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[Intervention Review]

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

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ABSTRACT

Rationale

Fluid therapy is one of the main interventions provided for critically ill patients, although there is no consensus regarding the type of solution that should be used. There are two main types: colloid and crystalloid. The most commonly administered crystalloid solution is 0.9% saline. Buffered solutions may offer some theoretical advantages (e.g. less metabolic acidosis, less electrolyte disturbance), but the clinical relevance of these remains unknown. This is an update of a review published in 2019.

Objectives

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

Search methods

We searched CENTRAL, MEDLINE, Embase, CINAHL, and four trial registers in July 2023. We checked references, conducted backward and forward citation searches for relevant articles, and contacted study authors to identify additional studies. Although we updated our search in June 2025, the results have not yet been fully incorporated into the review.

Eligibility criteria

We included randomised controlled trials (RCTs) with parallel or cross-over design that examined buffered solutions versus 0.9% saline in a critical care setting (resuscitation or maintenance). We included studies with participants who required intravenous fluid therapy due to critical illness (including trauma and burns) or undergoing emergency surgery during critical illness. We included studies of adults or children (or both). We excluded studies of people undergoing elective surgery and studies with multiple interventions in the same arm.

Outcomes

Our critical outcomes were overall (in-hospital) mortality and acute renal injury. Our important outcomes were organ system dysfunction, need for renal replacement therapy, days without organ support, electrolyte disturbances, blood loss or transfusion, coagulation disorders, total resuscitation fluid volume, quality of life, and cost.

To populate a table summarising the findings of our review, we selected key outcomes for decision-makers, which were our two critical outcomes and two of our important outcomes (organ system dysfunction and electrolyte disturbances).

Risk of bias

Two review authors independently assessed the risk of bias of each included study using the Cochrane risk of bias tool RoB 1. We considered pharmaceutical industry funding as a potential source of bias.

Synthesis methods

Where possible, we synthesised results for each outcome using random-effects meta-analysis. We reported outcomes using the odds ratio (OR) and 95% confidence intervals (CIs). We used the GRADE approach to assess the certainty of evidence.

Included studies

We included 34 studies, with a total of 37,859 participants. Two RCTs with 26,854 participants contributed more than 70% of the total sample. Adults were the participants in 22 trials, and children in 12. All studies enrolled critically ill participants: people with diabetic ketoacidosis (six studies), acute pancreatitis (five studies), severe dehydration (five studies), sepsis or septic shock (four studies), severe trauma (three studies), dengue shock syndrome (two studies), and mixed conditions (nine studies). The studies took place in 16 countries. All studies were published in English.

We judged 16 studies to have an overall low risk of bias (i.e. low risk of bias for allocation concealment, blinding of participants and blinding of assessors, incomplete outcome data, and selective reporting). In the remaining trials, we judged that some form of bias had been introduced or could not be ruled out.

Synthesis of results

We found that buffered solutions result in little to no difference in overall (in-hospital) mortality (OR 0.95, 95% CI 0.90 to 1.01; $I^2 = 0\%$; 23 studies, 36,452 participants; high-certainty evidence), when compared to 0.9% saline. Based on a mortality rate of 147 people per 1000, buffered solutions could reduce the number of deaths by 13 per 1000 or could increase deaths by 1 per 1000.

We found that buffered solutions likely result in little to no difference in acute renal injury (OR 0.87, 95% CI 0.75 to 1.02; $I^2 = 51\%$; 17 studies, 30,832 participants; moderate-certainty evidence). We downgraded the certainty of the evidence because of the risk of bias. Based on an acute renal injury rate of 140 per 1000, buffered solutions could reduce acute renal injury by 31 per 1000 or could increase acute renal injury by 2 per 1000.

We are very uncertain of the effects of buffered solutions versus 0.9% saline on organ system dysfunction (OR 0.83, 95% CI 0.41 to 1.70; $I^2 = 0\%$; 5 studies, 266 participants; very low certainty evidence), and on sodium (MD -0.26, 95% CI -2.29 to 1.77; $I^2 = 79\%$; 7 studies, 1246 participants; very low certainty evidence) and potassium (MD 0.11, 95% CI -0.04 to 0.25; $I^2 = 41\%$; 5 studies, 1086 participants; very low certainty evidence). Compared to 0.9% saline, buffered solutions may reduce chloride (MD -2.39, 95% CI -3.77 to -1.00; $I^2 = 90\%$; 11 studies, 1981 participants), and may increase pH (MD 0.06, 95% CI 0.02 to 0.10; $I^2 = 88\%$; 6 studies, 1224 participants) and bicarbonate (MD 2.16, 95% CI 1.06 to 3.25; $I^2 = 87\%$; 9 studies, 1368 participants) (all low-certainty evidence). We downgraded the certainty of the evidence because of the risk of bias and imprecision.

Authors' conclusions

Buffered solutions do not reduce overall (in-hospital) mortality compared to 0.9% saline solution in critically ill patients, and probably do not reduce acute renal injury. Evidence for organ system dysfunction and electrolyte disturbances is of low or very low certainty.

We have high-certainty evidence about the outcome of mortality, but further trials are needed to clarify the impact of buffered solutions on acute renal injury and other outcomes. Future studies should involve underrepresented populations (paediatric, neurocritical, female) and adopt standardised, patient-centred outcome measures to broaden the evidence base.

Once the 38 relevant ongoing studies are published and the nine studies that await classification are evaluated, the inclusion of new studies in this review may alter its conclusions regarding acute renal injury, organ dysfunction, and electrolyte disturbances.

Funding

The original review and this update received no funding.

Registration

This 2026 review is an update of the 2019 review. Both versions were conducted according to the published protocol.

Protocol (2016) available at <https://doi.org/10.1002/14651858.CD012247>

The protocol was registered with PROSPERO (CRD42016045988).

Original review (2019) available at <https://doi.org/10.1002/14651858.CD012247.pub2>

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of buffered solutions (given into a vein to keep acid levels stable in the blood) for treating very sick adults and children?

Key messages

1. Using buffered solutions (which contain substances that help keep acid levels in the blood stable) for critically ill adults and children makes little or no difference to the number of them who die while in hospital, when compared to using 0.9% saline (a solution of salt in water).
2. Using buffered solutions rather than saline probably makes little or no difference to the number of patients who have sudden damage to the kidney that affects how it works (acute kidney injury).

What is resuscitation in critically ill patients?

Resuscitation is a set of medical procedures used to treat patients who experience a serious and urgent health problem, especially to restore their heartbeat and breathing.

What are intravenous (into a vein) fluid therapies used in resuscitation?

Fluid therapies are water-based salt solutions. They are used as a medical treatment to make sure that the body's organs and tissues receive enough blood flow, receive enough fluids, and maintain electrolyte (salts) balance. Fluid therapy is the cornerstone of treatment for many serious conditions, like sepsis (life-threatening response of the body to infection), burns, trauma (injury), or undergoing emergency surgery.

Crystalloids are a type of fluid therapy that is commonly used and include two groups of solutions.

1. Buffered crystalloid solutions contain substances (buffers, like lactate, bicarbonate, or acetate) that help to maintain a constant pH (acidity) level in the blood
2. 0.9% saline has an osmolarity (concentration of dissolved substances) similar to blood, although its electrolyte composition is not identical. It contains only sodium and chloride, which are in a higher proportion than in blood.

What did we want to find out?

We wanted to find out the benefits of using buffered solutions in adults and children who are very seriously (critically) ill (including those with sepsis, trauma, burns, or shock) and have not had elective (planned) surgery. We also wanted to know if buffered solutions cause any unwanted effects.

What did we do?

In July 2023, we searched medical databases for relevant studies known as randomised controlled trials. We looked again in June 2025, but the studies we identified from the last two years have not yet been included in our findings.

We combined the results of the studies and rated our confidence in the evidence they provide, based on factors such as their size and the methods they used.

What did we find?

We found 34 studies that involved 37,859 adults and children with critical illness who required intravenous fluid therapy. Most of the studies were medium-sized (between 22 and 230 people), but the largest two studies together involved 26,854 people. The studies took place in 16 countries.

Main results

1. Compared with 0.9% saline, buffered solutions make little or no difference to the risk of death during the hospital stay.
2. Buffered solutions probably make little or no difference to the risk of acute kidney injury.
3. The evidence is very uncertain about the effect of buffered solutions on the risk of organ system dysfunction (body systems failing to perform normally).
4. The evidence is also very uncertain about the effect of buffered solutions on the electrolytes sodium and potassium. Buffered solutions may reduce chloride concentration, and may increase pH levels and bicarbonate concentration.

What are the limitations of the evidence?

We are confident in the evidence that compared the number of deaths when buffered solutions were used compared to when 0.9% saline was used.

We are moderately confident in the evidence for acute kidney injury. We do not have complete confidence because the assessment of kidney function (how well the kidneys work) may have been influenced by doctors knowing whether someone taking part in the study received a buffered solution or 0.9% saline. It is possible that future studies could find different results.

We are not confident in the evidence about organ system dysfunction because it is based on only a few cases, and the study that contributed most to the results did not clearly report the number of people or the results, and we could not get more information.

We are not confident in the evidence about electrolyte abnormalities because the evidence was based on too few studies to be certain about the findings.

Who paid for the studies?

Twenty of the studies were funded by governments or non-profit organisations; four received mixed funding; one was funded by a company, but it was not clear what business the company was in; and nine studies gave no details about funding.

How up to date is this review?

This review updates our previous review. The evidence in it is based on searches we did in July 2023. We conducted a further search in June 2025 and will include those results in our next update of the review.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings table - Buffered solutions compared to saline solution 0.9% for critically ill adults and children

Buffered solutions compared to saline solution 0.9% for 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: saline solution 0.9%

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with saline solution 0.9%	Risk with buffered solutions				
Overall mortality (in-hospital death)	147 per 1000	141 per 1000 (148 to 134)	OR 0.95 (0.90 to 1.01)	36452 (23 RCTs) ^a	⊕⊕⊕⊕ High	
Acute renal injury (as defined by study authors)	140 per 1000	124 per 1000 (143 to 109)	OR 0.87 (0.75 to 1.02)	30832 (17 RCTs) ^a	⊕⊕⊕⊖ Moderate ^b	
Organ system dysfunction	163 per 1000	139 per 1000 (249 to 74)	OR 0.83 (0.41 to 1.70)	266 (5 RCTs) ^a	⊕⊕⊕⊖ Very low ^{c,d}	
Sodium	The median Sodium was 138.05 mmol/L	MD 0.26 mmol/L lower (2.29 lower to 1.77 higher)	-	1246 (7 RCTs) ^a	⊕⊕⊕⊖ Very low ^{c,e}	
Potassium	The median Potassium was 3.85 mmol/L	MD 0.11 mmol/L higher (0.04 lower to 0.25 higher)	-	1086 (5 RCTs) ^a	⊕⊕⊕⊖ Very low ^{c,e}	
Chloride	The median Chloride was 104 mmol/L	MD 2.39 mmol/L lower (3.77 lower to 1 lower)	-	1981 (11 RCTs) ^a	⊕⊕⊕⊖ Low ^{c,f}	
pH	The median pH was 7.408	MD 0.06 higher (0.02 higher to 0.1 higher)	-	1224 (6 RCTs) ^a	⊕⊕⊕⊖ Low ^{c,f}	
Bicarbonate	The median Bicarbonate was 21.2 mmol/L	MD 2.16 mmol/L higher (1.06 higher to 3.25 higher)	-	1368 (9 RCTs) ^a	⊕⊕⊕⊖ Low ^{c,f}	

***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).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

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.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_450367056456867660.

^a RCT: randomised controlled trial

^b Certainty of the outcome was downgraded one level because of risk of bias. 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).

^c Certainty of the outcome was downgraded one level because of risk of bias. Several studies included have high or unclear risk of bias for blinding or incomplete reporting.

^d Certainty of the outcome was downgraded two levels because of imprecision. OIS (optimal information size) not met and CI fails to exclude important benefit or important harm.

^e Certainty of the outcome was downgraded two levels because of imprecision. CI fails to exclude important benefit or important harm.

^f Certainty of the outcome was downgraded one level because of imprecision. CI overlaps no clinically relevant effect.

BACKGROUND

This is an update of a Cochrane review first published in 2019 [1].

Description of the condition

Intravenous fluid therapy is very commonly given to critically ill patients [2]. More than a third of all hospitalised patients are given intravenous fluid therapy [3]. For many clinical scenarios, such as sepsis, acute pancreatitis, and severe trauma, intravenous fluid therapy serves as the cornerstone of treatment. 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 [4]. 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 [3, 4].

The cost of different intravenous solutions has been estimated at three to a hundred times greater than the cost of 0.9% saline [5]. Several medical societies and authors have developed consensus papers and have presented evidence-based guidelines intended to improve decisions about fluids and related outcomes [6, 7, 8]. Other guidelines have focused more on critical illness and have provided recommendations concerning fluid therapy [9, 10, 11, 12, 13, 14].

Fluid therapy solutions are classified as colloid or crystalloid solutions. Colloids are solutions composed of large molecules dispersed throughout a 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 [15].

However, according to two Cochrane reviews, colloids offer no benefit over crystalloids and may even increase risks of renal failure and death [16, 17]. Furthermore, 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 [18]. 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 [19, 20]. Accordingly, the use of colloid solutions has decreased in recent years due to the reported increase in the risk of mortality, kidney injury, and excess bleeding [21].

Although 0.9% saline is a widely used crystalloid solution, it causes hyperchloraemic acidosis, with significant consequences for patients that have been identified in several observational studies [22, 23, 24]. As safer crystalloids, buffered solutions have been assessed for their suitability for use in resuscitation. 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 [25]. However, the 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 extrapolated to critically ill patients [25].

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

Description of the intervention and how it might work

Crystalloids are aqueous solutions of ions that have different properties according to their ion concentrations (Supplementary material 8). Because of its low cost and general availability, 0.9% saline is the most commonly used intravenous fluid [26, 27]. In this review, we use the term '0.9% saline' because we do not recommend the use of terms such as 'normal' or 'physiological' saline. This is because, although 0.9% saline contains sodium and chloride in equal concentrations, it contains levels that are higher than the physiological levels in human plasma. The terms 'normal' and 'physiological' reflect historical issues rather than chemical properties [26].

Other crystalloid formulations, called 'balanced' or 'buffered' solutions, differ from 0.9% saline in terms of three properties: they have lower levels of sodium and chloride, bringing them closer to normal plasma levels; they contain 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 [28]; and they contain anions such as lactate, acetate, and gluconate, which are metabolised to bicarbonate by tissue cells and may exert an additional buffering effect.

Data from experimental human and animal studies suggest that an infusion of 0.9% saline may induce greater hyperchloraemic acidosis and interstitial oedema than an infusion of an intravenous buffered solution [29]. Experimental studies have shown that hyperchloraemic acidosis increases the risk of a deterioration in renal function through effects such as renal vasoconstriction, low renal perfusion pressure, and low glomerular filtration rate [30, 31]. Effects of acidosis on the immune system have been described in a rat model, with an increase in inflammatory markers observed [32]. Changes in systemic inflammation response have also been linked to acidosis in humans (Wu 2011 [33]). In a before-and-after trial, a chloride-restrictive strategy was associated with a reduction in the incidence of acute renal injury and in the need for renal replacement therapy in adult intensive care patients [24, 34]. In an observational study, hyperchloraemic acidosis was associated with increased mortality among critically ill patients [22]. The effect observed may be independent of the fluid volume administered and may be more closely related to the chloride load [23]. These data suggest that buffered solutions, having lower chloride concentrations than 0.9% saline, may reduce the incidence of hyperchloraemic acidosis, thus decreasing the risk of adverse outcomes such as renal failure, need for renal replacement therapy, and mortality [22, 35].

