+	-	+	+	+
Young 2014	+	+	+	+	+	+	-	+	+
Young 2015	+	+	+	+	+	+	+	+	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

All trials were randomized. A majority of studies explained their randomization and allocation concealment methods. The most frequently used method was web-based randomization. Because of this, we rated the majority as having low risk of bias. Five studies did not provide any information about the method used for randomization nor allocation concealment (Aditjaningsih 2017; Ratanarat 2017; Reddy 2014; Vasu 2013; Viaene 2014). We asked for this information by mail, but we received no information. We rated those studies as having unclear risk for selection bias. The number of participants in most trials was low (fewer than 50 participants in each arm). Five trials randomized more than 100 participants (Allen 2016; Ngo 2001; Semler 2016; Semler 2018; Young 2015).

Blinding

We included four open-label trials and eight participant-, personnel-, and assessor-blinded studies. We could not assess the blinding status of participants, personnel, or assessors in nine trials. We requested this information by emailing the study authors, but we received no information. We distinguished between objective outcomes (e.g. mortality) and subjective outcomes (e.g. AKI defined by study authors) in evaluating detection bias. Regarding mortality (considered objective), we rated 15 studies as having low risk of performance and detection bias (Allen 2016; de-Madaira 2018; Dung 1999; Hasman 2012; Mahajan 2012; Mahler 2011; Ngo 2001; Ratanarat 2017; Semler 2016; Semler 2018; Van Zyl 2012; Verma 2016; Young 2014; Young 2015; Wu 2011). Concerning subjective outcomes, we assessed eight studies as having low risk of bias (Allen 2016; de-Madaira 2018; Dung 1999; Mahajan 2012;

Van Zyl 2012; Verma 2016; Young 2014; Young 2015); nine trials did not detail the methods used in blinding assessors, and we rated them as having unclear risk; four studies were open-label and we categorized them as high risk.

Incomplete outcome data

Nine studies performed their analyses in an intention-to-treat way (Aditjaningsih 2017; Choosakul 2018; Dung 1999; Hasman 2012; Mahajan 2012; Semler 2016; Semler 2018; Wu 2011; Young 2015). We rated two trials as having high risk of attrition bias because they used a modified intention-to-treat analysis or a per-protocol analysis not prespecified in the protocol. Five studies reported incomplete outcome data or changes in the analysis plan or in the inclusion criteria; we rated them as high risk. The remaining five trials did not provide enough information, and we classified them as unclear risk.

Selective reporting

To assess reporting bias, we obtained information on published protocols or on clinical trials registers if it was available. Four studies had published protocols, and we identified no reporting bias (Semler 2016; Semler 2018; Verma 2016; Young 2015). Five studies had public information in clinical trials registers related to prespecified outcomes with no evidence of selective reporting (Allen 2016; Choosakul 2018; Mahajan 2012; Wu 2011; Young 2014). The remaining 12 studies did not provide information; we rated them as having unclear risk of reporting bias.

Other potential sources of bias

In our protocol (Barea-Mendoza 2016), we specified the criteria used to assess funding bias according to the other authors (Appendix 4). Most of the studies provided information about funding, and we rated them as having low risk of bias. Two studies received mixed funding through unrestricted grants from the companies involved (Verma 2016; Young 2015). We rated both trials as low risk of bias. One study stated no information about sponsorship source, and its authors declared no conflicts of interest (Hasman 2012). We rated this study as having low risk of bias. One study reported a company source of funding without providing information about the role of the company (e.g. design or analysis) (Allen 2016). We rated it as having high risk of bias with pre-specified criteria (Appendix 4). Five studies did not provide information about study funding, and we rated them as having unclear risk of bias (Aditjaningsih 2017; Mahler 2011; Reddy 2014; Vasu 2013; Viaene 2014). We included three cluster-randomized, multiple-cross-over trials (Semler 2016; Semler 2018; Young 2015). We rated all of them as having low risk of recruitment bias, baseline imbalance between groups, loss to follow-up of clusters, non-comparability, and carry-over effect. With regard to the risk of bias for incorrect analyses, we judged these three studies to be at low risk because adjustments of analyses for cluster were performed via individual-level analyses based on a multi-level model and generalized estimating equations (Semler 2016; Semler 2018; Young 2015).

Effects of interventions

See: [Summary of findings for the main comparison Buffered solutions compared to 0.9% saline for resuscitation in critically ill adults and children](#)

See [Summary of findings for the main comparison](#) for the main comparison buffered solutions versus 0.9% saline for resuscitation in non-surgical critically ill adults and children.

All included studies reported at least one outcome of interest, as specified previously in [Types of outcome measures](#). For primary outcomes, each outcome section is subdivided into six main subheadings: 'Overall effect', 'Bayes factor', 'Sensitivity analysis', and 'Subgroup analysis.'

We collected and analysed data from the 21 included studies (20,213 participants). Given that one trial dominated, with 75% of randomized participants, we used a fixed-effect model in the primary outcomes analysis (Semler 2018). For primary outcomes (overall mortality and acute renal injury), we presented pooled results as ORs with 95% CIs. We performed additional Bayes factor analyses for primary outcomes. We performed formal assessment of funnel plot asymmetry only for overall (in-hospital) mortality outcomes because more than 10 studies were combined. We presented secondary outcomes according to the protocol.

Primary outcomes

1. Overall (in-hospital) mortality

Fourteen trials including 19,664 participants reported results on mortality (Aditjaningsih 2017; Allen 2016; Choosakul 2018; de-Madaira 2018; Dung 1999; Mahajan 2012; Ngo 2001; Semler 2016; Semler 2018; Van Zyl 2012; Verma 2016; Young 2014; Young 2015; Wu 2011). A total of 1102/9927 (11.1%) participants in the buffered solutions group died versus a total of 1154/9737 (11.9%) participants in the 0.9% saline group. Meta-analysis showed no evidence of a difference between the two intravenous fluid therapies (odds ratio (OR) 0.91, 95% confidence interval (CI) 0.83 to 1.01; $P = 0.06$; $I^2 = 0\%$; 14 trials; high-certainty evidence). We did not observe any statistical heterogeneity among the studies ($P = 0.94$; $I^2 = 0\%$).

Bayes factor

We calculated the Bayes factor based on the intervention effect shown by the meta-analysis result (OR 0.91, 95% CI 0.83 to 1.01) and the intervention effect hypothesized in the estimation of the required information size (RRR 0.2). The Bayes factor was 3.9, which is above the Bayes factor threshold for significance of 0.1, seeming to provide more evidence for the null hypothesis compared to the evidence for an intervention effect of 20% RRR.

Sensitivity analysis

We performed sensitivity analysis as specified in the protocol (Barea-Mendoza 2016). A random-effects model revealed no differences between meta-analysis results showing analysis under the fixed-effect model because heterogeneity was low (OR 0.91, 95% CI 0.83 to 1.01; $P = 0.06$). We performed sensitivity analysis after excluding six studies with high risk of bias (Allen 2016; de-Madaira 2018; Ngo 2001; Van Zyl 2012; Verma 2016; Young 2014). The analysis showed no difference for mortality when only studies with low risk of bias were included (OR 0.91, 95% CI 0.83 to 1.00; $P = 0.06$).

Subgroup analysis

We planned to perform subgroup analysis for mortality outcomes by disease subsets, type of fluid received, age group, and risk of

bias when data were available. The included trials did not report outcomes by disease subsets.

Intravenous buffered fluid received

Four studies used Plasma-Lyte (Allen 2016; Verma 2016; Young 2014; Young 2015); seven studies used Ringer's lactate (Choosakul 2018; de-Madaira 2018; Dung 1999; Mahajan 2012; Ngo 2001; Van Zyl 2012; Wu 2011); and one study used Ringerfundin (Aditianingsih 2017). Two studies used Plasma-Lyte or Ringer's lactate indistinctly (Semler 2016; Semler 2018). Subgroup analysis comparing trials using different types of buffered solutions showed no difference in mortality (Analysis 1.1).

Age group

Only four studies with a total of 258 participants involved children during the resuscitation (Allen 2016; Dung 1999; Mahajan 2012; Ngo 2001). Ten studies with a total of 19,406 participants were performed in the adult population (Aditianingsih 2017; Choosakul 2018; de-Madaira 2018; Semler 2016; Semler 2018; Van Zyl 2012; Verma 2016; Wu 2011; Young 2014; Young 2015). Subgroup analysis showed no difference in mortality (Analysis 1.2).

See Figure 4.

Figure 4. Forest plot of comparison: 1 Buffered solutions vs SS 0.9% (saline solution), outcome: 1.1 Mortality.

2. Acute renal injury during hospitalization as defined by risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage kidney disease (RIFLE), or by Acute Kidney Injury Network (AKIN) criteria

This outcome was reported in nine studies including 18,701 participants (Aditianingsih 2017; Choosakul 2018; Ratanarat 2017; Semler 2016; Semler 2018; Verma 2016; Wu 2011; Young 2014; Young 2015). A total of 1077/9452 (11.39%) participants in the buffered solutions group developed an acute renal injury versus a total of 1118/9249 (12.09%) participants in the 0.9% saline group. Meta-analysis showed no evidence of a difference between the two intravenous fluid therapies (OR 0.92, 95% CI 0.84 to 1.00; P = 0.06; I² = 0%; 9 trials; low-certainty evidence). We did not observe any statistical heterogeneity among the studies (P = 0.93; I² = 0%).

Bayes factor

We calculated the Bayes factor based on the intervention effect shown by the meta-analysis result (OR 0.92, 95% CI 0.84 to 1.00) and the intervention effect hypothesized in the estimation of the required information size (RRR 0.2). Bayes factor was 5.3, which is above the Bayes factor threshold for significance of 0.1, seeming to provide more evidence for the null hypothesis compared to the evidence for an intervention effect of 20% RRR.

Sensitivity analysis

We performed a sensitivity analysis using a random-effects model. We found no differences between results obtained with a fixed-effect model and those obtained with a random-effects model (OR 0.92, 95% CI 0.84 to 1.00; P = 0.06). We performed sensitivity analysis, excluding studies with high risk of bias for the specified

domains in the protocol (allocation features, blinding of outcome data, and incomplete outcome data) (Barea-Mendoza 2016). There were no differences between results after exclusion of one study (Ratanarat 2017), and risk of bias for allocation features and blinding was unclear (OR 0.91, 95% CI 0.83 to 1.00; $P = 0.06$). We performed the analysis after excluding three studies with high risk of bias for incomplete outcome data (Ratanarat 2017; Verma 2016; Young 2014). The results were very similar (OR 0.91, 95% CI 0.83 to 1.00; $P = 0.06$).

Subgroup analysis

We planned to perform subgroup analyses for acute renal injury outcome by disease subsets, type of fluid received, and age group when data were available. However, the included trials did not report outcomes by disease subsets, and no trials reported renal injury in the paediatric population.

Intravenous buffered fluid received

Three studies used Plasma-Lyte as buffer solution (Verma 2016; Young 2014; Young 2015); two studies used Ringer's lactate (Choosakul 2018; Wu 2011); and two studies used Plasma-Lyte or Ringer's lactate indistinctly (decided by the treating clinician) (Semler 2016; Semler 2018). Both studies by Semler did not report individualized outcomes according to the type of fluid. Finally, two studies used Ringerfundin and Sterofundin as buffered solutions (Aditioningsih 2017; Ratanarat 2017). Subgroup analysis comparing trials using different types of buffered solutions showed no difference in acute renal injury Analysis 1.3.

See Figure 5.

Figure 5. Forest plot of comparison: 1 Buffered solutions vs SS 0.9% (saline solution), outcome: 1.3 Acute renal injury.

Secondary outcomes

1. Number of participants with organ system dysfunction as defined in the included studies

Six studies reported on organ system dysfunction. Five studies with a total of 266 participants were included in the analysis (Analysis 1.4) (Choosakul 2018; De Madaira 2018; Dung 1999; Ngo 2001; Wu 2011). None of the studies found a significant effect of Ringer's lactate solutions in preventing organ system dysfunction compared with control at an alpha level of 0.05. Overall, we found no clear

evidence of an effect of buffered solutions on the occurrence of organ system dysfunction in critically ill patients, as evidenced by a fixed-effect model (OR 0.80, 95% CI 0.40 to 1.61; $P = 0.53$; $I^2 = 0\%$; 5 trials; very low-certainty evidence). We could not include Vasu 2013, which examined the incidence of organ failure, in the analysis because total sample and event rates were not reported properly, and we were unable to get further information from the trial author.

2. Electrolyte disturbances (hyperchloraemic acidosis; serum sodium, potassium, calcium, and chloride concentrations;

**pH; serum bicarbonate; base excess; strong ion difference)
measured as serum levels or defined by study authors (e.g.
presence or absence of hyperchloraemic acidosis)**

2.1 Sodium

Seven studies reported sodium levels (Hasman 2012; Hassan 2017; Mahajan 2012; Semler 2016; Semler 2018; Van Zyl 2012; Young 2014). We excluded three studies from the analysis. We excluded the studies by Semler and colleagues because they reported only the highest sodium levels during hospitalization. We excluded Van Zyl 2012 because investigators did not report the standard deviation (SD). We included four studies with a total of 222 participants in the analysis (Analysis 1.5). Quantitative analysis showed no evidence of an effect (mean difference (MD) -0.48, 95% CI -1.67 to 0.70; $I^2 = 0\%$; 4 trials; very low-certainty evidence).

2.2 Potassium

Seven studies reported potassium levels (Hasman 2012; Mahajan 2012; Semler 2016; Semler 2018; Van Zyl 2012; Young 2015; Young 2014). We excluded four studies from the analysis. We excluded the two studies by Semler and colleagues because they reported only the highest potassium levels during hospitalization. We excluded Young 2015 because study authors reported no difference in the incidence of hyperkalaemia (risk ratio (RR) 1.93, 95% CI 0.35 to 10.50). We excluded Van Zyl 2012 because the SD was not reported. We included three studies with a total of 158 participants in the quantitative analysis (Analysis 1.6). Data showed no differences (MD 0.09, 95% CI -0.10 to 0.27; $I^2 = 0\%$; 3 trials; very low-certainty evidence).

2.3 Chloride

Nine studies reported chloride levels (Allen 2016; Hasman 2012; Hassan 2017; Mahajan 2012; Mahler 2011; Semler 2016; Semler 2018; Van Zyl 2012; Young 2014). We excluded three studies from the analysis. We excluded the two studies by Semler and colleagues because they reported only the highest chloride levels during hospitalization. We excluded Van Zyl 2012 because the SD was not reported. We included six studies with a total of 351 participants from the quantitative analysis (Analysis 1.7). Data showed lower levels of chloride in the buffer solution group (MD -3.02, 95% CI -5.24 to -0.80; 6 trials; very low-certainty evidence). Heterogeneity was significant ($I^2 = 89\%$); therefore, we used the random-effects model. The subgroup analysis showed significant differences between groups according to the type of buffer solution used ($P = 0.02$; $I^2 = 73.3\%$): Plasma-Lyte subgroup (MD -4.56, 95% CI -6.68 to -2.44); Ringer's lactate (MD -0.56, 95% CI -2.58 to 1.47); Sterofundin (MD -1.55, 95% CI -4.39 to 1.29).

2.4 pH

Four studies reported on this outcome (Hasman 2012; Hassan 2017; Van Zyl 2012; Young 2014). We excluded one study because the SD was not reported (Van Zyl 2012). We included three studies with a total of 200 participants in the quantitative analysis (Analysis 1.8). Data showed higher pH in the buffer solution group (MD 0.04, 95% CI 0.02 to 0.06; $I^2 = 59\%$; 3 trials; very low-certainty evidence).

2.5 Bicarbonate

Eight studies reported the bicarbonate levels (Allen 2016; Hasman 2012; Hassan 2017; Mahajan 2012; Mahler 2011; Semler 2016; Semler 2018; Young 2014). We excluded the two studies by Semler and colleagues because they reported only the highest bicarbonate

levels during hospitalization. We included six studies with a total of 344 participants in the quantitative analysis (Analysis 1.9). Data show higher levels of bicarbonate in the buffer solution group (MD 2.26, 95% CI 1.25 to 3.27; 6 trials; very low-certainty evidence). Heterogeneity was significant ($I^2 = 72\%$); therefore we used the random-effects model.

3. Blood loss or transfusion requirement

3.1 Blood loss

None of the included trials reported on this outcome.

3.2 Transfusion requirement

Two studies with a total of 16,776 participants reported on blood products (Analysis 1.10) (Semler 2016; Semler 2018). Blood products included the total of red blood units, fresh frozen plasma, platelets, and cryoprecipitate transfused. Neither of the two studies found a significant effect of buffered solutions reducing the volume of blood products compared with the control at an alpha level of 0.05. Overall, we found no clear evidence of an effect of buffered solutions on the requirement of blood products in critically ill patients, as evidenced by a fixed-effect model (MD -17.53, 95% CI -44.52 to 9.46; $P = 0.20$; $I^2 = 0\%$; moderate-certainty evidence).