Why it is important to do this review

As described above, several observational studies in the critical care setting have reported an association between hyperchloraemic acidosis and outcomes such as acute renal injury and mortality [22, 23, 24].

A Cochrane systematic review published in 2017 concluded that buffered intravenous fluids reduced the incidence of hyperchloraemia and metabolic acidosis in elective surgery [25]. However, the trials included in the review were not adequately powered to permit conclusions about renal failure or mortality, and they did not include critically ill patients. Several recent randomised trials have examined the effects of buffered solutions on critically ill patients. In one such study, faster pH normalisation was observed amongst severely dehydrated participants receiving buffered fluid therapy [36]. Two randomised controlled trials conducted in trauma patients described a reduction in the incidence of hyperchloraemic acidosis, without a rise in intracranial pressure [37, 38]. Other trials have explored the potential benefits of buffered solutions in clinical settings with patients with conditions such as diabetes [39], acute pancreatitis (Wu 2011; 40), dengue [41], and doxylamine-induced rhabdomyolysis [42]. However, in the SPLIT (0.9% Saline versus Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy) study, the use of a balanced solution rather than a 0.9% saline solution was not associated with a reduction in mortality or acute renal injury amongst critically ill patients [43].

Based on this evidence, we conducted a systematic review in 2019 [1]. The current review is an update of that original review. In the 2019 version of the review, we found no effect of buffered solutions on in-hospital mortality or acute renal injury compared to 0.9% saline solutions in critically ill patients. Notably, patients receiving buffered solutions exhibited decreased chloride levels, elevated bicarbonate levels, and higher pH values. Over the past few years, several new trials have been published in this field [44, 45]. In conducting this 2026 update, our objective was to include new relevant studies and retrieve previously unclassified data. By incorporating this updated evidence, we aimed to enhance the overall certainty of the review findings.

OBJECTIVES

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

METHODS

We followed the Methodological expectations for Cochrane intervention reviews (MECIR) when conducting the review [46], and PRISMA 2020 for reporting [47]. The differences between what we planned to do in the protocol and what we did in the review process have been reported in [Supplementary material 9](#).

Criteria for considering studies for this review

Types of studies

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

Types of participants

We included studies of participants with critical illness (including trauma, burns, or emergency surgery during critical illness) who required intravenous fluid therapy. We included studies of adults (defined as 18 years old or older) and children (defined as younger

than 18 years of age). We planned to include studies involving both adult and paediatric populations when data were disaggregated. When data were unavailable, we planned to contact the study author to request data. If we received no reply, we planned to assign the participants to the subset that accounted for 80% of the sample and explore this decision by conducting sensitivity analysis excluding those studies. We explored the effects of age in subgroup analysis (see [Synthesis of results](#)).

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 ([Supplementary material 8](#)). We consider all uses of fluids in a critical care setting for resuscitation or maintenance after enrolment. We required that included fluids were isotonic (osmolarity 250 to 350 mmol/L). Fluids before enrolment were registered and analysed if they had been reported. To minimise confounding factors, we did not consider studies with multiple interventions (e.g. colloids plus buffered solutions). We excluded studies comparing crystalloids with colloids, or different types of colloids, but multi-arm trials were eligible if they met all inclusion criteria and included a buffered solution versus 0.9% saline comparison.

Outcome measures

Critical outcomes

1. Overall (in-hospital) mortality
2. Proportion of participants with acute renal injury, as defined in the included studies

Important outcomes

1. Proportion of participants with organ system dysfunction (respiratory, haemodynamic, central nervous system, and hepatic), as defined in the included studies
2. Proportion of participants newly treated with renal replacement therapy
3. Number of days (up to day 28) with no organ-support therapy (ventilator- and vasopressor-free days)
4. 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)
5. Blood loss or transfusion requirement
6. Coagulation disturbances (expressed as thrombocytopenia or coagulopathy)
7. Total volume of intravenous fluid needed during resuscitation
8. Quality of life measured with Short Form (SF)-36 [48] and the EuroQOL quality of life questionnaire (EQ-5D) [49]
9. Cost. We considered any economic measure directly related to the intervention and reported by the included studies.

Search methods for identification of studies

This is an update of a review originally published in 2019 [1].

Electronic searches

We searched for studies using the methods described in the *Cochrane Handbook of Systematic Reviews of Interventions* [50] on 7 July 2023. We searched the following databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2023, Issue 7)
2. MEDLINE (access via Ovid, 1946 to July 2023)
3. Embase (access via Ovid SP, 1974 to July 2023)
4. CINAHL (access via Ebsco, 1989 to July 2023)

We used the search strategy detailed in [Supplementary material 1](#). The search strategy was identical to that used in the original review. We adapted the terms used in MEDLINE for searches of the other databases. Where appropriate, we used the highly sensitive search strategy designed by Cochrane for identifying RCTs as described in the *Cochrane Handbook for Systematic Reviews of Interventions* [51]. We imposed no language, publication year, or publication status restrictions.

Although we conducted a new search on 28 June 2025, these results have not been incorporated into this review. They have been added as 'studies awaiting classification' in [Supplementary material 4](#) and will be incorporated in the next review update.

Searching other resources

We looked for unpublished clinical trials by searching the following websites.

1. Clinicaltrials.gov (<https://www.clinicaltrials.gov>)
2. International Standard Randomised Controlled Trial Number Register (<http://www.isrctn.com/>)
3. World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int/)
4. Clinical Trial Results (<https://www.clinicaltrialresults.org/>)

We searched for abstracts from the most relevant medical society meetings from June 2018 to June 2025.

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 Anaesthesiology and Intensive Care (ESAIC)
6. American Society of Anaesthesiologists (ASA)
7. International Anaesthesia 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 authors of the included studies to ask whether they knew of any new eligible studies. We checked the reference lists of the included studies and of relevant systematic reviews. We looked for errata, corrigenda, or retractions of the included studies by exploring their current status in the publication source.

Data collection and analysis

Selection of studies

We used Covidence for the deduplication of the references before screening the search results [52]. We selected studies according to the methods of the Cochrane Critical and Emergency Care Group. Pairs of review authors (from FDM, LLG, JAB, and AA) 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 accuracy. We classified studies into three categories: 'excluded', 'uncertain' and 'included', according to pre-determined criteria for this review (see [Criteria for considering studies for this review](#)). At this stage, we excluded only papers classified as 'excluded'. In the second stage of the process, the same authors independently examined full-text reports to check whether studies complied with the review eligibility criteria. We resolved disagreements by discussion and consulted a third review author (JAB and MC) if we could not reach a consensus. If appropriate, we contacted study authors to clarify the eligibility of a study. Finally, if we were unable to obtain the necessary information, we labelled the study as "awaiting classification". We were not blinded to the names and affiliations of study authors, to journals, nor to study results at any stage of the study selection process.

Data extraction and management

We modified the Cochrane Critical and Emergency Care Group data extraction form ([Supplementary material 11](#)) and piloted this form with five studies to ensure its suitability. Pairs of review authors (from FDM, LLG, JAB, and AA) independently extracted data. We compared results and resolved discrepancies by discussion or by consultation with the third review author (JAB and MC). We extracted the following information from each trial.

1. Study authors, journals, 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: primary health condition, age, sex, previous diseases, fulfilment of inclusion criteria, and baseline comparability
6. Type of intervention and type of control
7. Extracted outcomes and outcome measures
8. Recruitment country for study
9. Conflicts of interest and funding

One review author (FDM, JBA, or AA) entered the data into Review Manager (RevMan) [53], and a second review author (LLG) checked the data for errors.

In terms of dealing with duplicate publications, if we found several publications that referred to the same trial, we indicated the primary version of the study and referenced all secondary reports. We selected the most complete data from all the publications found.

Risk of bias assessment in included studies

Pairs of review authors (from FDM, LLG, JAB, and AA) independently assessed the risk of bias in the studies using the Cochrane risk-of-bias tool RoB 1 [54]. We extracted information related to the risk of bias from each study according to the following domains: random sequence generation; allocation concealment; blinding of participants and investigators; outcome assessment; incomplete outcome data; and selective reporting [54]. If any of the above data were not available for the study of interest, or if it were unclear whether the criteria were met, we contacted the study author by email to request further information. If necessary, we considered other sources of bias related to the design of the studies, as specified in the *Cochrane Handbook for Systematic Reviews of Interventions* [55]. In accordance with the literature, we considered industry funding as a potential source of bias [56, 57]. We considered funding when workforce, materials, or grants were provided for the study. We established the risk of funding bias using criteria defined in [Supplementary material 10](#). We did not exclude trials on the basis of risk of bias but conducted sensitivity analyses to explore the effects of risk of bias in the meta-analyses (see [Investigation of heterogeneity and subgroup analysis](#)).

Measures of treatment effect

We performed all analyses according to standards specified in the *Cochrane Handbook for Systematic Reviews of Interventions* [58]. 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 standardised mean difference (SMD) when the original studies used different scales.

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

Unit of analysis issues

We dealt with trials with cluster, cross-over, or multiple-arm design as specified in the *Cochrane Handbook for Systematic Reviews of Interventions* [59, 60]. For cluster-randomised trials, we used adjusted effect estimates reported by the trialists when available, and applied the generic inverse variance (GIV) method. For cross-over trials, we included only data from the first period, when appropriate, to avoid carry-over effects. For multiple-arm trials, we combined relevant intervention groups or split the control group to avoid double-counting participants.

Dealing with missing data

We conducted analyses on an intention-to-treat basis, meaning the following.

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

For missing data, we used the following strategy.

1. We contacted study authors by email or by letter to request the missing data.

2. We reported missing outcome data as the proportion of participants for whom outcome data were unavailable, regardless of the reason.
3. We performed sensitivity analysis by using two alternative scenarios for participants with incomplete or missing data for our two critical outcomes (i.e. overall mortality and acute renal injury during hospitalisation) [61].
4. "Best-worst" case scenario analysis: 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.
5. "Worst-best" case scenario analysis: 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.

Reporting bias assessment

We minimised 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 predefined strategy for assessment of reporting bias consisted of the following.

1. If we combined data from more than 10 studies for an outcome, we created a funnel plot (a scatter plot of the intervention effect against a measure of study size).
2. We assessed the funnel plot for asymmetry visually and statistically.
3. We interpreted the results while considering all causes of asymmetry (not only publication bias).

Synthesis methods

We performed statistical tests according to the recommendations of the Cochrane Emergency and Critical Care Group using Review Manager [53], provided by Cochrane for data synthesis and analysis.

Assessment of significance

We assessed the effects of our intervention using the random-effects meta-analytical model, as we anticipated clinical diversity. The Restricted Maximum Likelihood (REML) estimator was used to estimate between-trial variance. The Hartung-Knapp-Sidik-Jonkman method was used to calculate confidence intervals for the meta-analysis effect estimate when there were at least three studies and the estimate of heterogeneity was greater than zero. In other scenarios (i.e. in pooled analyses of two studies or where the estimate of heterogeneity was equal to zero), we used the Wald-type method.

We used sensitivity analysis to compare the results of using the random-effects or fixed-effect model for meta-analysis (see [Sensitivity analysis](#)). There is no defined meaningful clinical threshold for ventilator-free days and vasopressor-free days. We chose a 1.5-day difference for these outcomes based on the approach of Laterre and colleagues [62], after considering recent trials. For continuous outcomes expressed as mean differences, we considered what the minimal important differences (MIDs) should be, in order to facilitate clinical interpretation. Based on prior literature and accepted physiological thresholds, we defined the following MIDs, which were chosen as they represent changes that

are small but clinically meaningful, being associated with relevant metabolic disturbances or therapeutic decision-making [63, 64, 65, 66].

1. Sodium \pm 3 mmol/L
2. Potassium \pm 0.5 mmol/L
3. Chloride \pm 5 mmol/L
4. pH \pm 0.03 units
5. Bicarbonate \pm 2 mmol/L
6. Base excess \pm 2 mmol/L

Investigation of heterogeneity and subgroup analysis

We checked for heterogeneity by considering the following.

1. Clinical and methodological characteristics of studies
2. Forest plots of study results to visually check for overlaps in confidence intervals.
3. Results of the χ^2 test for statistical heterogeneity (we considered trial results as heterogeneous when P value $<$ 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:
 - a. from 0% to 40% heterogeneity may not be important;
 - b. from 30 to 60% heterogeneity may be moderate;
 - c. from 50% to 90% heterogeneity may be substantial; and
 - d. from 75% to 100% heterogeneity is considerable).

We explored the reasons behind substantial or considerable heterogeneity by performing subgroup analyses.

We conducted subgroup analyses to examine the influence of disease pathophysiology, host response, and intervention composition. The interventions differ in chloride content, tendency to cause acidosis, and osmolarity. These factors could modify effects across clinically relevant subgroups. Therefore, we prespecified these subgroups and tested heterogeneity with interaction terms [67]. We also explored the potential impact of equity factors by considering the income country of studies (see post hoc amendments in [Supplementary material 9](#)). We conducted subgroup analyses only for the critical outcomes. We did not include secondary outcomes in subgroup analyses, as they were considered exploratory and not sufficiently powered to provide reliable estimates.

Condition

1. Neurocritical participants
2. Patients with sepsis or dengue
3. Trauma participants
4. Surgical critically ill participants
5. Participants with primary hydroelectrolytic imbalance (dehydration or diabetic ketoacidosis).

Intravenous buffered solution received

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

Age group

1. Adults \geq 18 years old
2. Children $<$ 18 years old

Country income, defined by World Bank country classification by income level

1. High income
2. Low income, lower middle-income, and upper middle-income

Equity-related assessment

We detailed characteristics of the population using the PROGRESS-Plus framework [68], by reporting data on the sex and place of residence of participants. We attempted to extract outcomes disaggregated by sex, but data were unavailable. We undertook subgroup analyses by place of residence using the World Bank income country classification. See [Investigation of heterogeneity and subgroup analysis](#).

Sensitivity analysis

We undertook the following sensitivity analyses for critical outcomes.

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

Certainty of the evidence assessment

To summarise the key results of our review, we designed a summary of findings table using GRADE profiler software [69]. We listed the population, intervention, and comparison in these tables, along with relevant outcomes, the point estimates and confidence intervals, the number of studies and participants contributing to each result, and our confidence in the certainty of the evidence.

We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) system to assess the certainty of evidence associated with each outcome [70]: overall (in-hospital) mortality, acute renal injury, organ system dysfunction, and electrolyte disturbances (i.e. sodium, potassium, chloride, pH, and bicarbonate). The GRADE approach is used to appraise the certainty 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 (FDM and JAB) independently assessed their confidence in the estimates of effects using the GRADE criteria of study limitations, consistency of effect, imprecision, indirectness, and publication bias [71]. Any disagreements about whether a finding should be described as high certainty, moderate certainty, low certainty, or very low certainty were resolved by discussion.

Consumer involvement

We did not involve consumers in this review due to limited resources. However, we used core outcome sets for the review's outcomes, which were developed with consumer involvement.

RESULTS

Description of studies

See Characteristics of included studies ([Supplementary material 2](#)), Characteristics of excluded studies ([Supplementary material 3](#)), Characteristics of studies awaiting classification ([Supplementary material 4](#)), and Characteristics of ongoing studies ([Supplementary material 5](#)).

Results of the search

Our official date of search is 7 July 2023 (because we have not fully incorporated the studies we found in the more recent search),

but we present here the combined totals of our searches on 7 July 2023 and 28 June 2025. We retrieved 13,678 new records, which we reduced to 9994 records after removal of duplicates ([Figure 1](#)). We excluded 9880 records after title and abstract screening. We identified 114 additional records for full-text review, of which, 13 were included, 54 were excluded, 9 await classification, and 38 are ongoing trials. Thus, we have included a total of 34 studies in this 2026 update, all of which were written in English. The three ongoing studies in the 2019 review were completed, published, and met eligibility criteria (Finfer 2022 [[44](#), [72](#), [73](#)]; Sankar 2023 [[74](#)]; Zampieri 2021 [[45](#), [75](#), [76](#), [77](#)]). Our total number of excluded studies is now 68.

Figure 1. PRISMA flow diagram of study identification and selection

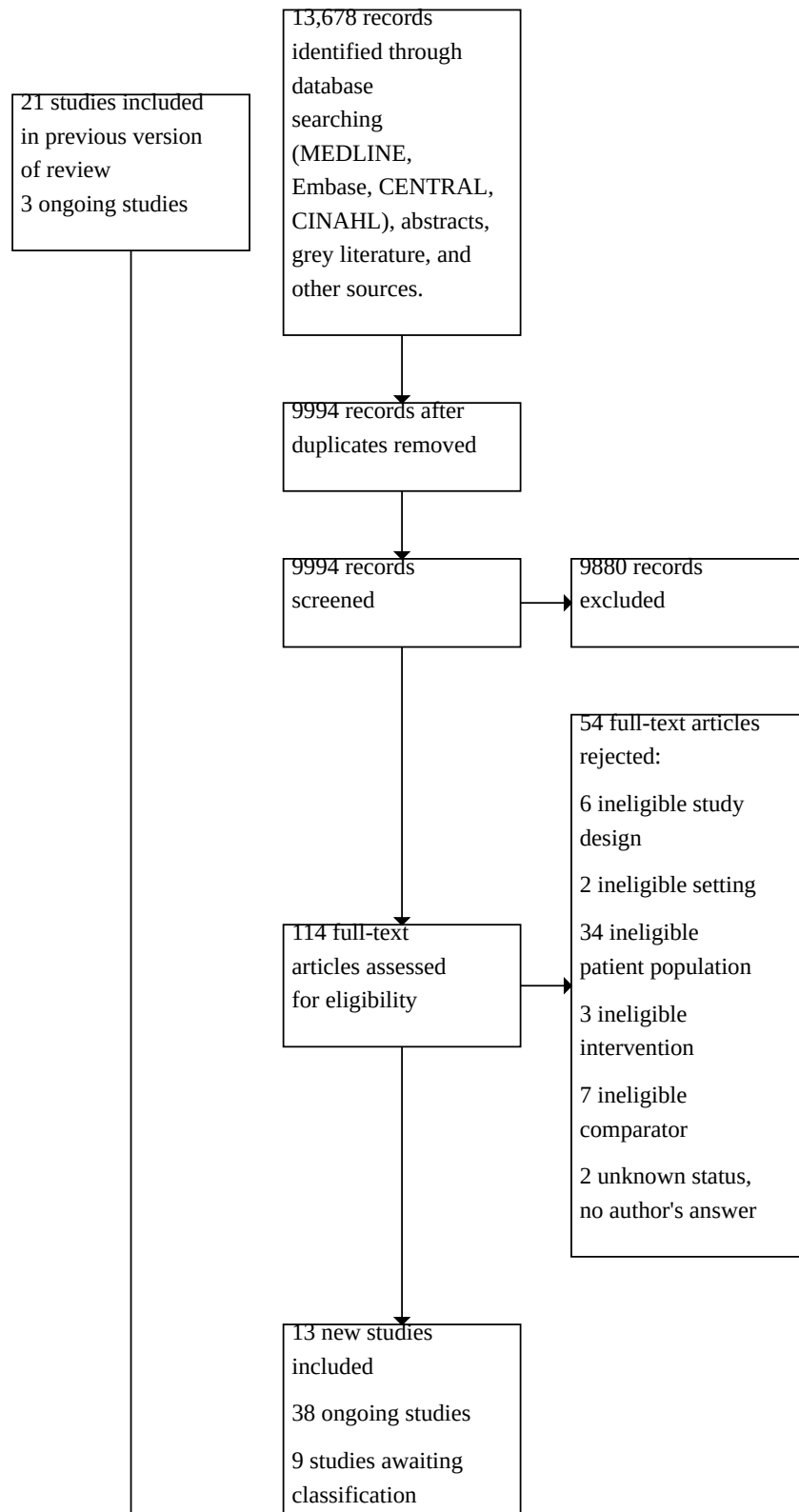
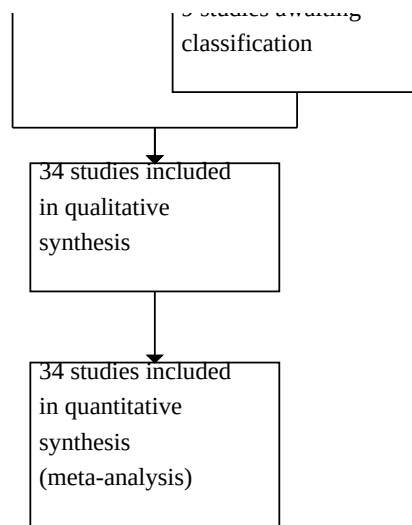


Figure 1. (Continued)



Results from the updated search we carried out in July 2025 have not yet been fully incorporated into the review. We listed 22 relevant records (which are included in the totals above) as ongoing studies (n = 13) or studies awaiting classification (n = 9).

Included studies

In this review, we have included 34 studies, with a total of 37,859 participants (Aditianingsih 2017 [78]; Allen 2016 [79]; Anantasit 2020 [80]; Balamuth 2019 [81]; Choosakul 2018 [82]; De-Madaira 2018 [83]; Dung 1999 [84]; Finfer 2022; Golla 2022 [85]; Hasman 2012 [86]; Hassan 2017 [87]; Mahajan 2012 [88]; Mahler 2011 [89]; Naseem 2020 [90]; Ngo 2001 [91]; Raman 2023 [92]; Ramanan 2021 [93]; Ratanarat 2017 [94]; Reddy 2014 [95]; Sankar 2023; Semler 2016 [96]; Semler 2018 [97]; Shaikh 2022 [98]; Singhal 2022 [99]; Van Zyl 2012 [100]; Vasudevan 2013 [101]; Verma 2016 [102]; Viaene 2014 [103]; Williams 2020 [104, 105]; Wu 2011; Young 2014 [38, 106, 107]; Young 2015 [43, 108]; Yu 2022 [109]; Zampieri 2021). Thirteen of the studies are new in this update (Anantasit 2020; Balamuth 2019; Finfer 2022; Golla 2022; Naseem 2020; Raman 2023; Ramanan 2021; Sankar 2023; Shaikh 2022; Singhal 2022; Williams 2020; Yu 2022; Zampieri 2021).

The details of the individual included studies are provided in [Table 1](#) and [Supplementary material 2](#).

Participants

Twenty-two of the included studies were conducted with adult participants, and 12 were conducted with child participants (Allen 2016; Anantasit 2020; Balamuth 2019; Dung 1999; Mahajan 2012; Naseem 2020; Ngo 2001; Raman 2023; Sankar 2023; Shaikh 2022; Singhal 2022; Williams 2020). All studies enrolled critically ill participants: six studies, diabetic ketoacidosis (Aditianingsih 2017; Mahler 2011; Ramanan 2021; Singhal 2022; Van Zyl 2012; Williams 2020); five, acute pancreatitis (Choosakul 2018; De-Madaira 2018; Reddy 2014; Vasudevan 2013; Wu 2011); five, severe dehydration (Allen 2016; Hasman 2012; Mahajan 2012; Naseem 2020; Shaikh 2022); four, sepsis or septic shock (Anantasit 2020; Balamuth 2019; Golla 2022; Sankar 2023); three, severe trauma (Hassan 2017; Young

2014; Yu 2022); and two, dengue shock syndrome (Dung 1999; Ngo 2001). The remaining nine studies involved mixed populations (Finfer 2022; Raman 2023; Ratanarat 2017; Semler 2016; Semler 2018; Verma 2016; Viaene 2014; Young 2015; Zampieri 2021).

Interventions

1. Fourteen studies administered Ringer's lactate (Balamuth 2019; Choosakul 2018; De-Madaira 2018; Dung 1999; Golla 2022; Mahajan 2012; Naseem 2020; Ngo 2001; Reddy 2014; Shaikh 2022; Singhal 2022; Vasudevan 2013; Van Zyl 2012; Wu 2011).
2. Ten studies used Plasma-Lyte A (Allen 2016; Finfer 2022; Mahler 2011; Ramanan 2021; Sankar 2023; Verma 2016; Williams 2020; Young 2014; Young 2015; Zampieri 2021).
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 study used Ringerfundin (Aditianingsih 2017).
7. One trial administered Ringer's acetate (Anantasit 2020).
8. One trial used sodium bicarbonated Ringer's (Yu 2022).
9. One trial administered either gluconate/acetate-buffered solution or lactate-buffered solution (Raman 2023).

Outcomes

Most of the included studies provided critical outcomes data. Overall (in-hospital) mortality data were reported by 23 studies (Aditianingsih 2017; Allen 2016; Anantasit 2020; Balamuth 2019; Choosakul 2018; De-Madaira 2018; Dung 1999; Finfer 2022; Golla 2022; Mahajan 2012; Ngo 2001; Ramanan 2021; Sankar 2023; Semler 2016; Semler 2018; Van Zyl 2012; Verma 2016; Williams 2020; Wu 2011; Young 2014; Young 2015; Yu 2022; Zampieri 2021). Acute renal injury data were reported by 17 studies (Aditianingsih 2017; Anantasit 2020; Balamuth 2019; Choosakul 2018; Golla 2022; Raman 2023; Ratanarat 2017; Sankar 2023; Semler 2016; Semler

2018; Singhal 2022; Verma 2016; Williams 2020; Wu 2011; Young 2014; Young 2015; Zampieri 2021). Our important outcomes were reported in a limited and heterogeneous manner in the included studies. For more details, see [Table 1](#).

Settings

Trials were performed in 16 countries: Belgium (Viaene 2014), Brazil (Zampieri 2021), Canada (Allen 2016), China (Yu 2022), India (Golla 2022; Mahajan 2012; Naseem 2020; Sankar 2023; Singhal 2022; Reddy 2014; Vasudevan 2013; Williams 2020), Indonesia (Aditiansih 2017), Malaysia (Hassan 2017), New Zealand and Australia (Finfer 2022; Raman 2023; Ramanan 2021; Verma 2016; Young 2015), Pakistan (Shaikh 2022), South Africa (Van Zyl 2012), Spain (De-Madaira 2018), Thailand (Anantasit 2020; Choosakul 2018; Ratanarat 2017), Turkey (Hasman 2012), USA (Allen 2016; Balamuth 2019; Mahler 2011; Semler 2016; Semler 2018; Wu 2011; Young 2014), and Vietnam (Dung 1999; Ngo 2001).

Nearly two-thirds of the studies ($n = 20$) were conducted in low- and middle-income countries (Brazil, China, India, Indonesia, Malaysia, Pakistan, South Africa, Thailand, Turkey, and Vietnam), and around one third ($n = 14$) were conducted in high-income countries (Australia, Belgium, Canada, New Zealand, Spain, and USA).

Study designs

Nine trials were multicentre studies (Allen 2016; Finfer 2022; Ramanan 2021; Sankar 2023; Semler 2018; Verma 2016; Wu 2011; Young 2015; Zampieri 2021). Most of the included trials were parallel studies, and four used a clustered multiple-cross-over design (Ramanan 2021; 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 (2x2) factorial design (Wu 2011).

Most of the included trials had medium sample sizes, enrolling between 22 and 230 participants. Two RCTs with 26,854 participants contributed more than 70% of the total sample (Semler 2018; Zampieri 2021).

Financial sponsorship

Financial sponsorship was provided by non-pharmaceutical-industry sources in most of the studies. One trial was supported by the pharmaceutical industry (Allen 2016), and four were supported by mixed funding (Finfer 2022; Verma 2016; Young 2015; Zampieri 2021). Nine studies did not report the sponsorship source (Aditiansih 2017; Hasman 2012; Mahler 2011; Naseem 2020; Reddy 2014; Shaikh 2022; Singhal 2022; Vasudevan 2013; Viaene 2014).

Contact with study authors

We contacted the study authors for further information. Four authors of the included studies responded: Dr De-Madaira provided the full-text publication (De-Madaira 2018); Dr Semler provided additional methodological details regarding the characteristics of clusters; Dr Aditiansih confirmed the data related to in-hospital mortality; and Dr. Young provided additional information. We contacted 14 other study authors regarding methodology and outcomes, but they did not respond.

Studies awaiting classification

We identified nine potentially relevant studies that await classification. The characteristics of these studies are summarised in [Supplementary material 4](#).

Ongoing studies

We found 38 ongoing trials in registries of clinical trials (Bhavani 2024 [110]; ChiCTR2000028952; ChiCTR2000040777; ChiCTR2100042334; ChiCTR2100044432; ChiCTR2100053514; ChiCTR2200059980; ChiCTR2300072358; CTRI/2018/02/011929; CTRI/2018/03/012372; CTRI/2018/05/014042; CTRI/2020/10/028620; CTRI/2020/11/029131; CTRI/2020/12/029450; CTRI/2021/04/033284; CTRI/2022/09/045580; CTRI/2022/12/048504; CTRI/2023/08/056814; CTRI/2023/11/060213; CTRI/2024/04/066542; CTRI/2024/06/068479; CTRI/2025/02/081031; IRCT20210201050199N2; NCT03528213; NCT03630224; NCT04043598; NCT04102371; NCT04365010; NCT04507672; NCT04621981; NCT05752279; NCT05869565; NCT06076590; NCT06374823; NCT06399510; NCT06541535; NCT06953674; Ramanan 2025 [111]). We summarised the characteristics of these studies in [Supplementary material 5](#).

Excluded studies

We excluded 68 studies in total because they did not fulfil our inclusion criteria. Fourteen were listed as exclusions in the previous review (Benoit 2016 [112]; Chen 2004 [113]; Cho 2007 [114]; Crivits 2016 [115]; Dybvik 1995 [116]; Fang 2008 [117]; Galas 2009 [118]; Kartha 2017 [119]; Martin 2018 [120]; Omar 2018 [121]; Rainier-Pope 1962 [122]; Roquilly 2013 [123]; Rowell 2016 [124]; Yung 2017 [125]). We excluded 54 studies after our new search (Agarwal 2022 [126]; Bedi 2019 [127]; ChiCTR2100045044 2021 [128]; Collins 2020 [129]; CTIS2024-511229-79-00 [130]; CTIS2024-511513-37-00 [131]; CTRI/2020/02/023411 2020 [132]; CTRI/2021/08/035924 2021 [133]; CTRI/2024/10/074986 [134]; CTRI/2024/12/077863 [135]; Farrel 2024 [136]; Farrell 2018 [137]; Farrell 2022 [138]; Guilabert 2024 [139]; Hayes 2022 [140]; Hizli 2023 [141]; IRCT20181105041562N1 2018 [142]; Kayhan 2021 [143]; KCT0007422 2022 [144]; Kunupakan 2018 [145]; Lee 2020 [146]; McIntyre 2018 [147]; McIntyre 2023 [148]; NCT03530046 2018 [149]; NCT03563378 2018 [150]; NCT03642769 2018 [151]; NCT03685214 2018 [152]; NCT04512950 2020 [153]; NCT04688645 2020 [154]; NCT04926740 2021 [155]; NCT05781243 2023 [156]; NCT05834257 2023 [157]; PACTR201804003190373 2018 [158]; Papisotiriou 2020 [159]; Pfortmueller 2017 [160]; Pfortmueller 2018 [161]; Pourfakhr 2020 [162]; Radovan 2022 [163]; Saini 2021 [164]; Shephali 2022 [165]; Singhal 2024 [166]; Smith 2014 [167]; Takia 2021 [168]; Trepatchayakorn 2021 [169]; Trifi 2025 [170]; Weinberg 2017 [171]; Weinberg 2021 [172]; Woo 2022 [173]; Wu 2022 [174]; Yan 2023 [175]; Yan 2024 [176]; Ye 2021 [177]; Yeoh 2019 [178]; Zhang 2018 [179]). Our reasons for exclusion were as follows: we excluded six studies for ineligible study designs; two studies for ineligible settings; 34 studies for ineligible participant populations; three studies for ineligible interventions; seven studies for ineligible comparators; and two studies for having unknown status and no response from the author. Reasons for the exclusion of each study are outlined in [Supplementary material 3](#).