Two studies examined the transfusion requirement detailing the total units of red blood cells, plasma, and platelet (Young 2014; Young 2015). We did not include them in the analyses because the mean and the SD were not reported. They are listed as orphan outcomes in Table 1.

4. Coagulation disturbances (expressed as thrombocytopenia or coagulopathy)

None of the included studies reported on this outcome.

5. Total volume of intravenous fluids needed during resuscitation

Nine studies with a total of 19,422 participants reported on the total volume of fluids needed during resuscitation (Aditjaningsih 2017; Allen 2016; de-Madaira 2018; Mahajan 2012; Ngo 2001; Semler 2016; Semler 2018; Young 2014; Young 2015). The data were heterogeneous in the types of measures of effect used, identification of study fluid infused per arm of comparison, and time scales, and we were unable to get further information from the investigators; therefore, we did not combine these for meta-analysis. Two trials found a significant difference in the total fluid requirement in favour of the intervention arm (de-Madaira 2018; Mahajan 2012). Four studies reported a similar cumulative volume of fluids administered between groups (Aditjaningsih 2017; Allen 2016; Ngo 2001; Semler 2016; Young 2014).

We did not subject these results to any further analysis, and this outcome is listed as orphan outcome in Table 1.

6. Quality of life measured with Short Form (SF)-36 and the EuroQOL quality of life questionnaire (EQ-5D) (Angus 2003)

None of the included trials reported on quality of life.

7. Cost

A single study examined cost inputs (Smith 2014 used data on participants enrolled in Young 2014). This study enrolled 65 participants and detailed an analysis that included costs for

intravenous fluid acquisition, electrolyte acquisition, and nurse labour. The cost-minimization analysis reported a 24-hour cost differential of USD 12.35 in favour of Plasma-Lyte A compared with non-buffered solutions. We did not subject this outcome to any further analysis, and we listed this outcome as an orphan outcome in [Table 1](#).

DISCUSSION

Summary of main results

We included in this review the data from 21 studies with 20,213 participants. Primary outcomes analyses showed that use of buffered solutions for resuscitation in non-surgical critically ill adults did not improve mortality or the incidence of acute renal injury. Fourteen trials including 19,664 participants contributed to the mortality analyses. Data showed no effect on mortality (odds ratio (OR) 0.91, 95% confidence interval (CI) 0.83 to 1.01; $P = 0.06$; [Figure 4](#)). We graded the certainty of evidence as high. We performed a sensitivity analysis for the analysis model (fixed-effect vs random-effects) and for risk of bias without changes in the results. Only four studies involved a paediatric population. Subgroup analysis by age showed no differences in mortality. Nine trials including 18,701 participants were included in the acute renal injury outcome. Data showed no effect on the incidence of acute renal injury (OR 0.92, 95% CI 0.84 to 1.00; $P = 0.06$; [Figure 5](#)). We graded the certainty of evidence as low because several studies were not blinded and publication bias was not excluded. The sensitivity analysis for the analysis model and for the risk of bias did not show any difference. Analyses of all secondary outcomes suggest that patients treated with buffer solutions have lower levels of chloride (mean difference (MD) -3.21, 95% CI -5.52 to -0.89), higher pH (MD 0.05, 95% CI 0.04 to 0.07), and higher levels of bicarbonate (MD 2.48, 95% CI 1.37 to 3.59). However, the clinical significance of these results for the incidence of hyperchloraemic acidosis in the critical care setting is doubtful. We have very low-certainty evidence for these outcomes. The analyses did not show differences between groups in terms of organ dysfunction or levels of sodium or potassium. The included trials did not report results on blood loss, coagulopathy, or quality of life.

Overall completeness and applicability of evidence

This current systematic review includes published trials comparing buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. We excluded trials carried out in the setting of major surgery because a recently updated Cochrane Review has already assessed this question ([Bampoe 2017](#)). Fluids are used in a wide range of situations in critically ill patients such as sepsis, trauma, or different shock profiles. These populations are well represented in the current review. We planned to carry out subgroup analysis according to clinical conditions (burns, neurocritical, septic, etc.). We did not perform these analyses because most of the trials included case mixed intensive care patients and reported pulled results. We think that most of our conclusions are applicable to a general critical care setting. However, some subgroups of patients could be not adequately represented in this systematic review, and they deserve additional comments. Only four trials with 258 participants were included

in the subset of the paediatric population ([Allen 2016](#); [Dung 1999](#); [Mahajan 2012](#); [Ngo 2001](#)). The subgroup analysis did not show differences ($P = 0.96$; $I^2 = 0\%$). No trial reported on acute renal injury in the paediatric population. Furthermore, participants included in these trials were less sick than participants included in the adult trials. For these reasons, we should be very cautious in interpreting results from the paediatric population. In addition, we consider that neurocritical patients need special attention. Buffered solutions trend to have lower osmolality than 0.9% saline ([Appendix 1](#)). For this reason, several studies excluded neurocritical patients. In our review, we included only one study, which included 66 participants with traumatic brain injury ([Hassan 2017](#)). The authors of this trial did not report any signal of harm. One other study carried out on neurocritical patients was excluded because it included colloid solutions as the co-intervention ([Roquilly 2013](#)). In this trial, intracranial pressure was not different between study groups (MD 4 mmHg, 95% CI -1 to 8; $P = 0.088$). A recent consensus for neurointensive care patients recommends the use of buffered solutions in this population based on lower rates of hyperchloraemia ([Oddo 2018](#)). Safety data, or patient-centred outcomes, were not considered in this consensus. The authors of this consensus graded the quality of these recommendations as low and very low. Due to the paucity of data in this population, we consider that our conclusions should be translated with caution for these patients. The 21 trials included in this current Cochrane Review included a total of 20,213 participants. The included trials reported many outcomes but inconsistently. Many trials did not report on our primary outcomes of mortality and acute renal injury. Reporting of secondary outcomes was highly variable in terms of time points, units, and measures. A potential confounder is related to volumes used due to range of lack of reporting data prior randomization (type and/or volume) or ability to combine them. Although analysing a dose-response relationship could have been interesting, the paucity of data related to doses of the intervention precluded this kind of analysis. Closely linked with the previous comment, we should highlight the wide range of enrolment timing (emergency criteria, intensive care unit (ICU) admission, within 60 minutes of hospital arrival, etc.). Furthermore, important outcomes such as costs and quality of life were never reported. Expected adverse events are related to electrolyte disturbances. They were broadly but inconsistently reported in the included studies. In spite of this, no signal of harm is related to the buffered solution.

Quality of the evidence

The certainty of evidence range in the included trials was between very low and high. For the two primary outcomes, certainty was high and low for mortality and acute renal injury, respectively ([Summary of findings for the main comparison](#)). Six out of 14 trials included in the mortality outcome were graded as high risk of bias, most because we could not rule out selective reporting bias nor attrition bias ([Figure 2](#)). Sensitivity analysis did not modify the results after high-risk studies were excluded; they represented only 1% of the overall weight. Relevant heterogeneity was not detected. Seven trials did not report mortality data. Reporting or publication bias was not suspected upon visual assessment of the funnel plot ([Figure 6](#)). For these reasons, we considered the certainty of evidence as high (no downgrading).

Figure 6.

In contrast with mortality, eight out of nine trials included in the acute renal injury outcome were graded as high risk of bias (Figure 2). The high risk of bias was related to detection bias. We considered acute renal injury as a subjective outcome, and several studies were not blinded (or unclear). Sensitivity analysis did not modify the results after exclusion of these studies, but they represented more than 90% of the overall weight. Only 9 out of 21 included studies reported acute renal injury data. We did not prepare a funnel plot because we included fewer than 10 studies in the analysis. We did not suspect inconsistency, indirectness, or imprecision in the acute renal injury certainty assessment. We therefore classified the certainty of evidence as low (risk of bias: -1; publication bias: -1).

For secondary outcomes, the certainty of evidence was very low (Summary of findings for the main comparison). Reasons for this included risk of bias (high in several trials), indirectness (surrogate outcomes), inconsistency (different time points across studies), and imprecision (few participants and events in the trial that reported these outcomes). The certainty of evidence was very low for the secondary outcomes, which means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. In the future, trial authors should improve the consistency of measures and reports of secondary outcomes.

Potential biases in the review process

Despite the fact that we used a broad search strategy, we may have missed published studies not listed in the resources searched for this review. We imposed no language restrictions on the search.

We requested additional data from authors of results published only in abstract form, and we did not receive an answer from three authors (Reddy 2014; Vasu 2013; Viaene 2014). All trials were independently evaluated by two review authors. We assessed the risk of bias of included studies by using published data and clinical trials registers. When the study's protocol was not available, we assessed reporting bias according to the methods detailed in the study's report. This may have introduced bias if study authors removed outcomes from their methods section. We attempted to make contact with several authors of included studies, and four investigators provided further information (Aditianingsih 2017; de-Madaira 2018; Semler 2018; Young 2015). The lack of universal definitions for concepts such as critical illness or resuscitation is a potential source of bias in the present review. As a result, we chose broad inclusion criteria for participants and decided to carry out a subgroup analysis by participant subsets. However, this was not conducted because the included studies did not state data by disease subsets. Moreover, we included inconsistent trials with regards to the time points. This is particularly relevant in studies with few participants in each arm, such as those with electrolyte disturbances. Chloride concentrations, pH, and bicarbonate level analyses showed moderate heterogeneity and may have undermined the confidence of the estimated effect (Analysis 1.7, Analysis 1.8 and Analysis 1.9, respectively). We considered a clinical cause as a possible explanation for this heterogeneity because the gradient of levels of electrolytes showed the same tendency as the chloride concentration and a strong ion difference among different buffered preparations (Sterofundin > Ringer's lactate > Plasma-Lyte A). We used a random-effects

model as defined in our protocol (Barea-Mendoza 2016). Moreover, we included studies with more than two intervention groups (Dung 1999; Hasman 2012; Ngo 2001). However, we feel confident about including them in meta-analyses because data were reported for each of the arms to which participants were randomized and contributed several independent comparisons (without interventions groups in common) in fixed-effect model analyses (Analysis 1.1; Analysis 1.4 (Higgins 2011)). We also included in the review some studies in which participants in the crystalloid and buffered groups received additional buffered or crystalloid fluids, respectively (Semler 2016; Semler 2018; Young 2015). This may have introduced clinical differences or bias, and we did not explore this in the review. Some trial outcomes did not contribute to the meta-analyses because they were reported in a different form than that defined by our protocol (Barea-Mendoza 2016), and we found methodological challenges in converting them to the desired format. Data on total volume of intravenous fluids needed during resuscitation were not combined in our analyses owing to the fact that the outcomes distribution was skewed, and it was not possible to estimate means and standard deviations from medians and interquartile ranges. In particular, the lack of meta-analysis of the total volume requirement hampers the general understanding of our findings because we ignored the dose of the intervention. The Review includes three ongoing studies that could be included in an updated version (NCT02721654; NCT02835157; NCT02875873).

Agreements and disagreements with other studies or reviews

Our findings are in line with those of other reviews, whilst making an additional contribution to the current knowledge base with some trials that were not included in any of these previous reviews. We identified four systematic reviews that focused on critically ill patients who received buffered solution compared to 0.9% saline fluids (Kawano-Dourado 2018; Rochweg 2014; Serpa 2017; Zayed 2018). Kawano-Dourado and colleagues examined 15 randomized trials with 4067 critically ill and perioperative adult patients who received intravenous high- versus low-chloride content solutions (colloids and crystalloids) for intravascular volume expansion or maintenance. The pooled effect did not differ between groups for all-cause mortality (odds ratio (OR) 0.90, 95% confidence interval (CI) 0.69 to 1.17; $P = 0.44$; $I^2 = 0\%$; 11 trials; 3710 participants; low-certainty evidence), AKI (risk ratio (RR) 0.99, 95% CI 0.78 to 1.25; $I^2 = 0\%$; 5 trials; 3245 participants), and allogenic blood transfusion rates (RR 0.69, 95% CI 0.44 to 1.09; $I^2 = 0\%$; 4 trials; 137 participants), highlighting that trial sequential analyses (TSA) carried out for mortality and AKI estimated an optimal sample size of 9517 and 12,000 participants, respectively (Kawano-Dourado 2018). Rochweg and colleagues examined 14 parallel-group randomized trials (including factorial designs) involving 18,916 adults with severe sepsis or septic shock who required fluid resuscitation. The indirect low-quality evidence from a network meta-analysis suggested no evidence of a significant effect of balanced fluids preventing mortality compared with saline solutions (OR 0.78, 95% CrI 0.58 to 1.05; low-certainty evidence) (Rochweg 2014).

The other two systematic reviews collected a subgroup of the population included in the present review (Serpa 2017 Zayed 2018). Serpa and colleagues evaluated three randomized clinical trials involving 2348 adults admitted to the ICU and randomized to receive either buffered or 0.9% saline solutions. Study authors did not find any significant differences in in-hospital mortality

(OR 0.87, 95% CI 0.65 to 1.17; $P = 0.36$; $I^2 = 0\%$) and AKI during hospital stay (OR 1.00, 95% CI 0.75 to 1.34; $P = 0.97$; $I^2 = 0\%$) (Serpa 2017). Zayed and colleagues evaluated six randomized clinical trials involving 19,332 participants who received either balanced crystalloids or 0.9% saline fluids in the ICU setting. Study authors did not find any significant differences in in-hospital mortality (OR 0.92, 95% CI 0.85 to 1.01; $P = 0.09$; $I^2 = 0\%$) or incidence of AKI (OR 0.92, 95% CI 0.84 to 1.01; $P = 0.1$; $I^2 = 0\%$) (Zayed 2018). We consider that despite differences in the types of trials included, data comparisons, and analyses, the data from our review probably support these conclusions. The European Society of Intensive Care Medicine consensus focused on fluid resuscitation in neurointensive care patients (Oddo 2018). The Society recommended buffered compared to isotonic crystalloids for subarachnoid haemorrhage (SAH) (GRADE low-quality evidence) (Oddo 2018). This recommendation was based on two small multi-intervention trials in patients with SAH - Lehmann 2013 - and with severe traumatic brain injury - Roquilly 2013, and investigators reported a statically significant reduction in hyperchloraemia rate in favour of buffered fluids when compared to 0.9% saline solutions (RR 0.57, 95% CI 0.37 to 0.75; $P < 0.001$). Although the results of our review show a small difference, this trend is consistent with this observation (MD -2.9, 95% CI -5.07 to 0.90; $P < 0.005$). Nevertheless, we ruled out the Lehmann 2013 and Roquilly 2013 trials from our review owing to their study design and intervention because Lehmann and colleagues randomized participants to receive 0.9% saline and hydroxyethyl starch dissolved in 0.9% saline, or balanced crystalloid and colloid solutions. Roquilly and colleagues randomized participants to isotonic balanced solutions (crystalloid and hydroxyethyl starch; balanced group) or isotonic sodium chloride solutions (crystalloid and hydroxyethyl starch; saline group). We are not aware of any other systematic reviews or good quality studies investigating the effects of buffered versus 0.9% saline solutions in non-surgical critically ill patients.

AUTHORS' CONCLUSIONS

Implications for practice

Many options are available for resuscitation in critically ill patients. Recently, the use of buffered solutions has increased and several trials have been published (Hammond 2017). According to our results, buffered solutions are similar to 0.9% saline in terms of mortality. We have high certainty of this finding, which means that the use of buffered solutions probably results in little or no difference in mortality. We performed an analysis by age and found that the effect on mortality was consistent. However, it should be highlighted that only four of the included trials involved paediatric patients. Likewise, the use of buffered solutions is similar to the use of 0.9% saline in terms of acute renal injury. Buffered solutions could be a safe alternative to 0.9% saline. The certainty of this finding is low, and further research could change this conclusion.

Patients treated with buffered solutions had lower chloride levels, higher levels of bicarbonate, and higher pH. We have very low certainty of these findings. The interpretation of secondary outcomes should be cautious. Changes in clinical practice should not be based on the secondary outcomes. It is important to point out that we do not have sufficient evidence to detect the effects of buffered solution on transfusion requirement, costs, or quality of life. Available data for some subgroups such as neurocritical

or paediatric patients were insufficient to enable us to reach any conclusion. According to our findings, the use of buffered solutions over 0.9% saline did not reduce mortality or the incidence of acute renal injury in critically ill patients. The three ongoing studies once published and assessed may alter the conclusions of the review.