Risk of bias in included studies

Details of the risk of bias assessments are available in [Supplementary material 2](#). [Figure 2](#) and [Figure 3](#) display the risk of bias summary and the risk of bias graph, respectively.

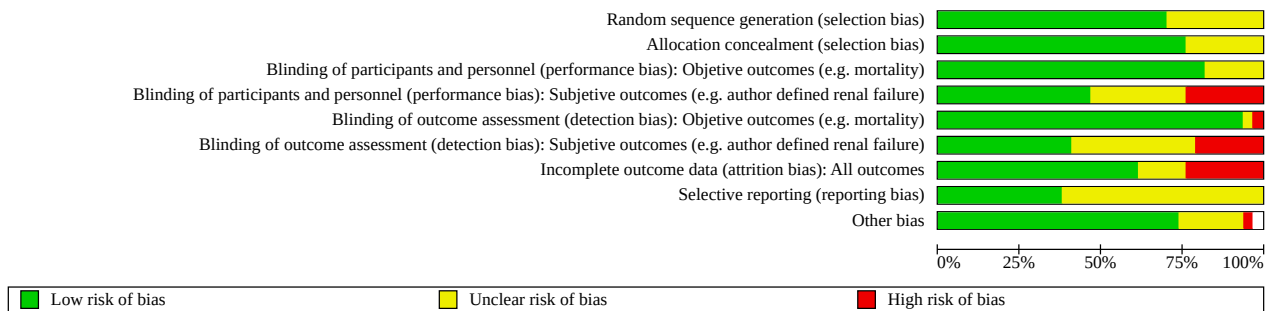
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

	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): All outcomes	Selective reporting (reporting bias)	Other bias
Aditianingsih 2017	?	+	?	?	+	?	+	?	?
Allen 2016	+	+	+	+	+	+	-	+	-
Anantasit 2020	+	+	+	+	+	+	+	?	+
Balamuth 2019	+	+	+	-	-	-	+	?	+
Choosakul 2018	+	+	?	?	+	?	+	+	+
De-Madaira 2018	+	+	+	+	+	+	?	?	+
Dung 1999	+	+	+	+	+	+	+	?	+

Figure 2. (Continued)

Dung 1999	+	+	+	+	+	+	+	?	+
Finfer 2022	+	+	+	+	+	+	+	+	+
Golla 2022	+	+	+	-	+	-	+	?	+
Hasman 2012	+	+	+	+	+	?	+	?	+
Hassan 2017	+	+	?	?	+	?	-	?	+
Mahajan 2012	+	+	+	+	+	+	+	+	+
Mahler 2011	+	+	+	+	+	?	-	?	?
Naseem 2020	?	+	+	?	+	?	+	?	+
Ngo 2001	+	+	+	+	+	?	-	?	+
Raman 2023	+	?	+	-	+	-	-	+	+
Ramanan 2021	+	+	+	-	+	-	+	?	+
Ratanarat 2017	?	?	+	-	?	?	?	?	+
Reddy 2014	?	?	?	?	+	?	?	?	?
Sankar 2023	+	+	+	+	+	+	+	+	+
Semler 2016	+	+	+	-	+	-	+	+	+
Semler 2018	?	+	+	-	+	-	+	+	+
Shaikh 2022	?	?	+	?	+	?	+	?	?
Singhal 2022	?	?	+	?	+	?	+	?	?
Van Zyl 2012	+	+	+	+	+	+	-	?	+
Vasudevan 2013	?	?	?	?	+	?	?	?	?
Verma 2016	+	+	+	+	+	+	-	+	+
Viaene 2014	?	?	?	?	+	?	?	?	?
Williams 2020	+	+	+	+	+	+	+	?	+
Wu 2011	+	+	+	-	+	-	+	+	+
Young 2014	+	+	+	+	+	+	-	+	+
Young 2015	+	+	+	+	+	+	+	+	+
Yu 2022	?	?	+	?	+	+	+	?	+
Zampieri 2021	+	+	+	+	+	+	+	+	+

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



To be included, the studies had to be randomised controlled trials. Most studies described their randomisation and allocation concealment methods. The most frequently used method was web-based randomisation. Because of this, we rated most studies at low risk of bias. Seven studies did not provide any information about the method used for randomisation nor allocation concealment (Ratanarat 2017; Reddy 2014; Shaikh 2022; Singhal 2022; Vasudevan 2013; Viaene 2014; Yu 2022). We judged those studies to have an unclear risk of selection bias.

Eight of the studies were open-label; 14 studies used participant-, personnel-, and assessor-blinding; and we could not assess the blinding status of participants, personnel, or assessors in 12 trials. We distinguished between objective outcomes (e.g. overall in-hospital mortality) and subjective outcomes (e.g. acute renal injury defined by study authors) in evaluating detection bias. Regarding overall in-hospital mortality, we judged 20 studies as having a low risk of performance and detection bias (Allen 2016; Anantasit 2020; De-Madaira 2018; Dung 1999; Finfer 2022; Hasman 2012; Mahajan 2012; Mahler 2011; Ngo 2001; Ratanarat 2017; Sankar 2023; Semler 2016; Semler 2018; Van Zyl 2012; Verma 2016; Williams 2020; Wu 2011; Young 2014; Young 2015; Zampieri 2021). Concerning subjective outcomes, we assessed 13 studies as having a low risk of bias (Allen 2016; Anantasit 2020; De-Madaira 2018; Dung 1999; Finfer 2022; Mahajan 2012; Sankar 2023; Van Zyl 2012; Verma 2016; Williams 2020; Young 2014; Young 2015; Zampieri 2021); 13 others in which details on methods used for blinding assessors were not provided as having unclear risk; and as 8 studies were open-label, we categorised them as high risk.

Twenty-one studies performed their analyses using an intention-to-treat approach (Aditianingsih 2017; Anantasit 2020; Balamuth 2019; Choosakul 2018; Dung 1999; Finfer 2022; Golla 2022; Hasman 2012; Naseem 2020; Mahajan 2012; Ramanan 2021; Sankar 2023; Shaikh 2022; Singhal 2022; Semler 2016; Semler 2018; Williams 2020; Wu 2011; Young 2015; Yu 2022; Zampieri 2021). We judged three trials as having a 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 judged them as high risk. The remaining five trials did not provide enough information, and we classified them as unclear risk.

To assess reporting bias, we obtained information on published protocols or on clinical trial registers when they were available.

Eight studies published protocols, and we identified no reporting bias in them (Finfer 2022; Raman 2023; Sankar 2023; Semler 2016; Semler 2018; Verma 2016; Young 2015; Zampieri 2021). 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 21 studies did not provide information; we assessed them as having an unclear risk of reporting bias.

In our protocol [180], we prespecified the criteria we would use to assess funding bias (Supplementary material 10). Most of the studies provided information about funding, and we judged them as having a low risk of bias. Five studies received mixed funding through unrestricted grants from the companies involved (Finfer 2022; Raman 2023; Verma 2016; Young 2015; Zampieri 2021). We judged these trials as low risk of bias. One study stated no information about sponsorship sources, and its authors declared no conflicts of interest (Hasman 2012). We judged this study as having a low risk of bias. One study reported a company's source of funding without providing information about the role of the company (e.g. design or analysis) (Allen 2016). We judged it to have a high risk of bias, according to our prespecified criteria (Supplementary material 10). Seven studies did not provide information about study funding, and we judged them as having an unclear risk of bias (Aditianingsih 2017; Mahler 2011; Reddy 2014; Shaikh 2022; Singhal 2022; Vasudevan 2013; Viaene 2014).

We included four cluster-randomised, multiple-cross-over trials (Ramanan 2021; Semler 2016; Semler 2018; Young 2015). We judged all of them as having a low risk of recruitment bias, baseline imbalance between groups, loss of follow-up of clusters, non-comparability, and carry-over effect. Regarding the risk of bias by incorrect analyses, we judged three out of these four studies to be at low risk because authors applied adjustments for analyses at the individual-level analyses using multi-level models and generalised estimating equations (Ramanan 2021; Semler 2016; Semler 2018; Young 2015).

Synthesis of results

See [Summary of findings 1](#) for the main comparison of 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 that we had specified in [Outcome measures](#). For our critical outcomes,

we have divided each outcome section into three: 'Overall effect', 'Sensitivity analysis', and 'Subgroup analysis.'

We collected and analysed data from the 34 included studies (37,859 participants). The analysis and all data extracted from the studies are available in [Supplementary material 6](#); [Supplementary material 7](#).

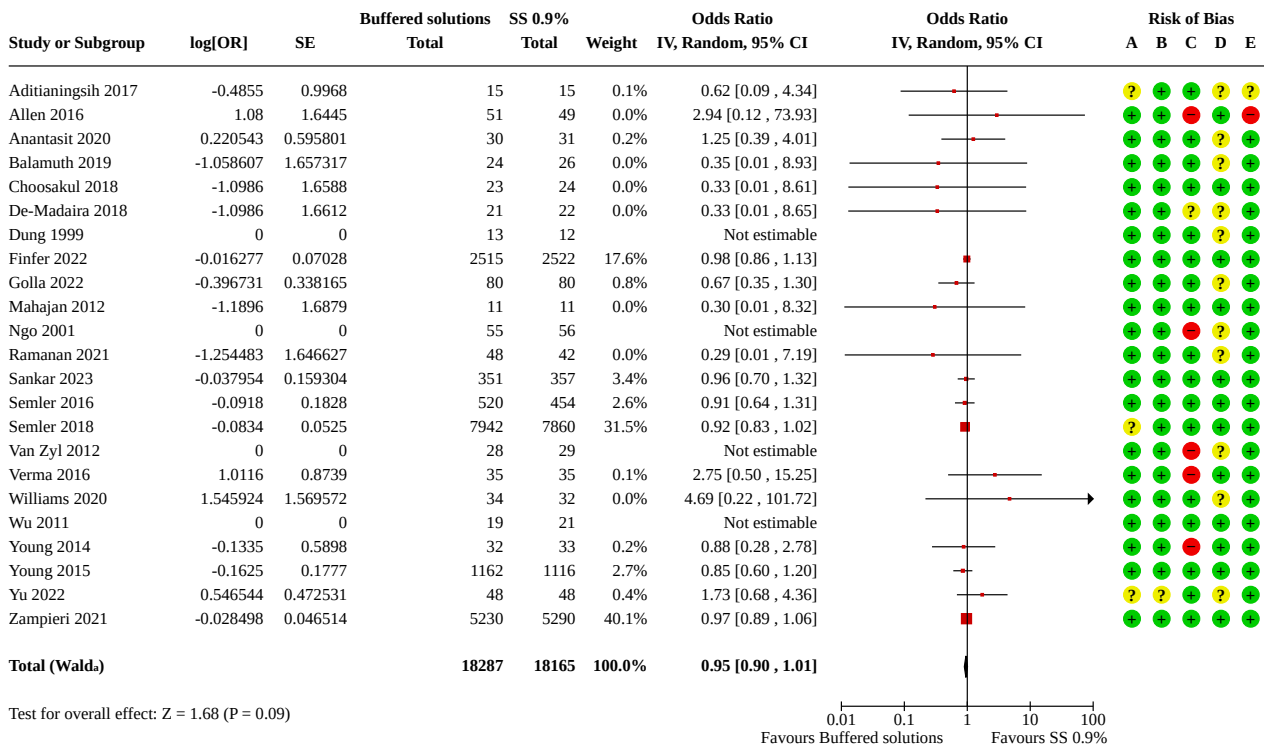
Critical outcomes

1. Overall (in-hospital) mortality

Twenty-three trials including 36,452 participants reported results for mortality (Aditjaningsih 2017; Allen 2016; Anantasit 2020;

Balamuth 2019; Choosakul 2018; De-Madaira 2018; Dung 1999; Finfer 2022; Golla 2022; Mahajan 2012; Ngo 2001; Ramanan 2021; Sankar 2023; Semler 2016; Semler 2018; Van Zyl 2012; Verma 2016; Williams 2020; Wu 2011; Young 2014; Young 2015; Yu 2022; Zampieri 2021). A total of 2569 of 18,287 (14%) participants in the buffered solutions groups died versus a total of 2672 of 18,165 (15%) participants in the 0.9% saline groups. Buffered solutions result in little to no difference in overall (in-hospital) mortality (OR 0.95, 95% CI 0.90 to 1.01; $I^2 = 0\%$; 23 studies, 36,452 participants; [Figure 4](#); high-certainty evidence). We did not observe any statistical heterogeneity amongst the studies ($P = 0.95$; $I^2 = 0\%$) (Analysis 1.1).

Figure 4.



Footnotes

aCI calculated by Wald-type method.
bTau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Incomplete outcome data (attrition bias)
- (D) Selective reporting (reporting bias)
- (E) Other bias

Sensitivity analysis

Use of the fixed-effect model revealed no differences between meta-analysis results (OR 0.95, 95% CI 0.90 to 1.01; $P = 0.09$).

We also performed a sensitivity analysis excluding nine studies at high risk of bias in the following domains: allocation features (random sequence generation and allocation concealment), levels of missing data, and blinding of outcome assessment (Allen 2016;

Balamuth 2019; Golla 2022; Ramanan 2021; Ngo 2001; Van Zyl 2012; Verma 2016; Young 2014; Yu 2022). The analysis had the same result as when we included only studies with low risk of bias (OR 0.95, 95% CI 0.90 to 1.01; $P = 0.09$).

Subgroup analysis**Intravenous buffered solution received**

Nine studies used Plasma-Lyte (OR 0.97, 95% CI 0.90 to 1.04; $I^2 = 0\%$; 18,934 participants; [Figure 5](#)); nine studies used Ringer's lactate (OR 0.61, 95% CI 0.33 to 1.12; $I^2 = 0\%$; 555 participants; [Figure 5](#)); one study used Ringerfundin (OR 0.62, 95% CI 0.09 to

4.34; 30 participants; [Figure 5](#)); one study used Ringer's acetate (OR 1.25, 95% CI 0.39 to 4.01; 61 participants; [Figure 5](#)), and one study used sodium bicarbonate Ringer's solution (OR 1.73, 95% CI 0.68 to 4.36; 96 participants; [Figure 5](#)). Two studies used Plasma-Lyte or Ringer's lactate (OR 0.92, 95% CI 0.83 to 1.01; $I^2 = 0\%$; 16,776 participants; [Figure 5](#)). Subgroup analysis comparing trials using different buffered solutions showed no difference between them in overall (in-hospital) mortality ($P = 0.44$) (Analysis 1.2).

Figure 5. Forest plot of comparison: 1 Buffered solutions vs SS 0.9% (saline solution), outcome: 1.1 Mortality.