Implications for research

The key research questions of whether buffered solutions reduce in-hospital mortality and acute kidney injury in critically ill patients are not completely resolved. First, some comments related to outcomes. Regarding in-hospital mortality, assessment of the certainty of evidence of included studies was high, and heterogeneity may not be considered important. We considered that, in this setting, identifying interventions that may lead to an important decrease in mortality is unlikely. Consequently, we would advise further research to ensure an optimal sample size and to allow detection of clinically relevant differences. Concerning acute renal injury, heterogeneity may not be considered important. However, we assessed the certainty of evidence as low; therefore, we would advise additional methodologically robust trials to detect potentially relevant differences. Relative to secondary outcomes, the certainty of evidence of our findings related to electrolyte disturbances and incidence of organ dysfunction was very low. Hence, we would advise additional studies to strengthen the evidence base. Moreover, we were unable to provide a meta-analysis of total volume of intravenous solutions required during resuscitation according to the type of crystalloid, given the variation in this outcome reporting. In terms of orphan outcomes, research is needed on the issues of blood loss, coagulopathy, costs, and quality of life, as insufficient or no data at all are available. Furthermore, the inclusion of patient-centred outcomes (Short-Form 36 or Euro-QoL5) seems highly desirable. Second, with regard to population, neurocritical and paediatric patients were unrepresented in the included trials. Well-designed trials are required in the future to assess the effects of buffered solutions in these settings. Likewise, female representation was lower in the included studies, and data were not presented disaggregated by sex. Sex as a relevant prognostic factor for critically ill conditions remains a question to be resolved. Last, concerning methods, future trials should improve some aspects such as blinding methods, inclusion criteria (critically ill patients, resuscitation), and outcome definitions (acute renal injury or volume of fluids). Study authors are encouraged to report not only physiological

outcomes but also mortality and renal function results. The use of acute renal injury or mortality in future trials could be insufficient. Composite outcomes such as MAKE30 (major adverse kidney event within 30 days) have been proposed, but the results have a difficult interpretation and could be flawed ([Molitoris 2012](#)). In addition, research should be designed in consensus on reporting outcomes (e.g. as in the Core Outcome Measures in Effectiveness Trials initiative - [COMET](#)). We would like to highlight that inconsistency in the measurement of outcomes hampers the evaluation of effectiveness of interventions, especially in the case of synthesized evidence, and complicates the detection of reporting bias.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Aditioningsih 2017

Methods	Study design: randomized controlled trial Study grouping: parallel group Intention-to-treat analysis: ITT No sample size calculation was reported
Participants	Single-centre trial; 30 patients admitted with diabetic ketoacidosis Pretreatment: at baseline, treatment groups were comparable Number assessed for eligibility: 30 Number enrolled: 30

Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children (Review)

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Aditianingsih 2017 (Continued)

Number randomized: 30

Ringerfundin group: 15 participants, median age of 57 years (23 to 65 years), 9 females (60%)

Saline solution 0.9% group: 15 participants, median age of 56 years (25 to 65 years), 10 females (67%)

Inclusion criteria

1. Patients with diabetic ketoacidosis aged 18 to 65 years old
2. Agreed to participate in the study
3. Had blood sugar level during hospital admission > 250 mg/dL
4. Had positive ketone bodies in the blood
5. Had arterial blood pH < 7.35

Exclusion criteria

1. Respiratory failure requiring mechanical ventilation
2. End-stage renal disease on haemodialysis
3. Congestive heart failure
4. Corrected sodium > 158 mg/dL or < 120 mg/dL
5. Myocardial infarction with signs of heart failure
6. Traumatic brain injury with cerebral oedema signs
7. Liver failure

Interventions	Ringerfundin vs 0.9% saline Co-interventions: yes
Outcomes	Extracted primary outcomes <ol style="list-style-type: none"> 1. In-hospital mortality 2. Acute renal injury Extracted secondary outcomes <ol style="list-style-type: none"> 1. Volume of intravenous fluid therapy 2. pH from baseline to 48 hours
Identification	Country: Indonesia Sponsorship source: not stated Identifier: not stated
Notes	An intention-to-treat analysis was performed on participants receiving at least 6 hours of fluid study Email sent to study authors in July 2018; reply received in July 2018

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomly allocated to the groups" Comment: information about the randomization methods not provided
Allocation concealment (selection bias)	Low risk	Quote: "the intervention given from the pharmacy for each subject was concealed"
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "single-blind randomised controlled" Comment: without additional information

Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children (Review)

Aditianingsih 2017 (Continued)

Objective outcomes (e.g. mortality)

Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Quote: "single-blind randomized controlled" Comment: without additional information
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: objective outcome
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Quote: "single-blind randomised controlled" Comment: without additional information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "an intention-to-treat analysis was performed on subjects receiving at least six hours of fluid study"
Selective reporting (reporting bias)	Unclear risk	No information in protocol or clinical trials registers
Other bias	Unclear risk	Information not provided

Allen 2016

Methods	Study design: randomized controlled trial Study grouping: parallel group Intention-to-treat analysis: modified ITT Sample size calculation reported
Participants	Multi-centre trial; 100 paediatric patients admitted with acute gastroenteritis (AGE) Pretreatment: at baseline; treatment groups were comparable except that the Plasma-Lyte group was older Number assessed for eligibility: 2669 Number enrolled: 100 Number randomized: 100 Plasma-Lyte group: 51 participants, mean age of 3.8 years, sex ratio not reported Saline solution 0.9% group: 49 participants, mean age of 2.8 years, sex ratio not reported Inclusion criteria 1. Patients ≥ 6 months to < 11 years of age were eligible for enrolment if they presented to the emergency department with moderate to severe dehydration due to AGE, defined as ≥ 3 episodes of diarrhoea or no bilious vomiting within the previous 24 hours and a Gorelick dehydration score ≥ 4

Allen 2016 (Continued)

Exclusion criteria

1. AGE that did not require intravenous treatment per clinicians' judgement
2. Chronic health conditions such as renal failure affecting the ability to tolerate fluids or resulting in electrolyte abnormalities
3. Use of prohibited medications (e.g. antacids/anti-diarrhoea or systemic corticosteroids within 24 hours or 72 hours before presentation, respectively)

Interventions	Plasma-Lyte vs 0.9% saline Co-interventions: yes
Outcomes	Extracted primary outcome <ol style="list-style-type: none"> 1. In-hospital mortality Extracted secondary outcomes <ol style="list-style-type: none"> 1. Volume and duration of intravenous fluid therapy 2. Changes in chloride, potassium, and bicarbonate concentrations between baseline and hour 4
Identification	Country: USA, Canada Sponsorship source: Baxter Healthcare Corporation Identifier: not stated
Notes	For primary and secondary outcomes, a modified intent-to-treat (mITT) analyses was used to focus on only those patients with a baseline serum bicarbonate level ≤ 22 mEq/L. 100 patients were enrolled and 77 were evaluable mITT subjects Email sent to study authors in May 2017; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "eligible patients were randomly assigned in a 1:1 ratio"
Allocation concealment (selection bias)	Low risk	Quote: "concealed treatment allocation was via an Interactive Voice Recognition System/Interactive Web-based System"
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	Quote from data available at https://clinicaltrials.gov/ Identifier: NCT01234883: "Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)"
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote from data available at https://clinicaltrials.gov/ Identifier: NCT01234883: "Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)"
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: objective outcome measure
Blinding of outcome assessment (detection bias)	Low risk	Quote from data available at https://clinicaltrials.gov/ Identifier: NCT01234883: "Masking: Double Blind (Investigator, Outcomes Assessor)"

Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children (Review)

31

Allen 2016 (Continued)

Subjective outcomes (e.g. author defined renal failure)

Comment: "objective outcome measure"

Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "the study was stopped early due to slow recruitment after 100 patients were enrolled with 77 evaluable mITT subjects. The ITT group was formed by 100 patients who were randomized to receive either PLA (n = 51) or 0.9 % NaCl (n = 49). ETR occurred in 23 patients due to baseline bicarbonate > 22 mEq/L. There were 77 patients (PLA: 39; 0.9 % NaCl: 38)"
Selective reporting (reporting bias)	Low risk	Comment: "no missing outcomes"
Other bias	High risk	Funding bias according to the protocol (Appendix 4) Quote: "Baxter Healthcare Corporation funded this study" Comment: "without information about the role of the corporation"

Choosakul 2018

Methods	Study design: randomized controlled trial Study grouping: parallel group Intention-to-treat analysis: yes Sample size calculation reported
Participants	Single-centre trial; 47 patients admitted with acute pancreatitis Pretreatment: at baseline, treatment groups were comparable Number assessed for eligibility: 52 Reasons for exclusion: cholangitis (n = 3), 1 CKD stage IV (n = 1), peptic perforation (n = 1) Number enrolled: 47 Number randomized: 47 Ringer's lactate group: 23 participants, mean age of 54.78 years ($\pm$ 20.42 years), 11 females (48%) Saline solution 0.9% group: 24 participants, mean age of 48.33 years ($\pm$ 13.56 years), 7 females (29%) Inclusion criteria 1. 18 to 80 years old 2. Admitted to the hospital with acute pancreatitis, which was diagnosed in accordance with the Revised Atlanta Classification (Banks 2013) Exclusion criteria 1. Post endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis 2. Transfer from another hospital 3. History of severe cardiovascular, respiratory, renal, hepatic, haematological, or immunological conditions defined as greater than those defined for New York Heart Association Class II heart failure (New York Heart Association) 4. Active myocardial ischaemia 5. Cardiovascular intervention within previous 60 days

Choosakul 2018 (Continued)

6. History of cirrhosis
7. Chronic kidney disease with creatinine clearance < 40 mL/min
8. Chronic obstructive pulmonary disease with requirement for home oxygen and hypercalcaemia
9. History of metastatic malignancy, autoimmune disease, chronic infectious disease including human immunodeficiency virus or tuberculosis, acute cholangitis, acute cholecystitis, bowel ischaemia or bowel perforation; due to increased systemic inflammation

Interventions	Ringer's lactate vs 0.9% saline Co-interventions: yes
Outcomes	Extracted primary outcomes <ol style="list-style-type: none"> 1. In-hospital mortality 2. Acute renal injury at 48 hours Extracted secondary outcomes <ol style="list-style-type: none"> 1. Volume of intravenous fluid therapy from baseline to 24 hours 2. Organ failure at 48 hours
Identification	Country: Thailand Sponsorship source: grant from the Gastroenterological Association of Thailand Identifier: TCTR20161010001 (Thai Clinical Trials Registry)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "groups using the technique of permuted block randomization with random block sizes of 4. Group 1 received NSS and group 2 received LRS"
Allocation concealment (selection bias)	Low risk	Quote: "opaque, sealed envelopes were numbered consecutively, and all the sealed envelopes were prepared by a research nurse who was not involved in the treatment procedure"
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Unclear risk	Quote: "participants were blinded to treatment allocation" Comment: no further information about the blinding methods for personnel
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Quote: "participants were blinded to treatment allocation" Comment: no further information about the blinding methods for personnel
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: objective outcome
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "participants were blinded to treatment allocation" Comment: no clear information about the blinding methods for personnel

Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children (Review)

33

Choosakul 2018 (Continued)

Subjective outcomes (e.g. author defined renal failure)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "twenty-four patients were treated with NSS and twenty three patients were treated with LRS. No patient was lost to follow-up"
Selective reporting (reporting bias)	Low risk	Comment: reported outcome well described in registry (TCTR20161010001)
Other bias	Low risk	Funding bias according to the protocol (Appendix 4) Quote: "the present study was supported by a grant from the Gastroenterological Association of Thailand"

de-Madaira 2018

Methods	Study design: randomized controlled trial Study grouping: parallel group Intention-to-treat analysis: ITT Sample size calculation reported
Participants	Single-centre trial; 100 patients admitted with acute pancreatitis (AP) Pretreatment: at baseline, treatment groups were comparable Number assessed for eligibility: 134 Reasons for exclusion: 86 did not meet inclusion criteria or met exclusion criteria; 5 patients declined to participate Number enrolled: 43 Number randomized: 43 Ringer's lactate group: 19 participants, mean age of 63.8 years ($\pm$ 19.1 years), 11 females (48%) Saline solution 0.9% group: 21 participants, mean age of 61.4 years ($\pm$ 15.5 years), 10 females (48%) Inclusion criteria 1. Patients aged 18 years or older who initially presented to the emergency room and were subsequently admitted with a first episode of acute pancreatitis Exclusion criteria 1. Time from pain onset to randomization > 24 hours 2. Known history of renal disease (basal creatinine > 2 mg/dL; patient under chronic haemodialysis) 3. Greater than New York Heart Association Class II heart failure (New York Heart Association) 4. Chronic lung disease requiring supplemental home oxygen 5. Active acute infection (including acute cholecystitis and acute cholangitis) 6. Hypernatraemia (serum sodium > 145 mEq/L) or hyponatraemia (< 135 mEq/L) 7. Rhabdomyolysis 8. Metastatic malignant disease 9. Autoimmune disease associated with inflammation (including inflammatory bowel disease) 10. Chronic infection (e.g. human immunodeficiency virus, tuberculosis)

de-Madaira 2018 (Continued)

Interventions	Ringer's lactate vs 0.9% saline Co-interventions: yes
Outcomes	Extracted primary outcome 1. In-hospital mortality Extracted secondary outcomes 1. Volume of intravenous fluid therapy from baseline to 72 hours 2. pH and bicarbonate levels from baseline to 72 hours 3. Persistent organ failure (defined by the Revised Atlanta Classification; Banks 2013)
Identification	Country: Spain Sponsorship source: RCT was funded by AIGPA, an association of researchers in gastroenterology from the province of Alicante, Spain. In vitro experiments were supported by a national Spanish public grant, project FIS PI13/00019 from Instituto de Salud Carlos III; LB is supported by a pre-doctoral fellowship from Generalitat de Catalunya (AGAUR, FI DGR 2013) EudraCT Number: 2011-004988-68
Notes	Of 43 randomized participants, 3 were later excluded from the study because of an incorrect diagnosis of acute pancreatitis: 2 in the Ringer's lactate arm had acute cholecystitis; and 1 in the saline solution 0.9% arm had acute cholangitis Email sent to study authors in May 2017; reply received in May 2017. Authors provided details of an additional recently published article
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Low risk Quote: "a random number list was generated by computer (SPSS 20.0, see below) and used for treatment assignment (simple randomisation, allocation ratio 1:1)"
Allocation concealment (selection bias)	Low risk Quote: "the Pharmacy Department of the Alicante General University Hospital (A.G.) conducted the randomisation and blinding"
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk Quote: "triple-blind RCT"; "the whole process of blinding was monitored by the Clinical Pharmacology Department"
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Low risk Quote: "triple-blind RCT"; "the whole process of blinding was monitored by the Clinical Pharmacology Department"
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk Quote: "triple-blind RCT"; "the whole process of blinding was monitored by the Clinical Pharmacology Department"

de-Madaira 2018 (Continued)

Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "triple-blind RCT"; "the whole process of blinding was monitored by the Clinical Pharmacology Department"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "three patients were excluded from analysis due to an incorrect diagnosis of AP; therefore, a total of 19 patients receiving LR and 21 receiving NS were analysed"
Selective reporting (reporting bias)	Unclear risk	Comment: without protocol or information available at ClinicalTrials.gov
Other bias	Low risk	Funding bias according to the protocol (Appendix 4) Quote: "the RCT was funded by AIGPA, an association of researchers in gastroenterology from the province of Alicante, Spain"

Dung 1999

Methods	Study design: randomized controlled trial Study grouping: parallel group Intention-to-treat analysis: not stated No sample size calculation was reported
Participants	Single-centre trial; 50 children admitted with dengue shock syndrome Pre-treatment: the mean age (SD) was 8.2 years (2.5 years) and did not differ between fluid groups. Although there were more boys than girls (33 vs 17), the gender difference did not vary between groups Number assessed for eligibility: not reported Reasons for exclusion: not reported Number enrolled: 50 Number randomized: 50 Ringer's lactate group: 13 participants, mean age not reported, sex proportion not reported Saline solution 0.9% group: 12 participants, mean age not reported, sex proportion not reported Inclusion criteria 1. Children between the ages of 5 and 15 years who had dengue shock syndrome (DSS) and had not received intravenous fluid therapy during their current illness Clinical diagnosis of dengue haemorrhagic fever (DHF) was made on the basis of: 1. a history of fever; 2. haemorrhagic phenomena, including a positive tourniquet test; and 3. a raised haematocrit value and exclusion of alternative diagnoses by clinical criteria and appropriate laboratory investigations DSS was defined as DHF with:

Dung 1999 (Continued)

1. low pulse pressure (< 20 mmHg); or
2. unrecordable blood pressure; along with
3. clinical signs of circulatory insufficiency such as cold extremities

Exclusion criteria

1. Not reported

Interventions	Ringer's lactate vs 0.9% saline Co-interventions: no
Outcomes	Extracted primary outcome <ol style="list-style-type: none"> 1. In-hospital mortality Extracted secondary outcome <ol style="list-style-type: none"> 1. Haemodynamic failure
Identification	Country: Vietnam Sponsorship source: the Wellcome Trust of Great Britain Identifier: not stated
Notes	4 arms, of which only 2 were included: 13 patients were enrolled into the Ringer's lactate arm; and 12 patients were enrolled into the 0.9% saline arm Email sent to authors in May 2017; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the envelopes were randomized in blocks of 10"
Allocation concealment (selection bias)	Low risk	Quote: "the randomization procedure involved opening a numbered opaque envelope to obtain a treatment pack"
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "each container was covered in opaque black insulating tape to ensure that the treating medical and nursing staff did not know which fluid was being administered"
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "each container was covered in opaque black insulating tape to ensure that the treating medical and nursing staff did not know which fluid was being administered"
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "each measurement was performed in duplicate, and the measurements were recorded on videotape for checking by a second ultrasonographer, blinded to the clinical details"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "each measurement was performed in duplicate, and the measurements were recorded on videotape for checking by a second ultrasonographer, blinded to the clinical details"

Dung 1999 (Continued)

Subjective outcomes (e.g.
author defined renal fail-
ure)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing data
Selective reporting (re- porting bias)	Unclear risk	No information in protocol nor at ClinicalTrials.gov
Other bias	Low risk	Funding bias according to the protocol (Appendix 4) Quote: "financial support: the Wellcome Trust of Great Britain"

Hasman 2012

Methods	Study design: randomized controlled trial Study grouping: parallel group Intention-to-treat analysis: no Sample size calculation reported
Participants	Single-centre trial; 90 patients admitted with moderate and severe dehydration Pre-treatment: at baseline, participants enrolled into the 0.9% saline arm were older Number assessed for eligibility: 137 Reasons for exclusion: meeting at least 1 of the pre-defined exclusion criteria or declining to participate Number enrolled: 96 Number randomized: 96 Plasma-Lyte group: 33 participants, mean age of 48.8 years ($\pm$ 19.7 years), 16 females (53%) Ringer's lactate group: 31 participants, mean age of 43.8 years ($\pm$ 22.2 years), 15 females (50%) Saline solution 0.9% group: 32 participants, mean age of 53.3 years ($\pm$ 18.4 years), 14 females (47%) Inclusion criteria 1. Definition of moderate and severe dehydration a. Dry mucous membranes b. Systolic blood pressure lower than 90 mmHg c. Heart rate higher than 100/min d. Intolerance of oral intake of liquids Exclusion criteria 1. Age < 18 years 2. Severe cardiovascular disease 3. Liver dysfunction 4. Serum potassium levels higher than 5.5 mM/L 5. Acute pulmonary oedema 6. Shock

Hasman 2012 (Continued)

Interventions	Plasma-Lyte vs Ringer's lactate vs 0.9% saline Co-interventions: no
Outcomes	Extracted secondary outcomes 1. Electrolyte disturbances (pH; serum bicarbonate, sodium, potassium, and chloride concentrations) measured at 60 and 120 minutes
Identification	Country: Turkey Sponsorship source: not stated Identifier: not stated
Notes	6 randomized participants (2 in the 0.9% saline arm, 1 in the Ringer's lactate arm, and 3 in the Plasma-Lyte arm) withdrew their consent during the study and were not included in the final analyses Email sent to authors in May 2017; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the randomization scheme was generated using a web-based..."
Allocation concealment (selection bias)	Low risk	Quote: "the randomization scheme was generated using a web-based..."
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "patients and treating physicians were blinded to the treatment (...) Another nurse, blinded to the study, administered the solutions"
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "patients and treating physicians were blinded to the treatment (...) Another nurse, blinded to the study, administered the solutions"
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: "objective outcome measure"
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Comment "no information"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: "no missing data"
Selective reporting (reporting bias)	Unclear risk	Comment: without protocol or information available at ClinicalTrials.gov

Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children (Review)

39

Hasman 2012 (Continued)

Other bias	Low risk	Funding bias according to the protocol (Appendix 4)
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Hassan 2017

Methods	<p>Study design: randomized controlled trial</p> <p>Study grouping: parallel group</p> <p>Intention-to-treat analysis: no</p> <p>Sample size calculation reported</p>
Participants	<p>Single-centre trial; 66 patients admitted with postoperative severe traumatic brain injury (TBI)</p> <p>Pre-treatment: at baseline, participants enrolled into Sterofundin arm had worse Glasgow Coma Scale (GCS) score on arrival and pre-operation GCS (Teasdale 1974)</p> <p>Number assessed for eligibility: 66</p> <p>Reasons for exclusion: N/A</p> <p>Number enrolled: 66</p> <p>Number randomized: 66</p> <p>Sterofundin group: 31 participants, median age of 25 years (30 years), 5 females (17%)</p> <p>Saline solution 0.9% group: 33 participants, median age of 20 years (22 years), 3 females (9%)</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> Age of at least 16 years and consent given by next of kin American Society of Anesthesiologists physical status I or II (ASA Physical Status Classification System 2014) Presented for emergency operation for TBI, with GCS pre-operation, with post-resuscitation < 9, and with no major chest injury, intra-abdominal injury, or associated cervical spine injury <p>Exclusion criteria</p> <ol style="list-style-type: none"> Pre-existing acid-base and electrolyte disturbance (pH < 7.30), as evidenced in the arterial blood gas, liver function test, and renal profile upon neuro-ICU admission <ol style="list-style-type: none"> Coagulopathy (INR > 1.8, APTT > 60) Liver impairment (ALT/AST > 200) Total bilirubin > 50 Renal impairment (creatinine clearance < 50) Patients with a history of allergy to the study solutions
Interventions	<p>Sterofundin vs 0.9% saline</p> <p>Co-interventions: yes</p>
Outcomes	<p>Extracted secondary outcomes</p> <ol style="list-style-type: none"> Electrolyte disturbances (pH; serum bicarbonate, sodium, potassium, and chloride concentrations) measured at baseline and at 24 hours
Identification	<p>Country: Malaysia</p> <p>Sponsorship source: supported by the Short Term Grant of University Sains Malaysia</p> <p>Identifier: not stated</p>

Hassan 2017 (Continued)

Notes Non-adequate sample size: "the sample size including a 10% dropout was 35 patients for each group"

After randomization, 2 patients in the balanced solution group were excluded from the study because they had severe coagulopathy and haemodynamic instability

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "postoperatively, the patients were randomised through block randomisation using eight ballots cards"
Allocation concealment (selection bias)	Low risk	Quote: "three different grouping sequences (BBB, SSS, BBS, SSB, BSB, SBS, BSS, and SBB) were made through the sealed envelope system by the neuro-ICU team leader in charge of receiving two different maintenance fluid regimes by double-blinded randomisation"
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Unclear risk	Quote: "charge of receiving two different maintenance fluid regimes by double-blinded randomisation" Comment: insufficient information
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Quote: "charge of receiving two different maintenance fluid regimes by double-blinded randomisation" Comment: insufficient information
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: objective outcome
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Quote: "charge of receiving two different maintenance fluid regimes by double-blinded randomisation" Comment: insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "however, two patients were excluded from the study in the balanced solution group because they had severe coagulopathy and haemodynamic instability"
Selective reporting (reporting bias)	Unclear risk	No information available in protocol or at ClinicalTrials.gov
Other bias	Low risk	Quote: "this study was financially supported by the Short Term Grant of Universiti Sains Malaysia"

Mahajan 2012

Methods Study design: randomized controlled trial

Study grouping: parallel group

Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children (Review)

Mahajan 2012 (Continued)

Intention-to-treat analysis: modified ITT

Sample size calculation reported

Participants	<p>Single-centre trial; 22 children admitted with acute diarrhoea and severe dehydration</p> <p>Pre-treatment: at baseline, treatment groups were comparable</p> <p>Number assessed for eligibility: 34</p> <p>Reasons for exclusion: persistent diarrhoea (n = 4), severe malnutrition (n = 3), denied consent (n = 3), hypoglycaemia (n = 2)</p> <p>Number enrolled: 22</p> <p>Number randomized: 22</p> <p>Ringer's lactate group: 11 participants, mean age of 73 months ($\pm$ 28 months), 3 females (27%)</p> <p>Saline solution 0.9% group: 11 participants, mean age of 58 months ($\pm$ 24 months), 6 females (54%)</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. Children from 1 month to 18 years 2. Acute diarrhoea (defined as 3 liquid stools in previous 24 hours) 3. Severe dehydration (defined as presence of hypotension or any of the 2 out of 4 signs) <ol style="list-style-type: none"> a. Lethargic or unconscious b. Sunken eyeballs c. Drinks poorly or not able to drink d. Skin pinch goes back very slowly <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. Persistent diarrhoea (> 14 days) 2. Clinical signs of severe malnutrition (WHO criteria; World Health Organization 2005) 3. Known systemic disease (cardiac, endocrine, neurological, chronic renal failure) 4. Lethal malformations 5. Hypoglycaemia (dextrostix value < 40 mg/dL)
Interventions	<p>Ringer's lactate vs 0.9% saline</p> <p>Co-interventions: yes</p>
Outcomes	<p>Extracted primary outcome</p> <ol style="list-style-type: none"> 1. In-hospital mortality <p>Extracted secondary outcomes</p> <ol style="list-style-type: none"> 1. Change in pH from baseline until resolution of hypotension and disappearance of clinical features of severe dehydration 2. Volume of intravenous fluid therapy until discharge 3. Change from baseline chloride, bicarbonate, sodium, and potassium concentrations until discharge from hospital
Identification	<p>Country: India</p> <p>Sponsorship source: Government Medical College and Hospital, Chandigarh, India</p> <p>Identifier: not stated</p>
Notes	<p>There was 1 protocol violation during the study period; 1 patient in the Ringer's lactate arm received 0.9% saline for 3 hours before being recognized</p>

Mahajan 2012 (Continued)

Email sent to study authors in May 2017; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "eligible children were randomly assigned"
Allocation concealment (selection bias)	Low risk	Quote: "random allocation sequence was computer generated by an independent paediatrician, not involved in patient management"
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "the participants, treating physicians, and assessors managing the patients were thereby blinded to the intervention"
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "the participants, treating physicians, and assessors managing the patients were thereby blinded to the intervention"
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: "objective outcome measure"
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "the participants, treating physicians, and assessors managing the patients were thereby blinded to the intervention"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: "no missing data"
Selective reporting (reporting bias)	Low risk	Comment: all outcomes were reported according to design at ClinicalTrials.gov
Other bias	Low risk	Funding bias according to the protocol (Appendix 4) Quote: "funding: none; competing interests: none stated"

Mahler 2011

Methods	Study design: randomized controlled trial Study grouping: parallel group Intention-to-treat analysis: no; per-protocol analyses No sample size calculation was reported
Participants	Single-centre trial; 52 patients admitted with moderate to severe diabetic ketoacidosis

Mahler 2011 (Continued)

Pre-treatment: at baseline, 0.9% saline group had lower mean baseline serum chloride than Plasma-Lyte group

Number assessed for eligibility: not provided

Reasons for exclusion: not provided

Number enrolled: 52

Number randomized: 52

Plasma-Lyte group: 26 participants, mean age of 33 years ($\pm$ 11 years), 10 females (45%)

Saline solution 0.9% group: 26 participants, mean age of 38 years ($\pm$ 14 years), 11 females (48%)

Inclusion criteria

1. Patients aged 18 to 65 years
2. Moderate to severe diabetic ketoacidosis: serum glucose $>$ 200 mg/dL, serum bicarbonate $\leq$ 15 mmol/L, and anion gap $\geq$ 16 mmol/L

Exclusion criteria

1. Hyperosmotic hyperglycaemic non-ketotic syndrome
2. Hyperglycaemia without signs of DKA
3. Mild DKA
4. Patients receiving greater than 500 mL of crystalloid or an insulin bolus before enrolment in the study
5. Myocardial infarction
6. Sepsis
7. Respiratory failure
8. Cerebral oedema

Interventions	Plasma-Lyte vs 0.9% saline Co-interventions: yes
Outcomes	Extracted secondary outcome 1. Change from baseline in bicarbonate and chloride concentrations during resuscitation
Identification	Country: USA Sponsorship source: not stated Identifier: not stated
Notes	An intention-to-treat analysis was performed on patients meeting inclusion criteria and receiving at least 4 hours of study fluid. 52 patients were enrolled. A total of 45 patients - 22 in the Plasma-Lyte group and 23 in the saline solution 0.9% group - met inclusion criteria and received a minimum of 4 hours of infusion. Of the 7 patients excluded from data analysis, 4 did not meet inclusion criteria and 3 did not receive at least 4 hours of study fluid Email sent to study authors in May 2017; no reply received
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Low risk Quote: "randomizations was achieved by block randomizations of 8 consecutive subjects"

Mahler 2011 (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "...and the investigators were blinded to the randomizations schedule"
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "research pharmacy provided blinded study"
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "research pharmacy provided blinded study"
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: "objective outcome measure"
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Comment: without information
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "of the 7 patients excluded from data analysis, 4 did not meet inclusion criteria and 3 did not receive at least 4 hours of study fluid- HMA: table 3"
Selective reporting (reporting bias)	Unclear risk	Comment: without protocol or information available at ClinicalTrials.gov
Other bias	Unclear risk	Funding bias according to the protocol (Appendix 4) Comment: no information provided

Ngo 2001

Methods	Study design: randomized controlled trial Study grouping: parallel group Intention-to-treat analysis: modified ITT No sample size calculation was reported
Participants	Single-centre trial; 230 children admitted with dengue shock syndrome Pre-treatment: at baseline, treatment groups were comparable Number assessed for eligibility: not reported Reasons for exclusion: not reported Number enrolled: 230 Number randomized: 230

Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children (Review)

Ngo 2001 (Continued)

Ringer's lactate group: 55 participants, mean age of 8.3 years ($\pm$ 3.2 years), 29 females (52%)

Saline solution 0.9% group: 56 participants, mean age of 7.3 years ($\pm$ 2.7 years), 36 females (64%)

Inclusion criteria

1. Children aged from 1 to 15 years who presented to the hospital with clinically diagnosed dengue haemorrhagic fever grade III or IV according to WHO guidelines were eligible ([World Health Organization 1997](#)), provided they had not received any IV fluid therapy and a parent or guardian gave informed consent

Exclusion criteria

1. Severe haemorrhagic manifestations at presentation for whom transfusion seemed likely to become necessary
2. Children with chronic disorders

Interventions	Ringer's lactate vs 0.9% saline Co-interventions: yes
Outcomes	Extracted secondary outcome <ol style="list-style-type: none"> 1. Volume of intravenous fluid therapy and haemodynamic failure until full recovery 2. "Re-shock" rate, no. (%) of patients. A child was considered to have developed "re-shock" if, in association with tachycardia and coolness of extremities, pulse pressure narrowed to < 20 mmHg, having previously reached a level > 30 mmHg
Identification	Country: Vietnam Sponsorship source: the Wellcome Trust of Great Britain Identifier: not stated
Notes	A total of 230 patients were recruited into the study; 222 of these had dengue haemorrhagic fever grade III, and the remaining 8 had grade IV. Because of the small number of children with dengue haemorrhagic fever grade IV who received treatment with a different regimen, study authors decided to focus the results on the 222 children with dengue haemorrhagic fever grade III. None of the patients were withdrawn from the study after randomization 4 arms, of which only 2 are included: 55 patients were enrolled into the Ringer's lactate arm; 56 patients were enrolled into the saline solution 0.9% arm Email sent to study authors in May 2017; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the envelopes had been randomized in blocks of 10"
Allocation concealment (selection bias)	Low risk	Quote: "the randomization envelopes were opaque and contained only a treatment pack number"
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "each bottle was covered in opaque black insulating tape to ensure that the treating medical and nursing staff did not know which fluid was being administered"

Ngo 2001 (Continued)

Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "each bottle was covered in opaque black insulating tape to ensure that the treating medical and nursing staff did not know which fluid was being administered"
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: objective outcome
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Comment: without information
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "in view of the small number of children with DHF grade IV who received treatment with a different regimen, we focused this report on the 222 children with DHF grade III"
Selective reporting (reporting bias)	Unclear risk	Comment: without protocol or information available at ClinicalTrials.gov
Other bias	Low risk	Funding bias according to the protocol (Appendix 4) Quote: "financial support: the Wellcome Trust of Great Britain"

Ratanarat 2017

Methods	Study design: randomized controlled trial Study grouping: parallel group Intention-to-treat analysis: information not provided Sample size calculation reported
Participants	Single-centre trial; 181 patients admitted with shock Pre-treatment: at baseline, treatment groups were comparable Number assessed for eligibility: not provided Reasons for exclusion: not provided Number enrolled: not provided Number randomized: 181 Sterofundin group: 88 participants, mean age not provided, sex proportion not reported Saline solution 0.9% group: 93 participants, mean age not provided, sex proportion not reported Inclusion criteria 1. > 18 years; shock patients (hypotension with signs of poor tissue perfusion) Exclusion criteria