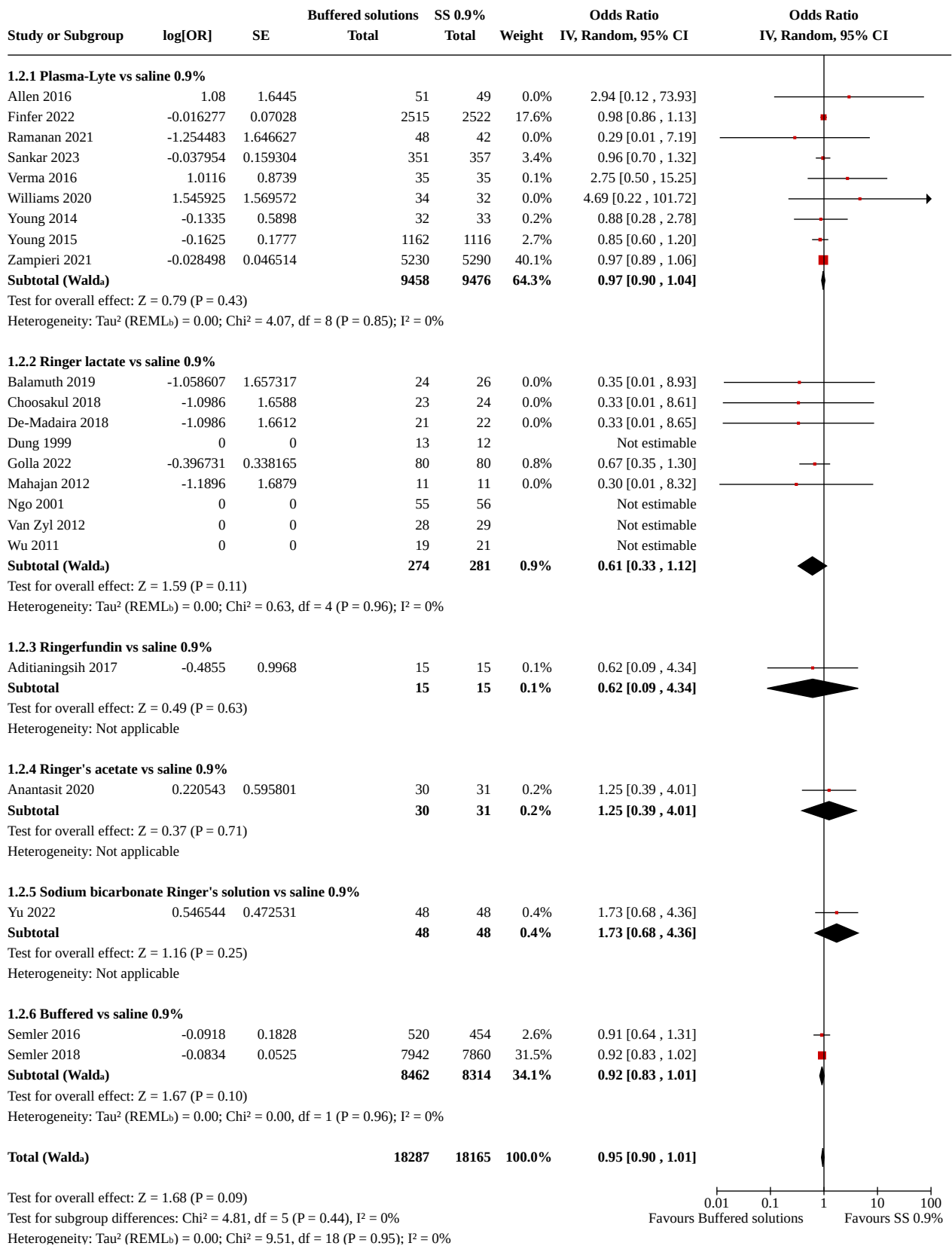


Figure 5. (Continued)

Test for subgroup differences: $\text{Chi}^2 = 4.81$, $\text{df} = 5$ ($P = 0.44$), $I^2 = 0\%$
Heterogeneity: Tau^2 (REML^b) = 0.00; $\text{Chi}^2 = 9.51$, $\text{df} = 18$ ($P = 0.95$); $I^2 = 0\%$

0.01 0.1 1 10 100
Favours Buffered solutions Favours SS 0.9%

Footnotes

^aCI calculated by Wald-type method.

^b Tau^2 calculated by Restricted Maximum-Likelihood method.

Age group

Eight studies involved children during the resuscitation (OR 0.99, 95% CI 0.73 to 1.33; $I^2 = 0\%$; 1143 participants). Fifteen studies were performed in the adult population (OR 0.95, 95% CI 0.90 to 1.01; $I^2 = 0\%$; 35,309 participants). Subgroup analysis showed no difference between age groups in overall (in-hospital) mortality ($P = 0.82$) (Analysis 1.3).

Condition

Six studies involved participants with sepsis or dengue (OR 0.91, 95% CI 0.69 to 1.20; $I^2 = 0\%$; 1115 participants). Two studies included trauma participants (OR 1.32, 95% CI 0.64 to 2.73; $I^2 = 0\%$; 161 participants). Six trials involved participants with primary hydroelectrolytic imbalance (OR 0.87, 95% CI 0.25 to 3.01; $I^2 = 0\%$; 365 participants). Subgroup analysis showed no difference between these subgroups in overall (in-hospital) mortality ($P = 0.82$) (Analysis 1.4).

Country income

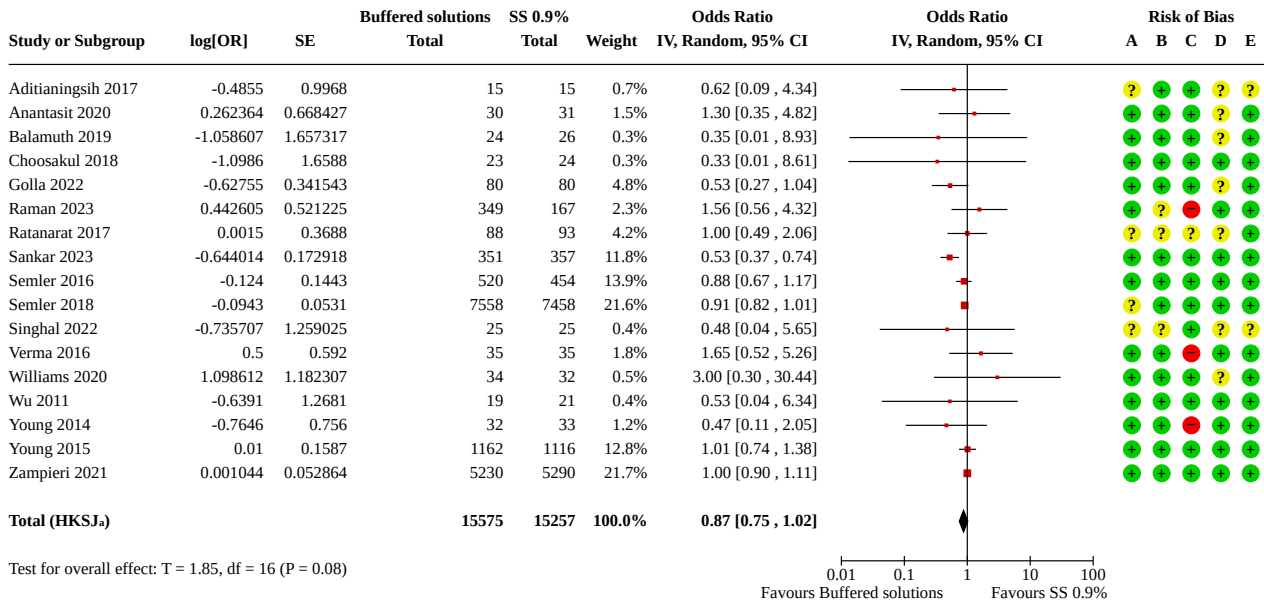
Twelve studies were conducted in low- and middle-income countries (OR 0.97, 95% CI 0.89 to 1.06; $I^2 = 0\%$; 11,903 participants).

Eleven studies were performed in high-income countries (OR 0.94, 95% CI 0.87 to 1.01; $I^2 = 0\%$; 24,549 participants). Subgroup analysis showed no difference between these income-level groups in overall (in-hospital) mortality ($P = 0.95$) (Analysis 1.5).

2. Acute renal injury during hospitalisation 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 17 studies involving 30,832 participants (Aditianingsih 2017; Anantasit 2020; Balamuth 2019; Choosakul 2018; Golla 2022; Raman 2023; Ratanarat 2017; Sankar 2023; Semler 2016; Semler 2018; Singhal 2022; Verma 2016; Williams 2020; Wu 2011; Young 2014; Young 2015; Zampieri 2021). A total of 2047 of 15,575 (13%) participants in the buffered solutions group developed acute renal injury versus a total of 2142 of 15257 (14%) participants in the 0.9% saline group. Buffered solutions likely result in little to no difference in the incidence of acute renal injury (OR 0.87, 95% CI 0.75 to 1.02; $I^2 = 51\%$; 17 studies, 30,832 participants; Figure 6; moderate-certainty evidence) (Analysis 1.6).

Figure 6.



Footnotes

^aCI calculated by Hartung-Knapp-Sidik-Jonkman (HKSJ) method.
^bTau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Incomplete outcome data (attrition bias)
- (D) Selective reporting (reporting bias)
- (E) Other bias

Sensitivity analysis

We performed sensitivity analysis excluding studies with a high risk of bias for the domains specified in the protocol (allocation features, blinding of outcome data, and incomplete outcome data) [180]. The results were similar whether we excluded one study with a high risk of bias for allocation features (Raman 2023) (OR 0.86, 95% CI 0.73 to 1.01; P = 0.06), excluded three studies with high risk of bias for blinding of outcome data (Balamuth 2019; Golla 2022; Raman 2023) (OR 0.89, 95% CI 0.76 to 1.04; P = 0.12), or excluded two studies with a high risk of bias for incomplete outcome data (Verma 2016; Young 2014) (OR 0.87, 95% CI 0.74 to 1.02; P = 0.08).

We also performed sensitivity analysis using the fixed-effect model. We found a slight difference between the result obtained with the random-effects model and that obtained with the fixed-effect model (OR 0.93, 95% CI 0.87 to 0.99; P < 0.001).

Subgroup analysis

We did not conduct our prespecified subgroup analysis by age due to the scarcity of studies reporting data on renal injury in the paediatric population.

Intravenous buffered solution received

Six studies used Plasma-Lyte as the buffer solution (OR 0.87, 95% CI 0.61 to 1.24; I² = 73%; 13,707 participants; Figure 7); five studies used Ringer's lactate (OR 0.51, 95% CI 0.28 to 0.94; I² = 0%; 347 participants; Figure 7); and two studies used Plasma-Lyte or Ringer's lactate (decided by the treating clinician) (OR 0.91, 95% CI 0.82 to 1.00; I² = 0%; 15,990 participants; Figure 7). Neither of these latter two studies reported outcomes according to the fluid type. Finally, one study used Ringerfundin (OR 0.62, 95% CI 0.09 to 4.34; Figure 7) and another Sterofundin (OR 1.00, 95% CI 0.49 to 2.06; Figure 7) as buffered solutions. Subgroup analysis comparing trials using different types of buffered solutions showed no difference between them in acute renal injury (P = 0.54) (Analysis 1.7).

Figure 7. Forest plot of comparison: 1 Buffered solutions vs SS 0.9% (saline solution), outcome: 1.3 Acute renal injury.

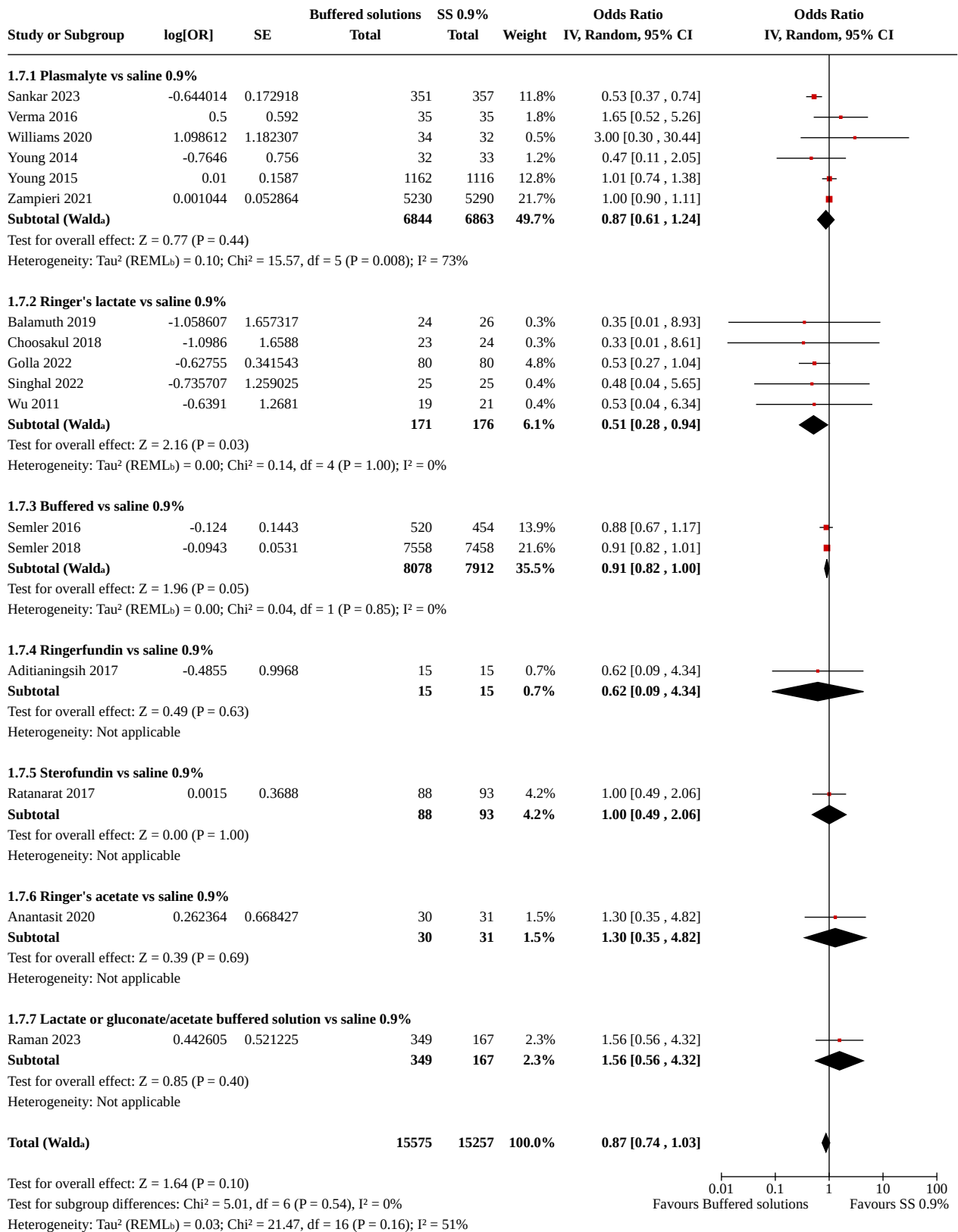


Figure 7. (Continued)

Heterogeneity: τ^2 (REML_b) = 0.03; $\chi^2 = 21.47$, $df = 16$ ($P = 0.16$); $I^2 = 51\%$

Footnotes

^aCI calculated by Wald-type method.

^b τ^2 calculated by Restricted Maximum-Likelihood method.

Condition

Four studies evaluated participants with sepsis or dengue (OR 0.55, 95% CI 0.41 to 0.74; $I^2 = 0\%$; 979 participants). One study included trauma participants (OR 0.47, 95% CI 0.11 to 2.05; I^2 not applicable; 65 participants). Three studies involved participants with primary hydroelectrolytic imbalance (OR 0.93, 95% CI 0.26 to 3.34; $I^2 = 0\%$; 146 participants). Subgroup analysis showed no difference between them in acute renal injury ($P = 0.71$) (Analysis 1.8).

Country income

Nine studies were carried out in low- and middle-income countries (OR 0.77, 95% CI 0.55 to 1.08; $I^2 = 51\%$; 11,823 participants). Eight studies were conducted in high-income countries (OR 0.92, 95% CI 0.84 to 1.01; $I^2 = 0\%$; 19,009 participants). Subgroup analysis showed no difference between them in acute renal injury ($P = 0.33$) (Analysis 1.9).