Ratanarat 2017 (Continued)

1. < 18 years; cardiogenic shock patients (history of ST elevation and left ventricular ejection fraction < 35%)
2. Prolonged shock > 24 hours
3. Received chloride-rich crystalloid (0.9% saline) or chloride-rich colloid > 1000 mL within 72 hours before recruitment
4. Do-not-resuscitate patients
5. Contraindication for IV fluid administration such as pulmonary oedema, stage V chronic kidney disease, chronic haemodialysis, or peritoneal dialysis

Interventions	Sterofundin vs 0.9% saline Co-interventions: information not provided
Outcomes	Extracted primary outcome 1. Acute kidney injury during the 7-day period after randomization
Identification	Country: Thailand Sponsorship source: Mahidol University https://clinicaltrials.gov/ Identifier: NCT02520804
Notes	Information available in abstract form and register. Median volume of fluid therapy reported without standard deviation Email sent to study authors in July 2018; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information not provided
Allocation concealment (selection bias)	Unclear risk	Comment: information not provided
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	Comment: open-label; seems unlikely that mortality was affected
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	High risk	Comment: open-label
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Unclear risk	Comment: mortality not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: open-label

Ratanarat 2017 (Continued)

Subjective outcomes (e.g. author defined renal failure)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: information not provided
Selective reporting (reporting bias)	Unclear risk	Comment: information not provided
Other bias	Low risk	Mahidol University

Reddy 2014

Methods	<p>Study design: randomized controlled trial</p> <p>Study grouping: parallel group</p> <p>Intention-to-treat analysis: information not provided</p> <p>No sample size calculation was reported</p>
Participants	<p>Single-centre trial; 50 patients admitted with acute pancreatitis</p> <p>Pre-treatment: insufficient data. There was no significant difference in the severity of acute pancreatitis between the 2 groups ($P = 0.77$)</p> <p>Number assessed for eligibility: not provided</p> <p>Reasons for exclusion: not provided</p> <p>Number enrolled: not provided</p> <p>Number randomized: 50</p> <p>Ringer's lactate group: 25 participants, mean age not provided, sex proportion not reported</p> <p>Saline solution 0.9% group: 25 participants, mean age not provided, sex proportion not reported</p> <p>Overall mean age 45.82 years (± 16.46 years); proportion of females 44%</p> <p>Inclusion criteria</p> <p>1. Patients with acute pancreatitis who presented within 5 days of onset of symptoms</p> <p>Exclusion criteria</p> <p>1. Information not provided</p>
Interventions	<p>Ringer's lactate vs 0.9% saline</p> <p>Co-interventions: no</p>
Outcomes	No outcomes of interest reported
Identification	<p>Country: India</p> <p>Sponsorship source: not stated</p>

Reddy 2014 (Continued)

Identifier: not stated

Notes

Information available in abstract form only

Email sent to study authors in May 2017; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: " were randomized to receive NS or RL" Comment: randomization methods not specified
Allocation concealment (selection bias)	Unclear risk	Comment: randomization methods not specified
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Unclear risk	Comment: not specified
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Comment: not specified
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: objective outcome measure
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no information
Selective reporting (reporting bias)	Unclear risk	Comment: without protocol or information available at ClinicalTrials.gov
Other bias	Unclear risk	Funding bias according to the protocol (Appendix 4) Comment: no information provided

Semler 2016

Methods

Study design: cluster-randomized controlled trial

Study grouping: multiple-cross-over

Semler 2016 (Continued)

Intention-to-treat analysis: modified ITT

Sample size calculation reported

Participants

Single-centre trial; 974 patients admitted to intensive care unit (ICU)

Pre-treatment: at baseline, treatment groups were comparable

Number assessed for eligibility: 1000

Reasons for exclusion: not reported

Number enrolled: 974

Number randomized: 974

Balanced crystalloids (Plasma-Lyte or Ringer's lactate) group: 520 participants, mean age of 57 years (44 to 68 years), 252 females (48%)

Saline solution 0.9% group: 454 participants, mean age of 58 years (46 to 70 years), 208 females (46%)

Inclusion criteria

1. All adults (age ≥ 18 years) admitted to the medical ICU at Vanderbilt University were automatically enrolled at the time of ICU admission

Exclusion criteria

1. Age < 18 years old

Interventions

Balanced crystalloids (Plasma-Lyte or Ringer's lactate) vs 0.9% saline

Co-interventions: yes

No. clusters randomized: 1

Crystalloid assigned to the ICU alternated monthly for the duration of the study

Outcomes
Extracted primary outcomes

1. In-hospital mortality within 30 days after enrolment
2. Acute renal injury within 30 days after enrolment

Extracted secondary outcomes

1. Volume of intravenous fluid therapy administered during admission to the intensive care unit
2. Change in chloride, potassium, sodium, and bicarbonate concentrations
3. Blood transfusion requirement within 30 days after enrolment

Identification

Country: USA

Sponsorship source

1. Biostatistical support was provided by the Vanderbilt Institute for Clinical and Translational Research (UL1 TR000445 from NCATS/NIH)
2. MWS was supported by a National Heart, Lung, and Blood Institute (NHLBI) T32 award (HL087738 09)
3. WHS was supported in part by the National Institute of General Medical Sciences (K23GM110469)
4. EDS was supported by the Vanderbilt Center for Kidney Disease (VCKD) and Veterans Affairs HS&RDIIR 13-073
5. TWR was supported in part by the NIH (R34HL105869)

The funding institutions had no role in

Semler 2016 (Continued)

1. Conception, design, or conduct of the study
2. Collection, management, analysis, interpretation, or presentation of the data
3. Preparation, review, or approval of the manuscript

<https://clinicaltrials.gov/> Identifier: NCT02345486

Notes	<p>The study included a single medical ICU</p> <p>The study evaluated Ringer's lactate solution or Plasma-Lyte together as a single 'balanced crystalloids' group, without performing subgroup analyses. In addition, treating clinicians in the study ICU chose Ringer's lactate for over 90% of the balanced crystalloid administered</p> <p>Various mail sent to study authors (2017-2018) to ask for publication dates; replies received</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated simple randomisation"
Allocation concealment (selection bias)	Low risk	<p>Quote: "the crystalloid used during the first month of the study (saline or balanced crystalloids) was selected by computer-generated simple randomisation"</p> <p>Comment: without allocation concealment because it is an open-label, cross-over design. Cluster-cross-over selection bias looks unlikely</p>
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	<p>Quote: "patients, clinicians, and investigators were not blinded"</p> <p>Comment: open-label; seems unlikely that mortality was affected</p>
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	High risk	Quote: "patients, clinicians, and investigators were not blinded"
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "patients, clinicians, and investigators were not blinded"
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	High risk	Quote: "patients, clinicians, and investigators were not blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing data
Selective reporting (reporting bias)	Low risk	Comment: all outcomes were reported according to the protocol
Other bias	Low risk	Funding bias according to the protocol (Appendix 4)

Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children (Review)

52

Semler 2016 (Continued)

Quote: "the funding institutions had no role in conception, design, or conduct of the study; collection, management, analysis, interpretation, or presentation of the data; or preparation, review, or approval of the manuscript"

Semler 2018

Methods	<p>Study design: cluster-randomized controlled trial</p> <p>Study grouping: multiple-cross-over</p> <p>Intention-to-treat analysis: yes (mITT, after exclusion)</p> <p>Sample size calculation reported</p>
Participants	<p>5-site trial; 15,802 patients admitted to intensive care unit (ICU). Around 20% of patients were admitted from the operating room</p> <p>Pre-treatment: at baseline, treatment groups were comparable</p> <p>Number assessed for eligibility: 15,904</p> <p>Reasons for exclusion: 102 patients excluded after randomization because reported age < 18 (supplementary appendix figure S2)</p> <p>Number enrolled: 15,904</p> <p>Number randomized: 15,904</p> <p>Balanced crystalloids (Plasma-Lyte or Ringer's lactate) group: 7942 participants, mean age of 58 years (44 to 69 years), 3402 females (43%)</p> <p>Saline solution 0.9% group: 7860 participants, mean age of 58 years (44 to 69 years), 3303 females (42%)</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. All adults (age ≥ 18 years) admitted to 1 of the participating ICUs were automatically enrolled <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. < 18 years old
Interventions	<p>Balanced crystalloids (Plasma-Lyte or Ringer's lactate) vs 0.9% saline</p> <p>Co-interventions: yes</p> <p>No. clusters randomized: 1</p> <p>Crystalloid assigned to the ICU alternated monthly for the duration of the study</p>
Outcomes	<p>Extracted primary outcomes</p> <ol style="list-style-type: none"> 1. In-hospital mortality within 60 days after enrolment 2. Acute renal injury within 30 days after enrolment <p>Extracted secondary outcomes</p> <ol style="list-style-type: none"> 1. Rate of hypokalaemia 2. Rate of renal replacement therapy 3. Volume of intravenous fluid therapy administered during admission to the intensive care unit

Semler 2018 (Continued)

Identification

Country: USA

Sponsorship source: biostatistical support was provided by the Vanderbilt Institute for Clinical and Translational Research (UL1 TR000445 and UL1TR002243)

<https://clinicaltrials.gov/> Identifier: SMART-MED and SMART-SURG, NCT02444988 and NCT02547779

Notes

Various emails sent to study authors (2017 to 2018) to ask for publication dates; replies received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "ICUs were randomly assigned to use saline during even-numbered months and balanced crystalloids during odd-numbered months, or vice versa"
Allocation concealment (selection bias)	Low risk	Comment: without allocation concealment because it is an open-label, cross-over design. Cluster-cross-over selection bias looks unlikely
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "patients, clinicians, and investigators were not blinded" Comment: even if we consider objective outcomes a performance bias, it is possible (not for detection bias)
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	High risk	Quote: "patients, clinicians, and investigators were not blinded"
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: objective outcome measure
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	High risk	Quote: "patients, clinicians, and investigators were aware of group assignments"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all outcomes were reported according to the protocol
Selective reporting (reporting bias)	Low risk	Comment: protocol published before the end of recruitment
Other bias	Low risk	Funding bias according to the protocol (Appendix 4) Quote: "supported by the Vanderbilt and National Center for Advancing Translational Sciences"

Van Zyl 2012

Methods	<p>Study design: randomized controlled trial</p> <p>Study grouping: parallel group</p> <p>Intention-to-treat analysis: ITT</p> <p>No sample size calculation was reported</p>
Participants	<p>Multi-centre trial; 57 patients admitted with diabetic ketoacidosis</p> <p>Pre-treatment: at baseline, treatment groups were comparable</p> <p>Number assessed for eligibility: 129</p> <p>Reasons for exclusion: 7 participants refused, 65 were excluded (details not provided)</p> <p>Number enrolled: not provided</p> <p>Number randomized: 57</p> <p>Ringer's lactate group: 28 participants, mean age of 36.1 years (24.1 to 46.6), 9 females (33%)</p> <p>Saline solution 0.9% group: 29 participants, mean age of 36.6 years (25.5 to 42.2), 14 females (52%)</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. Newly diagnosed or previously known to have diabetes mellitus 2. Type 1 or type 2 diabetes 3. Age $\geq$ 18 years 4. Venous blood pH at presentation 6.9 to 7.2 5. Presence of at least 2 plus ketones on urine dipstick test at presentation 6. Capillary blood glucose > 13 mmol/L at baseline 7. Able to give verbal informed consent <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. Another cause for acidosis was present 2. Severely ill and in need of inotropic or ventilatory support; more than 1 L of resuscitation fluid was administered before enrolment
Interventions	<p>Ringer's lactate vs 0.9% saline</p> <p>Co-interventions: yes</p>
Outcomes	<p>Extracted primary outcomes</p> <ol style="list-style-type: none"> 1. In-hospital mortality during resolution of acidosis period <p>Extracted secondary outcomes</p> <ol style="list-style-type: none"> 1. Change in chloride, potassium, sodium, and calcium concentrations between baseline and time to resolution of acidosis 2. Time to resolution of diabetic ketoacidosis was defined as fulfilment of the following criteria: venous pH > 7.3, serum bicarbonate $\geq$ 18 mmol/L, and blood glucose < 11.1 mmol/L
Identification	<p>Country: South Africa</p> <p>Sponsorship source: University of Pretoria, Research Development Programme</p> <p>South African National Clinical trials register; registration number: DOH-27-0607-1612</p>
Notes	<p>From a total of 43 randomized participants, 40 were analysed; 3 were excluded from the final analyses due to incomplete data: 1 in the Ringer's lactate arm, and 2 in the 0.9% saline arm</p>

Van Zyl 2012 (Continued)

Email sent to study authors in May 2017; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "stratified randomisation per centre was done by centre in blocks of 10 using a sequential numbered opaque box system"
Allocation concealment (selection bias)	Low risk	Quote: "using a sequential numbered opaque box system"
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "all clinicians, patients, and investigators were blinded for the coding of resuscitation fluid"
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "all clinicians, patients, and investigators were blinded for the coding of resuscitation fluid"
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: objective outcome
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "unblinding of the code was only done after analysis of the primary outcome was completed"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "three patients were excluded from the analysis due to missing data: one patient had baseline information absent, one the insulin infusion rate was not recorded, and one patient fluid administration was not recorded"
Selective reporting (reporting bias)	Unclear risk	Comment: without protocol or information available at ClinicalTrials.gov
Other bias	Low risk	Funding bias according to the protocol (Appendix 4) Quote: "funding: University of Pretoria, Research Development Programme. Conflict of interest: none declared"

Vasu 2013

Methods	Study design: randomized controlled trial Study grouping: parallel group Intention-to-treat analysis: information not provided No sample size calculation was reported
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Vasu 2013 (Continued)

Participants

Single-centre trial; 50 patients admitted with acute pancreatitis

Pre-treatment: insufficient data

Number assessed for eligibility: not provided

Reasons for exclusion: not provided

Number enrolled: not provided

Number randomized: 50

Ringer's lactate group: 25 participants, mean age not provided, sex ratio not reported

Saline solution 0.9% group: 25 participants, mean age not provided, sex ratio not reported

Overall mean age 41.64 years; sex ratio 34% females

Inclusion criteria

1. Acute pancreatitis > 18 years of age presenting within 5 days of onset of pain

Exclusion criteria

1. Information not provided

Interventions	Ringer's lactate vs 0.9% saline Co-interventions: no
Outcomes	Extracted secondary outcomes 1. Incidence of organ failure during resuscitation in the clinical course of acute pancreatitis
Identification	Country: India Sponsorship source: not stated Identifier: not stated
Notes	Information available in abstract form only Email sent to study authors in May 2017; no reply received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized into 2 groups to receive either 0.9% normal saline or ringer lactate for resuscitation and were compared for outcome parameters" Comment: randomization methods not specified
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment methods not specified
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Unclear risk	Comment: not specified

Vasu 2013 (Continued)

Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Comment: not specified
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: objective outcome measure
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no information
Selective reporting (reporting bias)	Unclear risk	Comment: without protocol or information available at ClinicalTrials.gov
Other bias	Unclear risk	Comment: no information

Verma 2016

Methods	Study design: randomized controlled trial Study grouping: parallel group Intention-to-treat analysis: information not provided No sample size calculation was reported
Participants	Multi-centre trial; 70 severely ill patients Number assessed for eligibility: 449 Reasons for exclusion: not provided Number enrolled: 70 Number randomized: 70 Saline solution 0.9% group: 35 participants, median age of 64 years, 13 females (38%) Plasma-Lyte group: 35 participants, median age of 62 years, 12 females (36%) Inclusion criteria 1. ICU patients who were 18 years or older and judged by the treating clinician to require crystalloid fluid resuscitation Exclusion criteria 1. Patients transferred from another hospital to a study ICU

Verma 2016 (Continued)

Interventions	Plasma-Lyte vs 0.9% saline Co-interventions: no	
Outcomes	Extracted primary outcomes 1. In-hospital mortality until hospital discharge 2. Acute renal injury in the first 4 days in the ICU	
Identification	Country: Australia Sponsorship source: "our study was funded by Austin Hospital and by an unrestricted grant from Baxter Healthcare, [which] supplied study fluids. Baxter Healthcare had no input into design, conduct, data collection, statistical analysis, or writing of the manuscript" Identifier: ANZCTRN 12615000158561 (New Zealand Clinical Trials Registry)	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was in permuted blocks, conducted using a computer-based randomisation program and sealed envelopes"
Allocation concealment (selection bias)	Low risk	Quote: "conducted using a computer-based randomisation program and sealed envelopes"; "the principal investigators at each site did not have access to the randomisation key, which was only available to the research coordinators in each study centre"
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "blinding of study fluids was done by Baxter Healthcare. Study fluid bags were indistinguishable 1 L Viaflex bags, and each bag was labelled with a unique participant number to ensure complete blinding"
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "blinding of study fluids was done by Baxter Healthcare. Study fluid bags were indistinguishable 1 L Viaflex bags, and each bag was labelled with a unique participant number to ensure complete blinding"
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: objective outcome measure
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "blinding of study fluids was done by Baxter Healthcare"; "statistical analyses were conducted with blinding to study allocation and with all data identified before assessment"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "randomised 70 patients to the study. In the NS group, one patient was incorrectly enrolled into a competing fluid trial, so was excluded, and in the PL-148 group, two patients withdrew consent, leaving a total of 67 patients participating"