Important outcomes**1. Proportion 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 (Choosakul 2018; De-Madaira 2018; Dung 1999; Ngo 2001; Wu 2011). None of the studies found evidence of a difference in the effect of Ringer's lactate solutions in preventing organ system dysfunction compared with control at an alpha level of 0.05. Buffered solutions may have little to no effect on outcome, but the evidence is very uncertain (OR 0.83, 95% CI 0.41 to 1.70; $I^2 = 0\%$; 5 studies, 266 participants; Analysis 1.10; very low certainty evidence). We could not include Vasudevan 2013 in the analysis because the total sample and event rates were not reported correctly, and we were unable to get further information from the trial author.

2. Renal replacement therapy

This outcome was reported in 13 studies involving 20,216 participants (Anantasi 2020; Balamuth 2019; Finfer 2022; Golla 2022; Ramanan 2021; Sankar 2023; Williams 2020; Zampieri 2021; Ratanarat 2017; Semler 2016; Verma 2016; Wu 2011; Young 2014). Meta-analysis showed no evidence of a difference between the two intravenous fluid therapies (OR 0.93, 95% CI 0.84 to 1.02; $I^2 = 0\%$; 13 studies, 20,216 participants; Analysis 1.11).

3. Number of days (up to day 28) with no organ-support therapy**3.1 Ventilator-free days to day 28**

This outcome was reported in six studies involving 33,083 participants (Finfer 2022; Sankar 2023; Semler 2016; Semler 2018; Young 2014; Zampieri 2021). Meta-analysis showed no evidence of a difference between the two intravenous fluid therapies (MD 0.23, 95% CI 0.00 to 0.46; $I^2 = 0\%$; Analysis 1.12).

3.2 Vasopressor-free days to day 28

This outcome was reported in four studies involving 22,521 participants (Finfer 2022; Sankar 2023; Semler 2016; Semler 2018). Meta-analysis showed no evidence of a difference between the two intravenous fluid therapies (MD 0.30, 95% CI 0.04 to 0.56; $I^2 = 0\%$; Analysis 1.13).

4. 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)**4.1 Sodium**

Eleven studies reported sodium levels (Hasman 2012; Hassan 2017; Mahajan 2012; Sankar 2023; Semler 2016; Semler 2018; Shaikh 2022; Van Zyl 2012; Young 2014; Yu 2022; Williams 2020). We excluded three studies from the analysis. We excluded the studies by Semler and colleagues because they reported only the highest sodium levels during hospitalisation. We excluded Van Zyl 2012 and Williams 2020 because investigators did not report the standard deviations (SDs), CIs, or P values for the comparison with baseline. We included seven studies with a total of 1246 participants in meta-analysis (Analysis 1.14). The evidence is very uncertain about the effect of buffered solutions on sodium (MD -0.26, 95% CI -2.29 to 1.77; $I^2 = 79\%$; very low-certainty evidence).

4.2 Potassium

Nine studies reported potassium levels (Hasman 2012; Mahajan 2012; Sankar 2023; Shaikh 2022; 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 hospitalisation. 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, CI, or P values were not reported. We included six studies with 1086 participants in meta-analysis (Analysis 1.15). The evidence is very uncertain about the effect of buffered solutions on potassium (MD 0.11, 95% CI -0.04 to 0.25; $I^2 = 41\%$; very low-certainty evidence).

4.3 Chloride

Fifteen studies reported chloride levels (Allen 2016; Hasman 2012; Hassan 2017; Mahajan 2012; Mahler 2011; Raman 2023; Ramanan 2021; Sankar 2023; Semler 2016; Semler 2018; Shaikh 2022; Van Zyl 2012; Young 2014; Yu 2022; Williams 2020). We excluded four studies from the analysis. We excluded the two studies by Semler and colleagues because they reported only the highest chloride levels during hospitalisation. We excluded Van Zyl 2012 and Williams 2020 studies because the SDs, CIs, or P values were not reported. We included 11 studies with a total of 1981 participants in meta-

analysis (Analysis 1.16). The use of buffered solutions may reduce chloride levels (MD -2.39, 95% CI -3.77 to -1.00; $I^2 = 90\%$; low-certainty evidence).

4.4 pH

Eight studies reported this outcome (Hasman 2012; Hassan 2017; Sankar 2023; Shaikh 2022; Van Zyl 2012; Young 2014; Yu 2022; Williams 2020). We excluded two studies because the SDs, CIs, or P values were not reported (Van Zyl 2012; Williams 2020). We included six studies with a total of 1224 participants in meta-analysis (Analysis 1.17). The use of buffered solutions may increase pH (MD 0.06, 95% CI 0.02 to 0.10; $I^2 = 88\%$; low-certainty evidence).

4.5 Bicarbonate

Twelve studies reported the bicarbonate levels (Allen 2016; Hasman 2012; Hassan 2017; Mahajan 2012; Mahler 2011; Sankar 2023; Semler 2016; Semler 2018; Shaikh 2022; Young 2014; Yu 2022; Williams 2020). We excluded the two studies by Semler and colleagues because they reported only the highest bicarbonate levels during hospitalisation. We excluded one additional study because the SD, CI, or P values were not reported (Williams 2020). We included nine studies with a total of 1368 participants in meta-analysis (Analysis 1.18). The use of buffered solutions may increase bicarbonate levels (MD 2.16, 95% CI 1.06 to 3.25; $I^2 = 87\%$; low-certainty evidence).

4.6 Base excess

Eight studies with a total of 604 participants reported on base excess (Aditiansih 2017; Hassan 2017; Mahajan 2012; Verma 2016; Viaene 2014; Young 2014; Shaikh 2022; Yu 2022). There is substantial uncertainty about the effect of buffered solutions on base excess, as the confidence interval ranged from -11.43 to 7.37 (MD -2.03, 95% CI -11.43 to 7.37; $I^2 = 99\%$; Analysis 1.19).

4.7 Hyperchloremic acidosis

This outcome was reported in only one study (Anantasit 2020), which involved 61 participants. There is substantial uncertainty about the effect of buffered solutions on hyperchloremic acidosis as the confidence interval ranged from 0.15 to 1.16 (OR 0.41, 95% CI 0.15 to 1.16; Analysis 1.20).

5. Blood loss or transfusion requirement

5.1 Blood loss

None of the included trials reported this outcome.

5.2 Transfusion requirement

Two studies with a total of 1453 participants reported on blood products (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 evidence of a difference in the effect of buffered solutions on reducing the volume of blood products compared with the control at an alpha level of 0.05. Buffered solutions probably result in little to no difference in the requirement for blood products in critically ill patients compared to 0.9% saline (MD -17.53, 95% CI -44.52 to 9.46; $I^2 = 0\%$; 2 studies, 1453 participants; Analysis 1.21).

Two studies examined the transfusion requirement detailing the total units of red blood cells, plasma, and platelets (Young 2014; Young 2015). We did not include them in the meta-analysis because the mean and SD were not reported. They are listed in [Table 2](#).

6. Coagulation disturbances (expressed as thrombocytopenia or coagulopathy)

None of the included studies reported this outcome.

7. Total volume of intravenous fluids needed during resuscitation

Sixteen studies with a total of 25,604 participants reported on the total volume of fluids needed during resuscitation (Aditiansih 2017; Allen 2016; Balamuth 2019; De-Madaira 2018; Finfer 2022; Golla 2022; Mahajan 2012; Ngo 2001; Raman 2023; Ramanan 2021; Semler 2016; Semler 2018; Williams 2020; Young 2014; Young 2015; Yu 2022). The data were heterogeneous in the types of measures of effect used, identification of study fluid infused per arm of comparison, and timescales, and we were unable to get further information from the investigators. Therefore, we did not combine these studies in meta-analysis. Two studies found evidence of a difference in the total fluid requirement in favour of the intervention arm (De-Madaira 2018; Mahajan 2012). Eight studies reported a similar cumulative volume of fluids administered between groups (Aditiansih 2017; Allen 2016; Golla 2022; Ngo 2001; Ramanan 2021; Semler 2016; Young 2014; Yu 2022). One study found evidence of a difference in the total fluid requirement in favour of the control arm (Finfer 2022).

We did not subject these results to any further analysis, and this outcome is listed in [Table 2](#).

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

None of the included trials reported on quality of life.

9. Cost

A single study examined cost inputs [181], using data from participants enrolled in Young 2014. This study enrolled 65 participants and analysed costs for intravenous fluid acquisition, electrolyte acquisition, and nurse labour. Their cost-minimisation 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 presented it in [Table 2](#).

Equity assessment

We found no differences in the effect of buffered solution on overall (in-hospital) mortality and acute renal injury among critically ill patients in low- and middle-income countries compared to high-income countries (test for subgroup differences: $P = 0.95$ (Analysis 1.5) and $P = 0.33$ (Analysis 1.9), respectively).

Reporting biases

We performed a formal assessment of funnel plot asymmetry only for critical outcomes. We did not suspect reporting or publication bias upon visual assessment of the funnel plot for overall (in-hospital) mortality ([Figure 8](#)) and acute renal injury ([Figure 9](#)).

Figure 8. Funnel plot for critical outcome all-cause (in-hospital) mortality

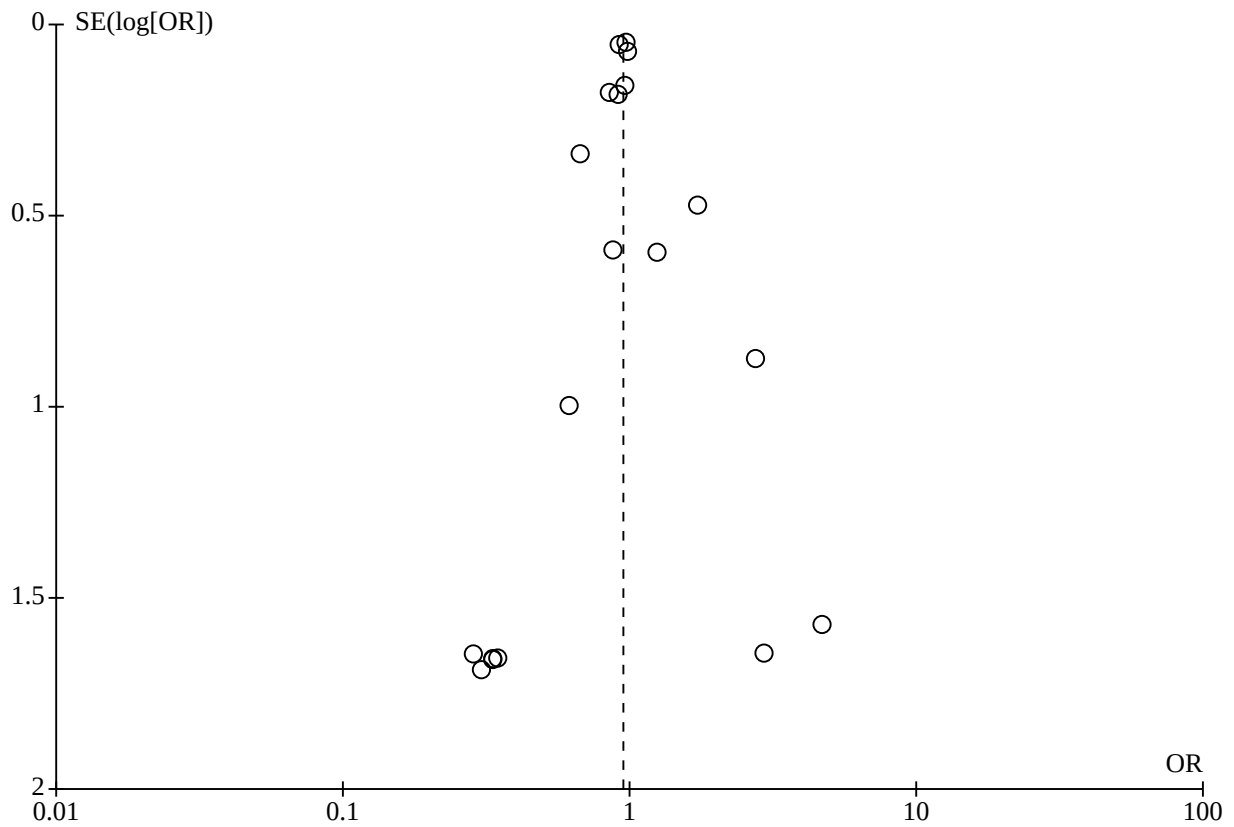
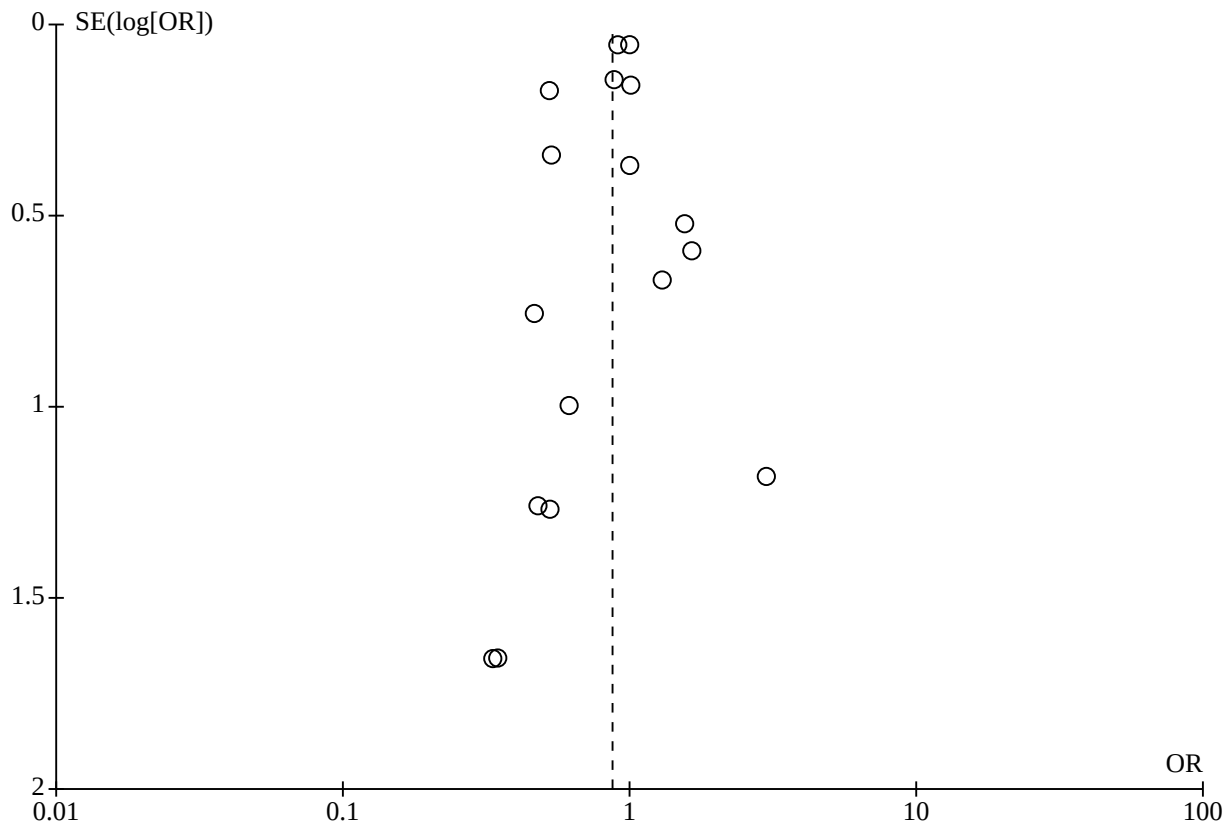


Figure 9. Funnel plot for critical outcome acute kidney injury



DISCUSSION

Summary of main results

This updated review included data from 34 studies with 37,859 non-surgical critically ill participants who received a buffered solution or 0.9% saline for resuscitation. Buffered solutions result in little to no difference in overall (in-hospital) mortality (high-certainty evidence) compared to saline. Buffered solutions probably result in little to no difference in the incidence of acute renal injury (moderate-certainty evidence). Buffered solutions may reduce chloride and may increase pH and bicarbonate compared to 0.9% saline (low-certainty evidence). We are very uncertain about the effect of buffered solutions versus 0.9% saline on organ system dysfunction, sodium, and potassium (very low certainty evidence).