Verma 2016 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: outcomes specified on ANZCTR N 12615000158561
Other bias	Low risk	Quote: "our study was funded by Austin Hospital and by an unrestricted grant from Baxter Healthcare, [which] supplied study fluids. Baxter Healthcare had no input into design, conduct, data collection, statistical analysis, or writing of the manuscript"

Viaene 2014

Methods	Study design: randomized controlled trial Study grouping: parallel group Intention-to-treat analysis: information not provided No sample size calculation was reported
Participants	Single-centre trial; 59 severely ill patients Pre-treatment: saline solution 0.9% group was older (69 years vs 62 years; $P = 0.027$) and had a lower albumin concentration (30.3 g/dL vs 32.8 g/dL; $P = 0.02$) Number assessed for eligibility: not provided Reasons for exclusion: not provided Number enrolled: not provided Number randomized: 59 Sterofundin group: 31 participants, mean age of 62 years, sex proportion not reported Saline solution 0.9% group: 28 participants, mean age of 69 years, sex proportion not reported Inclusion criteria 1. Information not provided Exclusion criteria 1. Information not provided
Interventions	Sterofundin vs 0.9% saline Co-interventions: information not provided
Outcomes	Extracted secondary outcomes 1. pH; chloride, sodium, and base excess difference between baseline and hour 4
Identification	Country: Belgium Sponsorship source: not stated Identifier: not stated
Notes	Information available in abstract form only. Details about sodium difference are qualitative information Email sent to study authors in May 2017; no reply received

Viaene 2014 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "prospective randomized single-blinded study" Comment: randomization methods not specified
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment methods not specified
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Unclear risk	Comment: methods not specified
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Comment: methods not specified
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: objective outcome measure
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Unclear risk	Comment: methods not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no information about follow-up and withdrawals
Selective reporting (reporting bias)	Unclear risk	Comment: not specified Comment: without protocol or information available at ClinicalTrials.gov
Other bias	Unclear risk	Funding bias according to the protocol (Appendix 4) Comment: not specified

Wu 2011

Methods	Study design: randomized controlled trial Study grouping: 4-arm (2×2), factorial design, parallel group Intention-to-treat analysis: yes Sample size calculation reported
Participants	Multi-centre trial; 40 patients admitted with acute pancreatitis

Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children (Review)

Wu 2011 (Continued)

Pre-treatment: at baseline, treatment groups were comparable

Number assessed for eligibility: 137

Reasons for exclusion: cancer, comorbidity, concurrent illness, hospital transfer, alternative diagnosis, declined participation, readmission/recurrent episode

Number enrolled: 97

Number randomized: 41

Ringer's lactate group: 19 participants, mean age of 50 years ($\pm$ 40.7 years), 11 females (56%)

Saline solution 0.9% group: 21 participants, mean age of 54 years ($\pm$ 40.6 years), 7 females (32%)

Inclusion criteria

1. Acute pancreatitis diagnosed by 2 or more of the following criteria
 - a. Epigastric abdominal pain
 - b. Elevation in serum amylase and/or lipase level $>$ 3 times the upper limit of normal
 - c. Confirmatory findings on cross-sectional imaging
2. Adult patients at least 18 years of age

Exclusion criteria

1. Known history of severe cardiovascular, respiratory, renal, hepatic, haematological, or immunological disease defined as:
 - a. greater than New York Heart Association Class II heart failure ([New York Heart Association](#));
 - b. active myocardial ischaemia;
 - c. cardiovascular intervention within previous 60 days;
 - d. history of cirrhosis;
 - e. chronic kidney disease with creatinine clearance $<$ 40 mL/min;
 - f. chronic obstructive pulmonary disease with requirement for home oxygen;
 - g. concurrent metabolic or physiological derangement that required specific fluid management, including sepsis (presence of suspected or confirmed infection in the setting of SIRS), hypernatraemia (serum sodium $<$ 150 mEq/L), or hyponatraemia (serum sodium $>$ 135 mEq/L); or
 - h. rhabdomyolysis
2. Patients transferred from an outside hospital were excluded
3. History of metastatic malignancy, active inflammatory bowel disease, autoimmune conditions such as systemic lupus erythematosus, autoimmune pancreatitis, giant cell arteritis, rheumatoid arthritis, or chronic infectious disease including human immunodeficiency virus or tuberculosis were excluded because of potential confounding related to markers of systemic inflammation

Interventions	Ringer's lactate vs 0.9% saline Co-interventions: yes
Outcomes	Extracted primary outcomes <ol style="list-style-type: none"> 1. In-hospital mortality 2. Acute renal injury until discharge Extracted secondary outcomes <ol style="list-style-type: none"> 1. Respiratory failure 2. Haemodynamic failure until discharge 3. (See notes*)
Identification	Country: USA Sponsorship source: Junior Faculty Career Development Award from the American College of Gastroenterology, Brigham and Women's Hospital

Wu 2011 (Continued)

<https://clinicaltrials.gov/> Identifier: NCT00853515

Notes	Four-arms with a factorial design; we included results regarding aim to compare impact of fluid type	
	1 participant was considered a protocol violation. This participant was randomized to Ringer's lactate but was taken off protocol because of hypercalcaemia. *Hypercalcaemia was subsequently added as an additional study exclusionary criterion	
	Non-adequate observed sample size	
	Email sent to study authors in May 2017; no reply received	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a computer random number generator was used to select treatment assignment on the basis of random permuted blocks"
Allocation concealment (selection bias)	Low risk	Quote: "after completion of enrolment, randomisation was performed in real time by using a centralized web-based data repository"
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "the study was open-label" Comment: objective
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	High risk	Quote: "the study was open-label" Comment: subjective
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "the study was open-label" Comment: objective
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	High risk	Quote: "the study was open-label" Comment: subjective
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "participants were followed for the duration of their hospitalization, with no losses to follow-up"
Selective reporting (reporting bias)	Low risk	Comment: all outcomes were reported according to the design available at ClinicalTrials.gov
Other bias	Low risk	Funding bias according to the protocol (Appendix 4) Quote: "there was no external funding source for this study"

Young 2014

Methods	<p>Study design: randomized controlled trial</p> <p>Study grouping: parallel group</p> <p>Intention-to-treat analysis: modified ITT</p> <p>Sample size calculation reported</p>
Participants	<p>Single-centre trial; 65 patients admitted with severe acute injury</p> <p>Pre-treatment: at baseline, treatment groups were comparable</p> <p>Number assessed for eligibility: 626</p> <p>Reasons for exclusion: not intubated, transfused within 60 minutes of arrival (n = 208), age < 18 years (n = 117), transferred from another hospital (n = 82), expected to die within 48 hours (n = 56), prisoner (n = 34), no apparent traumatic injury (n = 29), pregnancy (n = 1), subject missed (n = 34)</p> <p>Number enrolled: 65</p> <p>Number randomized: 65</p> <p>Plasma-Lyte group: 33 participants, mean age of 38 years ($\pm$ 19 years), 6 females (27%)</p> <p>Saline solution 0.9% group: 32 participants, mean age of 39 years ($\pm$ 14 years), 5 females (21%)</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. Triage criteria for severe acute injury, including penetrating injury to the neck, chest, abdomen, or pelvis 2. Glasgow Coma Scale score < 9 or deteriorating by 2 after injury 3. Systolic blood pressure < 90 mmHg 4. Pulseless, injured extremity 5. Need for endotracheal intubation 6. Intubated, transfused blood, or taken to an operating room or interventional radiology suite within 60 minutes of arrival <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. Younger than 18 years 2. Pregnant 3. Without apparent traumatic injury 4. On dialysis 5. Anticipated to die within 48 hours 6. Transferred from another hospital 7. Incarcerated 8. Study fluid could not be initiated within 60 minutes of arrival to the hospital
Interventions	<p>Plasma-Lyte vs 0.9% saline</p> <p>Co-interventions: yes</p>
Outcomes	<p>Extracted primary outcomes</p> <ol style="list-style-type: none"> 1. In-hospital mortality 2. Acute kidney injury within the first 5 days <p>Extracted secondary outcomes</p> <ol style="list-style-type: none"> 1. Change in pH, base excess, bicarbonate, chloride, potassium, and sodium from baseline to 24 hours 2. Volume and duration of intravenous fluid therapy from baseline to 24 hours 3. Total units of packed red blood cell, plasma, and platelet transfused from baseline to 24 hours

Young 2014 (Continued)

4. Average total cost

Identification	<p>Country: USA</p> <p>Sponsorship source: Department of Surgery, University of California, Davis Medical Center, Sacramento, CA. This was an investigator-initiated trial supported by Baxter Healthcare (Deerfield, IL)</p> <p>https://clinicaltrials.gov/ Identifier: NCT01270854</p>
Notes	<p>Patients for whom consent was obtained and the base deficit was measured became the modified intent-to-treat group on which all analyses were conducted. The Institute Review Board allowed mortality analysis of the ITT group</p> <p>Email sent to study authors in May 2017; no reply received</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomisation sequence in a 1:1 ratio using a variable block size"
Allocation concealment (selection bias)	Low risk	Quote: "they placed opaque wrappers around the IV fluid bags and labelled them with Study Isotonic Crystalloid Fluid"
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "the treating physicians, who were also blinded to the type of fluid being administered, determined the amount, frequency, and indications for fluid administration"
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "the treating physicians, who were also blinded to the type of fluid being administered, determined the amount, frequency, and indications for fluid administration"
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: objective outcome
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote (https://clinicaltrials.gov/ NCT01270854): "Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)"
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Quote: "we thus restricted the mITT analysis to the remaining 46 consented subjects"</p> <p>Comment: "mITT not pre-specified"</p>
Selective reporting (reporting bias)	Low risk	Comment: outcomes specified at https://clinicaltrials.gov/ NCT01270854
Other bias	Low risk	Funding bias according to the protocol (Appendix 4)

Young 2014 (Continued)

Quote: "this was an investigator-initiated trial supported by Baxter Healthcare (Deerfield, IL). All study activity, including design, enrolment, outcome assessment, analysis, creation of the manuscript, and the decision to publish, was conducted solely by the investigators independent of the sponsor. The investigators maintain full control of all study-related data. The authors declare no conflicts of interest"

Young 2015

Methods	<p>Study design: cluster-randomized controlled trial</p> <p>Study grouping: double-cross-over</p> <p>Intention-to-treat analysis: yes</p> <p>No sample size calculation was reported</p>
Participants	<p>Multi-centre trial; 2278 patients admitted to the intensive care unit (ICU) requiring crystalloid fluid therapy. Around 50% of participants were admitted after cardiovascular surgery</p> <p>Pre-treatment: at baseline, treatment groups were comparable</p> <p>Number assessed for eligibility: 3346</p> <p>Reasons for exclusion: patients did not require intravenous crystalloid fluid (n = 940), did not require IV fluids, received renal replacement therapy (RRT) or expected within 6 hours (n = 63), on dialysis (n = 47), admitted for palliative status or to facilitate organ donation (n = 18)</p> <p>Number enrolled: 2406</p> <p>Number randomized: 2278</p> <p>Plasma-Lyte group: 1162 participants, mean age of 60.1 years ($\pm$ 16.8 years), 413 females (36%)</p> <p>Saline solution 0.9% group: 1116 participants, mean age of 60.9 years ($\pm$ 16.2 years), 364 females (33%)</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. All ICU patients receiving crystalloid fluid therapy as clinically indicated <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. On RRT for end-stage renal failure, currently receiving RRT, or expected to require RRT within 6 hours 2. Admitted to the ICU solely for consideration of organ donation or for palliative care 3. Previously enrolled in the study
Interventions	<p>Plasma-Lyte vs 0.9% saline</p> <p>Co-interventions: yes</p> <p>No. clusters randomized: 4</p> <p>Participating ICUs were assigned a masked study fluid, either saline or a buffered crystalloid, for alternating 7-week treatment blocks. 2 ICUs commenced using 1 fluid and the other 2 commenced using the alternative fluid. 2 cross-overs occurred, so that each ICU used each fluid twice over the 28 weeks of the study</p>
Outcomes	<p>Extracted primary outcomes</p> <ol style="list-style-type: none"> 1. In-hospital mortality

Young 2015 (Continued)

2. Acute renal injury during the patient's stay in the ICU (censored at day 90)

Extracted secondary outcomes

1. Volume of intravenous fluid therapy during the course of ICU admission
2. Acidaemia with pH < 7.20
3. Hyperkalaemia with serum potassium > 6.5 mmol/L
4. Delta creatinine
5. Total red blood units, fresh frozen plasma, platelets, or cryoprecipitate transfusion during the course of ICU admission

Identification	<p>Countries: New Zealand and Australia</p> <p>Sponsorship source: this study was funded by the Health Research Council of New Zealand through a Research Partnership for Health Delivery grant and by Baxter Healthcare Corporation</p> <p>https://clinicaltrials.gov/ Identifier: ACTRN12613001370796</p>
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Notes	<p>3 study ICUs were adult or mixed (adult and paediatric) general medical and surgical ICUs and 1 ICU had a predominance of cardiothoracic and vascular surgical patients</p> <p>Email sent to study authors in May 2017; no reply received</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the initial fluid determined by the study statistician using computer-generated randomisation"
Allocation concealment (selection bias)	Low risk	Quote: "the initial fluid determined by the study statistician using computer-generated randomisation. Study fluids appropriate for each study block were provided in 1000-mL bags labelled fluid A or fluid B"
Blinding of participants and personnel (performance bias) Objective outcomes (e.g. mortality)	Low risk	Quote: "investigators and clinicians were blind to study fluid allocation for the duration of the study"
Blinding of participants and personnel (performance bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "investigators and clinicians were blind to study fluid allocation for the duration of the study"
Blinding of outcome assessment (detection bias) Objective outcomes (e.g. mortality)	Low risk	Comment: objective outcome measure
Blinding of outcome assessment (detection bias) Subjective outcomes (e.g. author defined renal failure)	Low risk	Quote: "investigators and clinicians were blind to study fluid allocation for the duration of the study"

Young 2015 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "we conducted all analyses on an intention-to-treat basis in accordance with the statistical analysis plan and did not impute missing values unless stated"
Selective reporting (reporting bias)	Low risk	Comment: all outcomes were reported according to design in the protocol
Other bias	Low risk	Quote: "this study is funded by a Research Partnership Grant from the Health Research Council of New Zealand along with an unrestricted Grant from Baxter Pty Ltd (protocol)"
Other bias	Low risk	

AGE = acute gastroenteritis; AIGPA = Association of Researchers in Gastroenterology from the Province of Alicante, Spain; ALT = alanine aminotransferase; AP = acute pancreatitis; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CKD = chronic kidney disease; ICU = intensive care unit; INR = international normalized ratio; ITT = intention-to-treat analysis; IV = intravenous; DHF = dengue haemorrhagic fever; DKA = diabetic ketoacidosis; DSS = dengue shock syndrome; ERCP = postendoscopic retrograde cholangiopancreatography; ERL = early treatment release; GCS = Glasgow Coma Scale; INR = international normalized ratio; L = litre; LR = lactated Ringer's; LRS = lactated Ringer's solution; mEq/L = milliequivalents per litre; mITT = modified intent-to-treat; mL = millilitre; mmHg = millimetres of mercury; N/A = not applicable; NS = normal saline; NSS = normal saline solution; RCT = randomized controlled trial; RRT = renal replacement therapy; SD = standard deviation; SIRS = systemic inflammatory response syndrome; ST = ST segment of electrocardiography; stage IV chronic kidney disease = glomerular filtrate rate 30 to 44 mL/min; TBI = traumatic brain injury; vs = versus; WHO = World Health Organization.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Benoit 2016	Different intervention (not resuscitation phase)
Chen 2004	Different patient population (no critically ill patients)
Cho 2007	Different patient population (no critically ill patients; doxylamine intoxication)
Crivits 2016	Different intervention (not resuscitation)
Dybvik 1995	Different intervention (sodium bicarbonate-trometamol)
Fang 2008	Different intervention (hypertonic solutions)
Galas 2009	Different intervention (study authors compared buffered solutions head-to-head but not buffered solutions vs SS 0.9%)
Kantha 2017	Different patient population (no critically ill patients)
Martin 2018	Different patient population (no critically ill patients)
Omar 2018	Different intervention (control group, not SS 0.9%)
Rainier-Pope 1962	Different intervention (isotonic Darrows and dextrose)

Study	Reason for exclusion
Roquilly 2013	Different intervention (included colloid solutions)
Rowell 2016	Different study design (post hoc analysis of PROspective Observational Multicenter Major Trauma Transfusion study; Rahbar 2012)
Yung 2017	Different intervention (not resuscitation phase)

SS = saline solution; vs = versus.

Characteristics of ongoing studies [ordered by study ID]

[NCT02721654](#)

Trial name or title	Plasma-Lyte 148® versUs saline study (PLUS)
Methods	Allocation: randomized, intervention model; parallel assignment, masking quadruple (participant, care provider, investigator, outcomes assessor)
Participants	Critically ill adults
Interventions	Plasma-Lyte 148® vs SS 0.9%
Outcomes	Death from all causes (primary outcome)
Starting date	1 September 2017
Contact information	Simon Finfer; sfinfer@georgeinstitute.org.au
Estimated Primary Completion Date	December 2017
Notes	

[NCT02835157](#)

Trial name or title	Balanced salt solutions vs normal saline in children with septic shock
Methods	Allocation: randomized, intervention model; parallel assignment, masking triple (participant, investigator, outcomes assessor)
Participants	Children 2 months to ≤ 15 years with features of septic shock
Interventions	Balanced salt solutions as boluses of 20 mL/kg would be administered (Sterofundin, Isolyte E, Plasmalyte 148, Compound lactate) vs SS 0.9%

NCT02835157 (Continued)

Outcomes	<ol style="list-style-type: none"> 1. Acute kidney injury defined as increase in serum creatinine by > 0.3 mg/dL within 48 hours or to 1.5 times baseline or more within the last 7 days, or urine output < 0.5 mL/kg/h for 6 hours (time frame: from time of randomization/intervention to 7 days of admission) 2. Incidence of AKI in first 7 days after randomization/intervention
Starting date	1 April 2017
Contact information	Jhuma Sankar; jhumaji@gmail.com
Estimated Primary Completion Date	31 December 2019
Notes	

NCT02875873

Trial name or title	Balanced solution versus 0.9% saline in intensive care study (BaSICS)
Methods	Allocation: randomized, intervention model: factorial assignment, masking quadruple (participant, care provider, investigator, outcomes assessor); primary purpose: prevention
Participants	Severe patients admitted to the ICU at moderate to high risk for death or acute kidney injury
Interventions	Plasmalyte 148 vs SS 0.9%
Outcomes	Mortality (time frame: 90 days)
Starting date	27 May 2017
Contact information	Alexandre B Cavalcanti, MD, PhD
Estimated Primary Completion Date	
Notes	

AKI = acute kidney injury; ICU = intensive care unit; SS = saline solution.

DATA AND ANALYSES

Comparison 1. Buffered solutions vs SS 0.9% (saline solution)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	14	19664	Odds Ratio (Fixed, 95% CI)	0.91 [0.83, 1.01]
1.1 Buffered vs saline 0.9%	2	16776	Odds Ratio (Fixed, 95% CI)	0.92 [0.83, 1.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Plasma-Lyte vs saline 0.9%	4	2513	Odds Ratio (Fixed, 95% CI)	0.90 [0.65, 1.25]
1.3 Ringer lactate vs saline 0.9%	7	345	Odds Ratio (Fixed, 95% CI)	0.32 [0.05, 2.14]
1.4 Ringerfundin vs saline 0.9%	1	30	Odds Ratio (Fixed, 95% CI)	0.62 [0.09, 4.34]
2 Mortality (by age)	14	19797	Odds Ratio (Fixed, 95% CI)	0.91 [0.83, 1.00]
2.1 Adults	12	19539	Odds Ratio (Fixed, 95% CI)	0.91 [0.83, 1.00]
2.2 Children	4	258	Odds Ratio (Fixed, 95% CI)	0.97 [0.10, 9.80]
3 Acute kidney injury	9	18701	Odds Ratio (Fixed, 95% CI)	0.92 [0.84, 1.00]
3.1 Plasmalyte vs saline 0.9%	3	2413	Odds Ratio (Fixed, 95% CI)	1.01 [0.75, 1.36]
3.2 Ringer lactate vs saline 0.9%	2	87	Odds Ratio (Fixed, 95% CI)	0.45 [0.06, 3.21]
3.3 Buffered vs saline 0.9%	2	15990	Odds Ratio (Fixed, 95% CI)	0.91 [0.82, 1.00]
3.4 Ringerfundin vs saline 0.9%	1	30	Odds Ratio (Fixed, 95% CI)	0.62 [0.09, 4.34]
3.5 Sterofundin vs saline 0.9%	1	181	Odds Ratio (Fixed, 95% CI)	1.00 [0.49, 2.06]
4 Organ system dysfunction	5	266	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.40, 1.61]
5 Sodium	4	222	Mean Difference (IV, Random, 95% CI)	-0.48 [-1.67, 0.70]
5.1 Plasma-Lyte vs saline 0.9%	2	91	Mean Difference (IV, Random, 95% CI)	-0.67 [-2.90, 1.55]
5.2 Ringer's lactate vs saline 0.9%	2	67	Mean Difference (IV, Random, 95% CI)	0.43 [-3.53, 4.38]
5.3 Sterofundin vs saline 0.9%	1	64	Mean Difference (IV, Random, 95% CI)	-0.66 [-4.95, 3.63]
6 Potassium	3	158	Mean Difference (IV, Random, 95% CI)	0.09 [-0.10, 0.27]
6.1 Plasma-Lyte vs saline 0.9%	2	91	Mean Difference (IV, Random, 95% CI)	0.10 [-0.13, 0.33]
6.2 Ringer's lactate vs saline 0.9%	2	67	Mean Difference (IV, Random, 95% CI)	0.07 [-0.24, 0.38]
7 Chloride	6	351	Mean Difference (IV, Random, 95% CI)	-3.02 [-5.24, -0.80]
7.1 Plasma-Lyte vs saline 0.9%	4	220	Mean Difference (IV, Random, 95% CI)	-4.56 [-6.68, -2.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Ringer's lactate vs saline 0.9%	2	67	Mean Difference (IV, Random, 95% CI)	-0.56 [-2.58, 1.47]
7.3 Sterofundin vs saline 0.9%	1	64	Mean Difference (IV, Random, 95% CI)	-1.55 [-4.39, 1.29]
8 pH	3	200	Mean Difference (IV, Random, 95% CI)	0.04 [0.02, 0.06]
8.1 Plasma-Lyte vs saline 0.9%	2	91	Mean Difference (IV, Random, 95% CI)	0.06 [0.03, 0.08]
8.2 Ringer's lactate vs saline 0.9%	1	45	Mean Difference (IV, Random, 95% CI)	0.04 [0.01, 0.07]
8.3 Sterofundin vs saline 0.9%	1	64	Mean Difference (IV, Random, 95% CI)	0.02 [0.00, 0.04]
9 Bicarbonate	6	344	Mean Difference (IV, Random, 95% CI)	2.26 [1.25, 3.27]
9.1 Plasma-Lyte vs saline 0.9%	4	213	Mean Difference (IV, Random, 95% CI)	2.58 [1.33, 3.84]
9.2 Ringer's lactate vs saline 0.9%	2	67	Mean Difference (IV, Random, 95% CI)	2.42 [-0.71, 5.55]
9.3 Sterofundin vs saline 0.9%	1	64	Mean Difference (IV, Random, 95% CI)	1.15 [0.21, 2.09]
10 Blood products	2	1453	Mean Difference (IV, Fixed, 95% CI)	-17.53 [-44.52, 9.46]

Analysis 1.1. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 1 Mortality.

Analysis 1.2. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 2 Mortality (by age).

Analysis 1.3. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 3 Acute kidney injury.

Analysis 1.4. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 4 Organ system dysfunction.

Analysis 1.5. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 5 Sodium.

Analysis 1.6. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 6 Potassium.

Analysis 1.7. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 7 Chloride.

Analysis 1.8. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 8 pH.

Analysis 1.9. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 9 Bicarbonate.

Analysis 1.10. Comparison 1 Buffered solutions vs SS 0.9% (saline solution), Outcome 10 Blood products.

ADDITIONAL TABLES

Table 1. Orphan outcomes

Study	Outcome	Participants	Results
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Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children (Review)

78

Table 1. Orphan outcomes (Continued)

Aditioningsih 2017	Total volume of intravenous fluids needed during resuscitation	30	Mean in the 0.9% saline group was 6.23 (4.3 to 8.2) litres and in the Riger-fundin group was 6.23 (4.1 to 8.4) litres
Allen 2016	Total volume of intravenous fluids needed during resuscitation	100	There were no significant differences in volume, duration of fluid administration, or maintenance fluid between groups
de-Madaira 2018	Total volume of intravenous fluids needed during resuscitation	40	Median from 0 to 72 hours after randomization was 6904 (6400 to 8600) mL for 0.9% saline and 5900 (4930 to 7002) mL for Ringer's lactate solution; P = 0.045
Mahajan 2012	Total volume of intravenous fluids needed during resuscitation	22	Median total fluids (including intravenous and oral rehydration solution) requirement was less in the Ringer's lactate group (310 mL/kg (IQR 230 to 365)) as compared to the 0.9% saline group (530 mL/kg (IQR 324 to 750)); P = 0.01
Ngo 2001	Total volume of intravenous fluids needed during resuscitation	111	Mean in the Ringer's lactate group was 134.2 ($\pm$ 19.9) mL/kg and in the 0.9% saline group was 132.9 ($\pm$ 16.6) mL/kg; P = 0.954
Semler 2016	Total volume of intravenous fluids needed during resuscitation	974	Patients in the saline and balanced groups received a similar total volume of intravenous crystalloid by 30 days (1424 (500 to 3377) mL vs 1617 (500 to 3628) mL); P = 0.40
Semler 2018	Total volume of intravenous fluids needed during resuscitation	15,802	Patients in the saline group received a mean of 2171 ($\pm$ 3942) mL of saline solution and 216 ($\pm$ 1394) mL of buffered solution. Patients in the buffered group received a mean of 492 ($\pm$ 2303) mL of saline solution and 2083 ($\pm$ 3310) mL of buffered solution
Young 2014	Total volume of intravenous fluids needed during resuscitation	65	There was no significant difference in the amount of study fluid administered
Young 2015	Total volume of intravenous fluids needed during resuscitation	2,278	Patients in the saline group received a mean of 2554 ($\pm$ 2120) mL of saline solution and 1.8 ($\pm$ 60) mL of buffered solution. Patients in the Plasma-Lyte group received a mean of 0.5 ($\pm$ 15) mL of saline solution and (2655 $\pm$ 3052) mL of Plasma-Lyte solution
Young 2014	Transfusion requirement	65	16 (67%) patients in the saline group and 11 (50%) patients in the buffered solution group received pRBC transfusion (mean difference of 0.75, 95% CI 0.5 to 1.2) 13 (54%) patients in the saline group and 11 (50%) patients in the buffered solution group received plasma transfusion (mean difference of 0.9, 95% CI 0.5 to 1.6) 8 (33%) patients in the saline group and 10 (45%) patients buffered solution group received platelet transfusion (mean difference of 1.4, 95% CI 0.7 to 2.8)

Table 1. Orphan outcomes (Continued)

Young 2015	Transfusion re-quirement	2,278	<p>Packed red blood cells: 26 (9%) patients in the saline group received a mean of 45 ($\pm$ 277) mL, and 29 (9%) patients in the buffered group received a mean of 39 ($\pm$ 199) mL of packed red blood cells at study day 3</p> <p>Fresh frozen plasma: 5 (2%) patients in the saline group received a mean of 12 ($\pm$ 120) mL, and 3 (1%) patients in the buffered group received a mean of 8 ($\pm$ 100) mL of fresh frozen plasma at study day 3</p> <p>Platelets: 9 (3%) patients in the saline group received a mean of 17 ($\pm$132) mL, and 6 (2%) patients in the buffered group received a mean of 8 ($\pm$ 61) mL of platelets at study day 3</p> <p>Cryoprecipitate: 1 (0%) patient in the saline group received a mean of 1 ($\pm$ 17) mL, and 1 (1%) patient in the buffered group received a mean of 0 ($\pm$ 5) mL of cryoprecipitate at study day 3</p>
Young 2014	Cost	65	The cost-minimization analysis reported a 24-hour cost differential of USD 12.35 in favour of Plasma-Lyte A compared with non-buffered solutions

Data potentially of interest to this review but reported with variation in outcome measures or reported in single study, and therefore not suitable for numerical analysis. IQR: interquartile range; mL: millilitres; mL/kg: millilitres per kilogram; pRBC:packed red blood cells; vs: versus; USD: USA dollars.

APPENDICES

Appendix 1. Types of fluids/solutions

	Plasma	0.9% saline	Buffered so-lutions (rel-ative low-chloride so-lutions)		
Hartmann's	Ringer's lac-tate	Ringer's acetate	Sterofundin	Plasma-Lyte 148	
Osmolarity (mOsm/L)	280-296	308	278	273	275
pH	7.4	4.5 to 7	5 to 7	5.5 to 7	6.7
Sodium (mmol/L)	140	154	131	130	131
Potassium (mmol/L)	5	-	5.4	4	4
Calcium (mmol/L)	2.2	-	1.8	1.5	1

Magnesium (mmol/L)	1	-	-	-	-
Chloride (mmol/L)	100	154	112	111	109
Buffers (mmol/L)	Bicarbonate (24) Lactate (1)	-	Lactate (29)	Lactate (28)	Acetate (28)

Appendix 2. Search strategies

MEDLINE search strategy

#1 exp Isotonic Solutions/ or Fluid Therapy/ or Hydroxyethyl Starch Derivatives/ or Electrolytes/ or Sodium Chloride/ or Plasma Substitutes/ or crystalloid*.ti,ab. or (hydroxyethyl starch or HES).mp. or (saline adj4 (isotonic or normal or plasma?lyte)).mp. or (fluid* adj3 (therap* or resuscitat* or administrat* or intraven* or IV or solution* or composition or regimen* or management or buffer* or (chloride adj3 (liberal or restrictive))))).ti,ab. or (solution* adj4 (buffer* or non?buffer* or isotonic or sodium chloride or NaCL or bocarbonat* or lactated ringer* or electrolyte or balanced or ringer or hartmann or acetated or (chlorid* adj2 rich) or infused)).ti,ab. or (bocarbonat* adj3 (buffer* or precursor*)).mp.

#2 exp Resuscitation/ or exp Intensive Care/ or exp Critical Care/ or exp Critical Illness/ or resuscitat*.ti,ab. or ((department* or care*) adj4 (critical* or intensive or emergency)).ti,ab. or (critical* adj3 ill*).ti,ab. or (shock adj3 syndrom*).ti,ab. or ((burn* or trauma*) adj3 severe).ti,ab. or (pancreatitis or septic or sepsis or intoxicat* or dehydrat*).ti,ab. or injurie*.ti,ab. or (hemorrhagic adj3 shock).ti,ab. or (diabetic adj3 ketoacidosis).ti,ab. or (hyperchloremic adj3 acidosis).ti,ab.

#3 1 and 2

#4 ((randomised controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.