Limitations of the evidence included in the review

Our certainty in the evidence ranges between high and very low. For one of our critical outcomes, mortality, our certainty is high, and for our other critical outcome, acute renal injury, it is moderate (Summary of findings 1). We assessed seven of the 23 trials included in the mortality outcome at high risk of bias, because, for most of them, we could not rule out selective reporting bias nor attrition bias (Figure 2). The results did not change after sensitivity analysis excluding high-risk studies; they represented only 1% of the overall weight. Relevant heterogeneity was not detected. Eleven trials did not report mortality data. We did not suspect reporting or publication bias based upon visual assessment of the funnel plot

(Figure 8). For these reasons, we considered the certainty of the evidence for mortality to be high (no downgrading).

In contrast, we assessed 11 of the 17 trials included in the acute renal injury outcome at high risk of bias (Figure 2). The high risk of bias was related to detection bias. We considered acute renal injury to be a subjective outcome, and several studies were not blinded (or whether they were blinded was unclear). The results did not change after sensitivity analysis excluding these studies. Only 17 out of 34 included studies reported acute renal injury data. We did not suspect reporting or publication bias based upon visual assessment of the funnel plot (Figure 9). We did not observe inconsistency, indirectness, or imprecision in the acute renal injury result. We therefore classified the certainty of evidence as moderate (i.e. we downgraded it one level for risk of bias).

For important outcomes, we assessed the certainty of evidence as low or very low (Summary of findings 1). Our reasons for these assessments included risk of bias (high in several trials) and imprecision (few participants and events in the trials that reported these outcomes). This level of certainty in the evidence means that further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Although this 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 of an updated Cochrane

review that has already addressed this question [25]. 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. Subgroup analyses across the different groups of critically ill patients revealed no effect other than one finding that buffered solutions may confer renal benefits in patients with sepsis (OR 0.55, 95% CI 0.41 to 0.74; $I^2 = 0\%$; 4 studies, 979 participants). Future trials should specifically evaluate whether the effects of buffered versus non-buffered solutions differ in this clinically important subgroup.

We believe that most of our conclusions are applicable to a general critical care setting. However, some subgroups of patients are not adequately represented in this systematic review, and they deserve additional comments. Twelve studies involved children (Allen 2016; Anantasit 2020; Balamuth 2019; Dung 1999; Mahajan 2012; Naseem 2020; Ngo 2001; Raman 2023; Sankar 2023; Shaikh 2022; Singhal 2022; Williams 2020). The subgroup analysis for mortality did not show differences between age groups ($P = 0.81$; $I^2 = 0\%$). Furthermore, participants included in these trials were less sick than participants included in the adult trials. Therefore, we should be very cautious in interpreting results from the paediatric studies and applying them to children generally. In addition, we consider that neurocritical patients need special attention. Buffered solutions tend to have lower osmolarity than 0.9% saline (Supplementary material 8). For this reason, several studies excluded neurocritical patients. In our review, we included only two studies involving neurocritical patients, which involved 66 and 483 participants with traumatic brain injury (Hassan 2017; Zampieri 2021). The authors of the first trial did not report any sign of harm. In contrast, Zampieri and colleagues found an association between the use of balanced fluids and mortality in this subgroup. We excluded one other study carried out on neurocritical patients because it included colloid solutions as a co-intervention (Roquilly 2013). In that trial, intracranial pressure was not different between study groups (MD 4 mmHg, 95% confidence interval (CI) -1 to 8; $P = 0.088$). Nevertheless, the published guidelines recommend the preferential use of 0.9% saline solution in patients with brain trauma [14].

The 34 trials included in this 2026 Cochrane review included a total of 37,859 participants. The included trials reported many outcomes but with great variation. Many trials did not report on the critical outcomes of mortality and acute renal injury. Reporting of important outcomes was highly variable in terms of time points, units, and measures. A potential confounder relates to the volumes administered, given that data on fluids received prior to randomisation (type and/or volume) were frequently not reported or were not amenable to pooling across studies. Although analysing a dose-response relationship would have been interesting, the paucity of data related to doses of the intervention precluded this kind of analysis. We should also highlight the variability of enrolment timing across studies (e.g. based on emergency department criteria, intensive care unit admission, or hospital arrival). Such variability in defining the acute phase and the intervention window may substantially influence both the patient's condition at baseline and the potential impact of fluid therapy, thus representing an important source of heterogeneity. Although variables such as ventricular function, dynamic fluid responsiveness, and detailed haemodynamic trends could act as confounders of the intervention, they pertain to a different clinical question not included in our predefined PICO (participants,

interventions, comparators, outcomes) and remain targets for future research that is specifically designed to investigate this. Finally, important outcomes such as costs and quality of life were not reported in most studies (cost was only reported for Young 2014). Expected adverse events related to electrolyte disturbances were reported in several studies; however, reporting was inconsistent in terms of definitions, thresholds, outcome measures, and timing of assessment, which limited comparability across studies.

Limitations of the review processes

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 requested additional data from authors of results published only in abstract form, and we did not receive an answer from four authors (Reddy 2014; Vasudevan 2013; Viaene 2014; Ramanan 2021). We assessed the risk of bias in the 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 (Aditioningsih 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 subgroup analysis using participant subsets. However, this was not conducted because the included studies did not present data on disease subsets. Moreover, the included studies were very variable with regard to the time points when outcomes were measured and reported. This is particularly relevant in studies with few participants in each arm, such as those with electrolyte disturbances. Chloride concentration, pH, and bicarbonate level analyses showed moderate heterogeneity (Analysis 1.16; Analysis 1.17; Analysis 1.18). 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 amongst different buffered preparations (Sterofundin > Ringer's lactate > Plasma-Lyte A).

We used the random-effects model as defined in our protocol [180]. Moreover, we included studies with more than two intervention groups (Dung 1999; Hasman 2012; Ngo 2001; Ramanan 2021). However, we felt confident about including them in meta-analyses because data were reported for each of the arms to which participants were randomised and contributed several independent comparisons (without intervention groups in common) in random-effects analyses (Analysis 1.2; Analysis 1.10) [54]. We also included in the review some studies in which participants in the crystalloid and buffered groups received additional buffered or crystalloid fluids, respectively (Naseem 2020; Semler 2016; Semler 2018; Shaikh 2022; 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 [180], and we had methodological challenges in converting them to the desired format.

Data on the total volume of intravenous fluids needed during resuscitation were not combined in our analyses owing to the fact that the outcome's distribution was skewed, and it was not possible to estimate means and standard deviations from median 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. There are 38 ongoing studies and 9 studies await classification that could be included in a future updated version of this review and may change some of our conclusions.

Agreements and disagreements with other studies or reviews

We identified six systematic reviews published between 2022 and 2024 that focused on critically ill patients who received buffered solution compared to 0.9% saline fluids. Four of them included adult patients [182, 183, 184, 185], and two of them were with a paediatric population [186, 187]. Our findings are in line with these other reviews. However, our review includes a larger number of studies, incorporating trials not captured in earlier reviews, and therefore provides a more comprehensive and up-to-date synthesis of the available evidence.

Chen and colleagues examined 18 randomised trials with 36,224 critically ill and perioperative adult patients who received either balanced crystalloids or 0.9% saline solution as resuscitation fluid. Thirteen of these trials were also included in our review. The pooled effect did not differ between groups for mortality using the Hartung-Knapp method or the DerSimonian-Laird method. Trial sequential analysis demonstrated that, with 80% power, the effect of balanced crystalloid is not larger than a 10% relative decrease in composite mortality compared with normal saline. Almost thirty thousand patients (28,918) were evaluated for the incidence of acute kidney injury, showing reduced incidence with balanced solutions. No evidence of a difference between balanced solutions and saline was observed in other outcomes: need for renal replacement therapy, hospital stay, ventilator-free days [182].

Dong and colleagues included data from seven trials in their meta-analysis (35,456 participants in total), all of which were included in our review [183]. The Dong review investigated the effect of balanced solutions on critically ill adult patients. There was no evidence of a difference between balanced crystalloid solutions and saline in mortality. There was also no evidence of a difference in moderate to severe acute kidney injury or new renal replacement therapy. The subgroup analysis with traumatic brain injury showed lower mortality in patients receiving normal saline [183].

The other two systematic reviews that involved adult patients employed Bayesian meta-analysis in addition to frequentist analysis [184, 185]. Hammond and colleagues included 13 studies (11 of them were also included in our review) comprising 35,884 critically ill adults (medical and surgical) who received resuscitative or maintenance fluids [184]. The pooled estimated risk ratio (RR) for 90-day mortality for balanced solutions in the six studies with low risk of bias was 0.96 (95% CI 0.91 to 1.01). The effect of fluid allocation on mortality was similar when all studies were pooled regardless of risk of bias, with an estimated RR of 0.93 (95% CI 0.76 to 1.15). The Bayesian meta-analysis for the studies at low risk of bias showed a RR of 0.96 (95% CI 0.88 to 1.04), with an 89.5% probability that balanced crystalloid solution was associated with lower mortality compared with saline. Regarding important

outcomes, no evidence of a difference was found for acute renal injury incidence, need for renal replacement therapy, ventilator-free days, and vasopressor-free days [184].

Zampieri and colleagues performed an individual patient meta-analysis with data from six RCTs including 34,685 critically ill adult patients randomised to receive either buffered or 0.9% saline solutions [185]. All six studies were also included in our review. No differences were found in terms of mortality when the frequentist model was employed. With Bayesian analysis, the posterior probability that balanced solutions reduced mortality was 0.895. They identified a higher risk of dying in traumatic brain injury patients who received balanced solutions. No differences were found in the use of new renal replacement therapy [185].

Lehr and colleagues included 13 studies (nine RCTs and four observational studies) with a total of 11,848 critically ill children (28 days to 18 years old) that investigated the effect of resuscitation with either balanced or unbalanced fluids [186]. Six of the nine RCTs were also included in our review. Lehr found higher bicarbonate levels and pH levels in children treated with balanced fluids. No differences were found in chloride serum level, acute renal injury, renal replacement therapy, or mortality [186].

Mhanna and colleagues examined six RCTs (four of them included in our analysis) comprising 8753 children with sepsis treated with 0.9% saline or balanced solution. They found that the overall mortality rate was lower in the balanced solution group, as was the incidence of acute renal injury [187].

Despite differences in the types of trials included, comparisons, and analytical approaches, our findings are broadly consistent with these reviews, showing no evidence of a difference in mortality between balanced solutions and 0.9% saline (high-certainty evidence), and no evidence of a difference in acute kidney injury (moderate-certainty evidence).

Recently, a new guideline regarding fluid therapy in adult critically ill patients has been published by the European Society of Intensive Care Medicine (ESICM) [14]. It was formulated by an international panel of clinical experts using GRADE methodology. Based mainly on the results of two of the meta-analyses mentioned above [184, 185], they suggest using balanced crystalloids rather than isotonic saline for volume expansion (conditional recommendation, low certainty of evidence). In addition, they recommend the use of 0.9% saline solution in patients with traumatic brain injury until new evidence emerges. They also acknowledge that in settings where balanced solutions are unavailable or limited, 0.9% saline is an acceptable alternative, and balanced solutions should be prioritised in patients who require large volumes of fluids and those with hyperchloraemia or acidosis.

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

High-certainty evidence shows that buffered solutions do not reduce overall (in-hospital) mortality amongst non-surgical critically ill patients. We do not expect any further research to change this conclusion. Moreover, buffered solutions probably

do not reduce the risk of acute renal injury (moderate-certainty evidence). The evidence is very uncertain about the effect of buffered solutions on organ system dysfunction, sodium, and potassium (very low certainty evidence). Buffered solutions may reduce chloride, and increase pH and bicarbonate plasma levels when compared to 0.9% saline (low-certainty evidence). There are 38 ongoing studies and nine studies awaiting classification. In the future, the findings of these studies may alter the conclusions of the review regarding acute renal injury, organ dysfunction, and electrolyte disturbances.

Equity-related implications for practice

We found no differences in the effect of buffered solutions on overall (in-hospital) mortality, or acute renal injury, amongst non-surgical critically ill patients in low- and middle-income countries compared to high-income countries.

Implications for research

The key research questions of whether buffered solutions reduce overall in-hospital mortality or acute renal injury in critically ill patients are not completely resolved. Regarding in-hospital mortality, our assessment of the certainty of evidence from included studies is high. We consider that, in the intensive care setting, it is unlikely that any single intervention will lead to a significant reduction in mortality. Concerning acute renal injury, we assessed the certainty of evidence as moderate. Therefore, we would advise that additional methodologically robust trials are conducted, with particular emphasis on improving blinding procedures (both of caregivers and outcome assessors).

In terms of other outcomes, the certainty of evidence related to electrolyte disturbances and incidence of organ system dysfunction is low to very low. Hence, we would advise that additional studies should be conducted to strengthen the evidence base. In future, trial authors should provide more consistent definitions, measurements, and reporting of secondary outcomes (e.g. acute renal injury, need for renal replacement therapy, or length of intensive care unit stay), to allow valid comparisons across studies and facilitate meta-analyses. Moreover, we were unable to conduct a meta-analysis of the total volume of intravenous solutions required during resuscitation according to the type of crystalloid, given the variation in the reporting of this outcome. Additional research is needed on blood loss and coagulopathy as there are insufficient data or no data at all. Future trials should ensure the incorporation of important outcomes for patients and caregivers, such as neurological sequelae (e.g. cerebral oedema), quality of life, post-intensive-care complications, and costs. Incorporating consumers' perspectives through consumer involvement in study design and in discussion of findings of research on resuscitation of critically ill patients can contribute meaningful insights in terms of values, preferences, and acceptability.

With regard to population, neurocritical patients were underrepresented in the included trials. Although 12 of the trials tested buffered solutions for children, the paediatric population is still underrepresented in the body of evidence. Well-designed trials are required in the future to assess the effects of buffered solutions in these groups. Additionally, females were underrepresented in the included trials, and sex-disaggregated data were not reported. Whether sex is a relevant prognostic factor for critically ill conditions is a question still to be resolved.

Concerning methods, future trials should improve some aspects such as blinding, inclusion criteria (critically ill patients, resuscitation), and outcome definitions (acute renal injury or volume of fluids). Trial authors are encouraged to report not only physiological outcomes but also mortality and renal function results. The use of only acute renal injury or mortality in future trials would be insufficient. Composite outcomes such as MAKE30 (major adverse kidney event within 30 days) have been proposed, but the results are difficult to interpret and could be flawed [188]. In addition, research should be designed in consensus on reporting outcomes (e.g. as in the Core Outcome Measures in Effectiveness Trials initiative – COMET initiative [189]). We would like to highlight that inconsistency in the measurement of outcomes hampers the evaluation of the effectiveness of interventions, especially in the case of synthesised evidence, and complicates the detection of reporting bias.

Equity-related implications for research

Further research is needed to evaluate the effects of buffered solutions in different places of residence (using the income level of a country as a proxy). Future studies should report data disaggregated by sex.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: [10.1002/14651858.CD012247.pub3](https://doi.org/10.1002/14651858.CD012247.pub3).

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Characteristics of studies awaiting classification

Supplementary material 5 Characteristics of ongoing studies

Supplementary material 6 Analyses

Supplementary material 7 Data package

Supplementary material 8 Types of fluids/solutions

Supplementary material 9 Differences between protocol and review

Supplementary material 10 Criteria for other bias (funding source)

Supplementary material 11 Data extraction form

ADDITIONAL INFORMATION

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Editorial and peer reviewer contributions

Cochrane Emergency and Critical Care supported the authors in the development of this systematic review.