#5 3 and 4

Embase search strategy

#1 'isotonic solution'/exp OR 'fluid therapy'/exp OR 'hetastarch'/exp OR 'electrolyte'/exp OR 'sodium chloride'/exp OR 'plasma substitute'/exp

#2 crystalloid*:ab,ti

#3 'hydroxyethyl starch' OR hes

#4 saline NEAR/4 (isotonic OR normal OR plasmalyte)

#5 fluid* NEAR/3 (therap* OR resuscitat* OR administrat* OR intraven* OR iv OR solution* OR composition OR regimen* OR management OR buffer*)

#6 chloride NEAR/3 (liberal OR restrictive)

#7 solution* NEAR/4 (buffer* OR 'non buffer*' OR 'non buffer' OR isotonic OR 'sodium chloride' OR nacl OR bicarbonat OR 'lactated ringer' OR electrolyte OR ringer OR hartmann OR acetated OR infused)

#8 solution* NEAR/4 chlorid* NEAR/2 rich*

#9 bicarbonat* NEAR/3 (buffer* OR precursor*)

#10 1-9 OR

#11 'resuscitation'/exp OR 'intensive care'/exp OR 'critical illness'/exp

- #12 resuscitat*:ab,ti
- #13 department* NEAR/4 (critical* OR intensive OR emergency)
- #14 care* NEAR/4 (critical* OR intensive OR emergency)
- #15 critical* NEAR/3 ill*
- #16 shock NEAR/3 syndrom*
- #17 severe NEAR/3 (burn* OR trauma*)
- #18 pancreatitis:ab,ti OR septic:ab,ti OR sepsis:ab,ti OR intoxicat*:ab,ti OR dehydrat*:ab,ti OR injurie*:ab,ti
- #19 hemorrhagic NEAR/3 shock
- #20 diabetic NEAR/3 ketoacidosis
- #21 hyperchloremic NEAR/3 acidosis
- #22 11-21 OR
- #23 10 AND 22
- #24 'randomised controlled trial':pt OR 'controlled clinical trial':pt OR randomized:ab OR placebo:ab OR ramdomly:ab OR trial:ti
- #25 'clinical trial'/exp
- #26 24 OR 25
- #27 [animals]/lim NOT ([animals]/lim AND [humans]/lim)
- #28 26 not 27
- #29 23 and 28

CINAHL search strategy

- #1 MH isotonic solutions OR MH fluid therapy OR MH hydroxyethyl starch OR MH electrolytes OR MH sodium chloride OR MH plasma substitutes
- #2 TI crystalloid* OR AB crystalloid*
- #3 TX "hydroxyethyl starch" OR hes
- #4 TI ((saline* and (isotonic or normal or plasmalyte)) OR AB ((saline* and (isotonic or normal or plasmalyte))
- #5 TI (fluid* and (therap* or resuscitat* or administrat* or intraven* or iv or solution* or composition or regimen* or management or buffer*)) OR AB (fluid* and (therap* or resuscitat* or administrat* or intraven* or iv or solution* or composition or regimen* or management or buffer*))
- #6 TI ((chloride and (liberal or restrictive)) OR AB ((chloride and (liberal or restrictive))
- #7 TI (solution* and (buffer* or non-buffer* or isotonic or "sodium chloride" or nacl or bicarbonat* or "lactated ringer*" or electrolyte or balanced or ringer or hartmann or acetated or infused)) OR AB (solution* and (buffer* or non-buffer* or isotonic or "sodium chloride" or nacl or bicarbonat* or "lactated ringer*" or electrolyte or balanced or ringer or hartmann or acetated or infused))
- #8 TI (solution* and chlorid* and rich) OR AB (solution* and chlorid* and rich)
- #9 TI (bicarbonat* and (buffer* or precursor*)) OR AB (bicarbonat* and (buffer* or precursor*))
- #10 S1-S9 OR
- #11 MH resuscitation OR MH intensive care OR MH critical care OR MH critical illness
- #12 TI-AB resuscitat*
- #13 TI-AB (department* or care*) and (critical* or intensive or emergency)

- #14 TI-AB (critical* and ill*) or (shock and syndrom*)
- #15 TI-AB (burn* or trauma) and severe)
- #16 TI-AB pancreatitis or septic or sepsis or intoxicat* or dehydrat* or injurie*
- #17 TI-AB (hemorrhagic and shock)
- #18 TI-AB (diabetic and ketoacidosis)
- #19 TI-AB (hyperchloremic and acidosis)
- #20 S11-S19
- #21 S10 AND S20
- #22 PT randomized controlled trial OR AB randomized OR AB placebo OR SU clinical trials OR AB randomly OR TI trial
- #23 SU animals NOT SU ((humans and animals))
- #24 S22 NOT S23
- #25 S21 AND S24

CENTRAL search strategy

- #1 MeSH descriptor: [Isotonic Solutions] explode all trees
- #2 MeSH descriptor: [Fluid Therapy] explode all trees
- #3 MeSH descriptor: [Hydroxyethyl Starch Derivatives] explode all trees
- #4 MeSH descriptor: [Electrolytes] explode all trees
- #5 MeSH descriptor: [Sodium Chloride] explode all trees
- #6 MeSH descriptor: [Plasma Substitutes] explode all trees
- #7 crystalloid*:ti,ab,kw
- #8 'hydroxyethyl starch' OR hes:ti,ab,kw
- #9 saline and (isotonic or normal or plasmalyte):ti,ab,kw
- #10 fluid* and (therap* or resuscitat* or administrat* or intraven* or iv or solution* or composition or regimen* or management or buffer*):ti,ab,kw
- #11 chloride and (liberal or restrictive):ti,ab,kw
- #12 solution* and (buffer* or 'non buffer*' or 'non buffer' or isotonic or 'sodium chloride' or nacl or bicarbonat or 'lactated ringer' or electrolyte or ringer ORhartmann or acetated or infused):ti,ab,kw
- #13 solution* and chlorid* and rich*:ti,ab,kw
- #14 bicarbonat* and (buffer* or precursor*):ti,ab,kw
- #15 1-14 OR
- #16 MeSH descriptor: [Resuscitation] explode all trees
- #17 MeSH descriptor: [Critical Care] explode all trees
- #18 MeSH descriptor: [Critical Illness] explode all trees
- #19 resuscitat*:ti,ab,kw
- #20 department* and (critical* or intensive or emergency):ti,ab,kw
- #21 care* and (critical* or intensive or emergency):ti,ab,kw

#22 critical* and ill*:ti,ab,kw

#23 shock and syndrom*:ti,ab,kw

#24 severe and (burn* or trauma*):ti,ab,kw

#25 pancreatitis or septic or sepsis or intoxicat* or dehydrat* or injurie*:ti,ab,kw

#26 hemorrhagic and shock:ti,ab,kw

#27 diabetic and ketoacidosis:ti,ab,kw

#28 hyperchloremic and acidosis:ti,ab,kw

#29 16-28 OR

#30 15 AND 29

#31 "randomized controlled trial":pt

#32 'controlled clinical trial':pt

#33 randomized or placebo or ramdomly:ab

#34 trial:ti

#35 clinical trials:kw

#36 31-35 OR

#37 animals and humans:kw

#38 animals:kw

#39 38 NOT 37

#40 36 NOT 39

#41 30 AND 40

Appendix 3. Data extraction form

Review title or ID

Study ID (*surname of first author and year first full report of study was published, e.g. Smith 2001*)

Report IDs of other reports of this study (*e.g. duplicate publications, follow-up studies*)

Notes:

3.1 General information
3.2 Study eligibility

Study characteristics	Eligibility criteria <i>(insert eligibility criteria for each characteristic as defined in the protocol)</i>	Yes	No
Type of study	Randomized controlled trial		
	Controlled clinical trial		
Participants			
Types of interventions			
Types of outcome measures			
INCLUDE			EXCLUDE
Reason for exclusion			
Notes:			

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3.3 Population and setting

	Description	Location in text
	<i>Include comparative information for each group (i.e. intervention and control), if available</i>	<i>(pg & ¶/fig/table)</i>
Population description		
<i>(from which study participants are drawn)</i>		
Setting		
<i>(including location)</i>		

(Continued)
and social context)

Inclusion criteria

Exclusion criteria

**Method/s of
recruitment of
participants**

**Informed consent
obtained**

Yes/No/Unclear

Notes:

3.4 Methods

	Descriptions as stated in re- port/paper	Location in text (pg & ¶/fig/table)
Aim of study		
Design (e.g. parallel, cross-over, cluster)		
Unit of allocation (by individuals, cluster/groups, or body parts)		
Start date		
End date		
Total study duration		
Funding (if present indicate)	Yes/No	
Conflict of interest	Report: Yes/No Present: Yes/No	
Ethical approval needed/obtained for study	Yes/No/Unclear	
Notes:		

3.5 Risk of bias assessment

Domain	Risk of bias			Support for judge- ment	Location in text (pg & ¶/ fig/table)
	Low	High	Unclear		
Random sequence generation (selection bias)					
Allocation concealment (selection bias)					
Blinding of participants and personnel (performance bias)				Outcome group: All/	
(if required)				Outcome group:	
Blinding of outcome assessment (if required)				Outcome group: All/	
(if required)				Outcome group:	
Incomplete outcome data (attrition bias)					
Selective outcome reporting? (reporting bias)					
Funding (Appendix 4)					
Other bias					
Notes:					

3.6 Participants

Provide overall data and, if available, comparative data for each intervention and comparison group.

	Descriptions as stated in re- port/paper	Location in text (pg & ¶/fig/table)
Total no. randomized <i>(or total pop. at start of study for NRCTs)</i>		
Clusters <i>(if applicable, no., type, no. people per cluster)</i>		
Baseline imbalances		
Withdrawals and exclusions <i>(if not provided below by outcome)</i>		
Age		
Sex		
Race/Ethnicity		
Severity of illness		
Comorbidities		
Other treatment received <i>(additional to study intervention)</i>		
Other relevant sociodemographics		
Subgroups measured		
Subgroups reported		
Notes:		

3.7 Intervention groups

Copy and paste table for each intervention and comparison group.

Intervention group 1

	Descriptions as stated in re- port/paper	Location in text (pg & ¶/fig/table)
Group name		
No. randomized to group <i>(specify whether no. people or clusters)</i>		
Theoretical basis <i>(include key references)</i>		
Description <i>(include sufficient detail for replication, e.g. content, dose, components)</i>		
Duration of treatment period		
Timing <i>(e.g. frequency, duration of each episode)</i>		
Delivery <i>(e.g. mechanism, medium, intensity, fidelity)</i>		
Providers <i>(e.g. no., profession, training, ethnicity, etc., if relevant)</i>		
Co-interventions		
Economic variables <i>(i.e. intervention cost, changes in other costs as result of intervention)</i>		
Resource requirements to replicate intervention		

(Continued)
(e.g. staff numbers,
cold chain, equipment)

Notes:

3.8 Outcomes

Copy and paste table for each outcome.

Outcome 1

	Descriptions as stated in re- port/paper	Location in text (pg & ¶/fig/table)
Outcome name		
Time points measured		
Time points reported		
Outcome definition (with diagnostic criteria if relevant)		
Person measuring/reporting		
Scales: upper and lower limits (indicate whether high or low score is good)		
Is outcome/tool validated?	Yes/No/Unclear	
Imputation of missing data (e.g. assumptions made for ITT analysis)		
Assumed risk estimate (e.g. baseline or population)		

(Continued)
risk noted in Background)

Power

Notes:

3.9 Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Dichotomous outcome

Descriptions as stated in report/paper				Location in text (pg & ¶/ fig/table)
Comparison				
Outcome				
Subgroup				
Time point (specify whether from start or end of intervention)				
Results	Intervention		Comparison	
	No.	No.	No.	No.
	events	partici- pants	events	partici- pants
No. missing participants and reasons				
No. participants moved from other group and reasons				
Any other results reported				
Statistical methods				

(Continued)

and appropriateness

of these methods

(e.g. adjustment for

correlation)

Reanalysis

Yes/No/

required?

Unclear

(specify)

Reanalysis

Yes/No/

possible?

Unclear

Reanalysed results

Notes:

Continuous outcome

Descriptions as stated in report/paper							Location in text (pg & ¶/fig/table)
Comparison							
Outcome							
Subgroup							
Time point (specify whether from start or end of intervention)							
Results	Intervention			Comparison			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							
No. participants moved from other group and reasons							
Any other results reported							
Statistical methods							

(Continued)
and appropriateness

of these methods

(e.g. adjustment for
correlation)

Reanalysis	Yes/No/Unclear
-------------------	----------------

required?

(specify)

Reanalysis	Yes/No/Unclear
-------------------	----------------

possible?

Reanalysed results

Notes:

Other outcome

Descriptions as stated in report/paper				Location in text (pg & ¶/fig/table)
Comparison				
Outcome				
Subgroup				
Time point (specify whether from start or end of intervention)				
Results	Intervention result	SD (or other variance)	Control result	SD (or other variance)
	Overall results		SE (or other variance)	
No. participants	Intervention		Control	
No. missing participants and reasons				
No. participants moved from other group and reasons				
Any other				

(Continued)

results reported

**Statistical methods
and appropriateness
of these methods**
*(e.g. adjustment for
correlation)*

**Reanalysis
required?** Yes/No/Un-
clear
(specify)

**Reanalysis
possible?** Yes/No/Un-
clear

Reanalysed results

Notes:

3.10 Applicability

Have important populations been excluded from the study? <i>(consider disadvantaged populations, possible differences in the intervention effect)</i>	Yes/No/Unclear
Is the intervention likely to be aimed at disadvantaged groups? <i>(e.g. lower socioeconomic groups)</i>	Yes/No/Unclear
Does the study directly address the review question? <i>(any issues of partial or indirect applicability)</i>	Yes/No/Unclear
Notes:	

3.11 Other information

	Descriptions as stated in report/paper	Location in text (pg & ¶/fig/table)
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information <i>(from whom, what, and when)</i>		
Notes:		

Appendix 4. Criteria for other bias (funding source)

Funding

Criteria for a judgement of 'low risk' of bias	<ol style="list-style-type: none"> 1. Study authors report non-profit sources of funding (hospital or governmental funding) 2. Non-funded trials
Criteria for a judgement of 'high risk' of bias	<ol style="list-style-type: none"> 1. Study authors report profit sources of funding 2. Study authors report mixed sources (profit and non-profit) 3. Sponsor involved in analysis or design
Criteria for a judgement of 'unclear risk' of bias	<ol style="list-style-type: none"> 1. Funding not reported or sponsor's role not clearly specified

HISTORY

Protocol first published: Issue 6, 2016

Review first published: Issue 7, 2019

Date	Event	Description
3 January 2019	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

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AMA and JAB: These authors contributed equally to this work as first authors.

Conceiving of the review: JAB.

Designing the review: JAB, AMA.

Co-ordinating the review: JAB, AMA, MNP.

Collecting data for the review: AMA, JAB.

Designing search strategies: JME, JAB, AMA.

Screening search results: AMA, JAB, JME.

Organizing retrieval of papers: JAB, AMA, JME, IS.

Screening retrieved papers against eligibility criteria: JAB, AMA, IS, MC.

Appraising the quality of papers: AMA, JAB, IS, MC, MNP.

Extracting data from papers: AMA, JAB, IS.

Writing to authors of papers for additional information: AMA, IS, JAB.

Providing additional data about papers: JME, AMA.

Obtaining and screening data from unpublished studies: JME, AMA, JAB.

Managing data for the review: AMA, JAB, MNP.

Entering data into RevMan: JAB, AMA.

Analysing data: MNP, AM, JAB, AMA.

Interpreting data: AMA, JBA, MNP, AM, MC, IS.

Providing a methodological perspective: MNP, AM.

Providing a clinical perspective: JAB, IS, MC.

Providing a policy perspective: MC, JAB.

Writing the review: AMA, JBA, MNP, AM, IS, MC.

Providing general advice on the review: JAB, AMA.

Performing previous work that was the foundation of the current review: JAB, AMA.

DECLARATIONS OF INTEREST

Alba M Antequera has no conflicts of interest to declare.

Jesús A Barea-Mendoza has no conflicts of interest to declare.

Maria N Plana has no conflicts of interest to declare.

Mario Chico-Fernández received payment from Bard Medical Pharmaceutical for a lecture and a review related to hypothermia in brain injury in 2018, and travel expenses from CSL Behring to attend the European Trauma and Surgery Congress in 2018.

Alfonso Muriel has no conflicts of interest to declare.

Ignacio Sáez has no conflicts of interest to declare.

Jose M Estrada-Lorenzo has no conflicts of interest to declare.

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Internal sources

- Cochrane Collaborating Centre of the Comunidad Autónoma de Madrid (CCC-CAM), Spain.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol ([Barea-Mendoza 2016](#)).

1. We redefined the age groups of children and adults. We changed the age threshold from 16 to 18 years old to obtain more information from the analyses because some trials in children extended the paediatric age until 18 years, and likewise, most of the studies in adults defined the inclusion criteria to be older than 18 years.
2. We added cost to 'Secondary outcomes'.
3. We did not carry out the following analyses specified in the protocol.
 - a. Mortality: subgroup analyses by disease subsets due to included trials reporting this combined outcome.
 - b. Acute renal injury: subgroup analyses by disease subsets owing to included trials reporting this combined outcome, and by age group due to lack of data in the population of children.
 - c. Total volume of intravenous fluids needed during resuscitation; data presented in multiple formats were not meta-analysed.
 - d. Blood loss, coagulation disturbances, and quality of life because included studies did not provide data.
 - e. Trial sequential analysis because a recent statement (November 2018) from the Scientific Committee discouraged its use in Cochrane Reviews.
4. As a result of previous comments, outcomes were reported with 95% CIs.
5. After discussion, we reported in the 'Summary of findings' table only the most relevant outcomes for patients.
6. Following comments during the review phase, we decided to remove the term "no surgical" from the title.

INDEX TERMS**Medical Subject Headings (MeSH)**

*Critical Illness; Critical Care; Fluid Therapy [*methods]; Hospital Mortality; Randomized Controlled Trials as Topic; Rehydration Solutions; Saline Solution [*therapeutic use]

MeSH check words

Adult; Child; Humans