The following people conducted the editorial process for this 2026 update.

- Sign-off Editor (final editorial decision): Professor Harald Herkner, Cochrane Emergency and Critical Care

- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Justin Mann, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, and supported the editorial team): Cynthia Stafford, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Laura MacDonald, Cochrane Central Production Service
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Providing general advice on the review: JAB

Performing previous work that was the foundation of the current review: FDM, LLG, JAB

Declarations of interest

Francisco de Paula Delgado Moya has no conflicts of interest to declare.

Alba Antequera has no conflicts of interest to declare.

Alfonso Muriel has previously collaborated with Astellas Pharma in delivering a conference. This activity was entirely unrelated to the subject matter of this review. The author declares that this collaboration has had no influence on the conduct, analysis, or conclusions of the present review. The author has no other conflicts of interest to declare.

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Registration and protocol

The current review is an update of the previous version. Both the original review and the update were conducted according to

What's new

the published protocol [1, 180]. The review was registered with PROSPERO (CRD42016045988).

Data, code and other materials

As part of the published Cochrane review, the following is made available for download for users of the Cochrane Library: full search strategies for each database ([Supplementary material 1](#)); characteristics of included, excluded, awaiting classification, or ongoing studies at the full text screen in the final review ([Supplementary material 2](#); [Supplementary material 3](#); [Supplementary material 4](#); [Supplementary material 5](#); respectively); analysis data, including overall estimates and settings, subgroup estimates, and individual data rows ([Supplementary material 6](#)); data from included studies ([Supplementary material 7](#)); types of fluids/solutions ([Supplementary material 8](#)); differences between protocol and review ([Supplementary material 9](#)); criteria for other bias ([Supplementary material 10](#)) and data extraction form ([Supplementary material 11](#)). Analyses and data management were conducted within Cochrane's authoring tool, RevMan, using the inbuilt computation methods.

Date	Event	Description
21 April 2026	New search has been performed	A new search was run and 13 new studies included
21 April 2026	New citation required and conclusions have changed	We upgraded the certainty of evidence for acute kidney injury to 'moderate' and identified critical gaps in underrepresented populations, such as paediatric and female patients.

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

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ADDITIONAL TABLES

Table 1. Overview of synthesis and included studies table (OSIS)

Study ID	Location/country	Study design	Sample size	Age group (paediatric or adults)	Population	Extracted outcomes
Intervention fluid: Plasma-Lyte						
Allen 2016	USA, Canada	RCT Parallel-group	100	Paediatric	Children ≥ 6 months to < 11 years with moderate to severe dehydration due to AGE	In-hospital mortality Electrolyte disturbances (changes in chloride, potassium, and bicarbonate concentrations between baseline and hour 4) Total volumes of intravenous fluids needed during resuscitation
Finfer 2022	Australia and New Zealand	RCT Parallel-group	5037	Adults	Critical care patients needing fluid resuscitation	In-hospital mortality Haemodynamic failure Need for renal replacement therapy Total volumes of intravenous fluids needed during resuscitation

Table 1. Overview of synthesis and included studies table (OSIS) (Continued)

Mahler 2011	USA	RCT Parallel-group	52	Adults	Patients with moderate to severe diabetic ketoacidosis	Electrolyte disturbances (change from baseline in bicarbonate and chloride concentrations during resuscitation)
Ramanan 2021	Australia	Cluster-RCT Cross-over	90	Adults	Patients with severe diabetic ketoacidosis	In-hospital mortality Need for renal replacement therapy Total volumes of intravenous fluids needed during resuscitation
Sankar 2023	India	RCT Parallel-group	708	Paediatric	Children 15 years of age or younger with septic shock	In-hospital mortality Acute renal injury Need for renal replacement therapy Number of days (up to day 28) with no organ-support therapy (vasopressor) Electrolyte disturbances (sodium, potassium, chloride, and bicarbonate after 72 hours)
Verma 2016	Australia	RCT Parallel-group	70	Adults	Critical care patients needing fluid resuscitation	In-hospital mortality Acute renal injury Need for renal replacement therapy Electrolyte disturbances (serum base excess)
Williams 2020	India	RCT Parallel-group	66	Paediatric	Children > 1 month to < 12 years with severe diabetic ketoacidosis	In-hospital mortality Acute renal injury Need for renal replacement therapy
Young 2014	USA	RCT Parallel-group	65	Adults	Patients with triage criteria for severe acute traumatic injury	In-hospital mortality Acute renal injury Number of days (up to day 28) with no organ-support therapy (ventilator) Electrolyte disturbances (change in pH, base excess, bicarbonate, chloride, potassium, and sodium from baseline to 24 hours) Total units of packed red blood cells, plasma, and platelets transfused from baseline to 24 hours Total volumes of intravenous fluids needed during resuscitation Average total cost
Young 2015	New Zealand	Cluster-RCT	2278	Adults	Critical care patients needing	In-hospital mortality

Table 1. Overview of synthesis and included studies table (OSIS) (Continued)

		Dou- ble-cross- over			fluid resuscita- tion	Acute renal injury Need for renal replacement therapy Electrolyte disturbances (acidaemia with pH < 7.20, hyperkalaemia with serum potassium > 6.5 mmol/L, delta creatinine) Total red blood units, fresh frozen plasma, platelets, or cryoprecipitate transfusion during the course of ICU admission Volume of intravenous fluid therapy during the course of ICU admission
Zampieri 2021	Brazil	RCT Paral- lel-group	11052	Adults	Critical care pa- tients needing fluid resuscita- tion	In-hospital mortality Acute renal injury Number of days (up to day 28) with no organ-support therapy (ventilator) Need for renal replacement therapy
Intervention fluid: Ringerfundin						
Adition-ingsih 2017	Indonesia	RCT Paral- lel-group	30	Adults	Patients with diabetic ke- toacidosis	In-hospital mortality Acute renal injury Electrolyte disturbances (pH and base excess from baseline to 48 hours) Total volumes of intravenous fluids needed during resuscitation
Intervention fluid: Ringer-Acetate						
Anantasit 2020	Thailand	RCT Paral- lel-group	61	Paediatric	Children from 1 month to 18 years of age with septic shock	In-hospital mortality Acute renal injury Need for renal replacement therapy Electrolyte disturbances (hyperchlo- raemic acidosis)
Intervention fluid: Ringer-Bicarbonate						
Yu 2022	China	RCT Paral- lel-group	96	Adults	Patients with traumatic haemorrhagic shock	In-hospital mortality Electrolyte disturbances (pH; base ex- cess; serum bicarbonate, sodium, and chloride concentrations) were mea- sured at baseline and at 24 hours. Total volumes of intravenous fluids needed during resuscitation
Intervention fluid: Ringer-Lactate						

Table 1. Overview of synthesis and included studies table (OSIS) *(Continued)*

Balamuth 2019	USA	RCT Parallel-group	50	Paediatric	Children > 6 months and < 18 years of age with septic shock	In-hospital mortality Acute renal injury Need for renal replacement therapy Total volumes of intravenous fluids needed during resuscitation
Choosakul 2018	Thailand	RCT Parallel-group	47	Adults	Patients with acute pancreatitis	In-hospital mortality Acute renal injury Organ failure at 48 hours Total volumes of intravenous fluids needed during resuscitation
De-Madaira 2018	Spain	RCT Parallel-group	43	Adults	Patients with acute pancreatitis	In-hospital mortality Persistent organ failure (defined by the Revised Atlanta Classification [190]) Electrolyte disturbances (pH and bicarbonate levels from baseline to 72 hours) Total volumes of intravenous fluids needed during resuscitation
Dung 1999	Vietnam	RCT Parallel-group	25	Paediatric	Children between the ages of 5 and 15 years who had dengue shock syndrome	In-hospital mortality Haemodynamic failure
Golla 2022	India	RCT Parallel-group	160	Adults	Patients with sepsis	In-hospital mortality Acute renal injury Need for renal replacement therapy
Mahajan 2012	India	RCT Parallel-group	22	Paediatric	Children from 1 month to 18 years with severe dehydration due to acute diarrhoea	In-hospital mortality Electrolyte disturbances (change from baseline chloride, bicarbonate, sodium, potassium, and base excess concentrations until discharge from hospital and change in pH from baseline until resolution of hypotension) Total volumes of intravenous fluids needed during resuscitation
Naseem 2020	India	RCT Parallel-group	72	Paediatric	Children from 1 year to 12 years with severe dehydration due to acute diarrhoea	Electrolyte disturbances (sodium, potassium, base excess, bicarbonate, and pH after correcting dehydration)

Table 1. Overview of synthesis and included studies table (OSIS) (Continued)

Ngo 2001	Vietnam	RCT Parallel group	230	Paediatric	Children aged from 1 to 15 years who were presented to the hospital with clinically diagnosed dengue haemorrhagic fever grade III or IV	Total volumes of intravenous fluids needed during resuscitation “Re-shock” rate, number (%) of patients
Reddy 2014	India	RCT Parallel-group	50	Adults	Patients with acute pancreatitis	No outcomes of interest reported
Shaikh 2022	Pakistan	RCT Parallel-group	220	Paediatric	Children aged between 1 and 5 years with acute watery diarrhoea and severe dehydration	Electrolyte disturbances (pH; base excess; serum bicarbonate, sodium, potassium, and chloride concentrations) measured at 6 hours
Singhal 2022	India	RCT Parallel-group	50	Paediatric	Children aged 6 months to 18 years with diabetic ketoacidosis	Acute renal injury
Van Zyl 2012	South Africa	RCT Parallel-group	57	Adults	Patients with severe diabetic ketoacidosis	In-hospital mortality Electrolyte disturbances (change in chloride, potassium, sodium, and calcium concentrations between baseline and time to resolution of acidosis) Time to resolution of diabetic ketoacidosis
Vasudevan 2013	India	RCT Parallel-group	50	Adults	Patients with acute pancreatitis	Incidence of organ failure during resuscitation in the clinical course of acute pancreatitis
Wu 2011	USA	RCT 4-arm (2x2), factorial design, parallel-group	40	Adults	Patients with acute pancreatitis	In-hospital mortality Acute renal injury Respiratory failure Haemodynamic failure until discharge Need for renal replacement therapy
Intervention fluid: Sterofundin						
Hassan 2017	Malaysia	RCT Parallel-group	66	Adults	Patients needing emergency neurosurgery	Electrolyte disturbances (pH, base excess, serum bicarbonate, sodium, potassium, and chloride concentra-

Table 1. Overview of synthesis and included studies table (OSIS) (Continued)

					due to severe TBI	tions) measured at baseline and at 24 hours
Ratanarat 2017	Thailand	RCT Parallel-group	181	Adults	Patients with shock (any cause except cardiogenic)	Acute renal injury Need for renal replacement therapy
Viaene 2014	Belgium	RCT Parallel-group	59	Adults	Critical care patients needing fluid resuscitation	Electrolyte disturbances (pH, chloride, sodium, and base excess difference between baseline and hour 4)
Several intervention fluids: Plasma-Lyte or Ringer's lactate						
Hasman 2012	Turkey	RCT Parallel-group	96	Adults	Patients with moderate and severe dehydration	Electrolyte disturbances (pH; serum bicarbonate, sodium, potassium, and chloride concentrations) measured at 60 and 120 minutes
Semler 2016	USA	Cluster-RCT Multiple-cross-over	974	Adults	Critical care patients	In-hospital mortality Acute renal injury Number of days (up to day 28) with no organ-support therapy (ventilator) Number of days (up to day 28) with no organ-support therapy (vasopressor) Need for renal replacement therapy Electrolyte disturbances (change in chloride, potassium, sodium, and bicarbonate concentrations) Blood transfusion requirement within 30 days after enrolment Total volumes of intravenous fluids needed during resuscitation
Semler 2018	USA	Cluster-RCT Multiple-cross-over	15,904	Adults	Critical care patients	In-hospital mortality Acute renal injury Number of days (up to day 28) with no organ-support therapy (ventilator) Number of days (up to day 28) with no organ-support therapy (vasopressor) Need for renal replacement therapy Rate of hypokalaemia Total volumes of intravenous fluids needed during resuscitation
Several intervention fluids: gluconate/acetate-buffered solution or lactate-buffered solution						

Table 1. Overview of synthesis and included studies table (OSIS) (Continued)

Raman 2023	Australia	RCT Parallel-group	516	Paediatric	Critical care children needing fluid resuscitation	Acute renal injury Electrolyte disturbances (chloride concentrations) Total volumes of intravenous fluids needed during resuscitation
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AGE: acute gastroenteritis; ICU: intensive care unit; RCT: randomised controlled trial; TBI: traumatic brain injury

Table 2. Outcome data not combined in meta-analysis

Study ID	Outcome	Participants	Results
Aditianingsih 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 Rigerfundin group was 6.23 (4.1 to 8.4) litres.
Allen 2016	Total volume of intravenous fluids needed during resuscitation	100	There was no evidence of differences in volume, duration of fluid administration, or fluid maintenance between groups.
De-Madaira 2018	Total volume of intravenous fluids needed during resuscitation	40	The median from 0 to 72 hours after randomisation 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	The 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	Participants in the saline and balanced groups received a similar total volume of intravenous crystalloid at 30 days (1424 (500 to 3377) mL versus 1617 (500 to 3628) mL); P = 0.40.
Semler 2018	Total volume of intravenous fluids needed during resuscitation	15,802	Participants in the saline group received a mean of 2171 (\pm 3942) mL of saline solution and 216 (\pm 1394) mL of buffered solution. Participants 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 evidence of a difference between buffered solution and placebo in the amount of fluid administered.
Young 2015	Total volume of intravenous fluids	2,278	Participants in the saline group received a mean of 2554 (\pm 2120) mL of saline solution and 1.8 (\pm 60) mL of buffered solution. Participants in the Plasma-Lyte group received a mean of

Table 2. Outcome data not combined in meta-analysis (Continued)

	needed during re-suscitation		0.5 (\pm 15) mL of saline solution and (2655 \pm 3052) mL of Plasma-Lyte solution.
Young 2014	Transfusion requirement	65	<p>16 (67%) participants in the saline group and 11 (50%) participants in the buffered solution group received pRBC transfusion (mean difference of 0.75, 95% CI 0.5 to 1.2).</p> <p>13 (54%) participants in the saline group and 11 (50%) participants in the buffered solution group received plasma transfusion (mean difference of 0.9, 95% CI 0.5 to 1.6).</p> <p>8 (33%) participants in the saline group and 10 (45%) participants in the buffered solution group received platelet transfusion (mean difference of 1.4, 95% CI 0.7 to 2.8).</p>
Young 2015	Transfusion requirement	2,278	<p>Packed red blood cells: 26 (9%) participants in the saline group received a mean of 45 (\pm 277) mL, and 29 (9%) participants in the buffered group received a mean of 39 (\pm 199) mL of packed red blood cells on study day 3.</p> <p>Fresh frozen plasma: 5 (2%) participants in the saline group received a mean of 12 (\pm 120) mL, and 3 (1%) participants in the buffered group received a mean of 8 (\pm 100) mL of fresh frozen plasma on study day 3.</p> <p>Platelets: 9 (3%) participants in the saline group received a mean of 17 (\pm 132) mL, and 6 (2%) participants in the buffered group received a mean of 8 (\pm 61) mL of platelets on study day 3.</p> <p>Cryoprecipitate: 1 (0%) participant in the saline group received a mean of 1 (\pm 17) mL, and 1 (1%) participant in the buffered group received a mean of 0 (\pm 5) mL of cryoprecipitate on study day 3.</p>
Young 2014	Cost	65	The cost-minimisation 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 not suitable for meta-analysis because of variation in the outcome measures reported, or being measured in a single study.

CI: confidence interval; IQR: interquartile range; mL: millilitres; mL/kg: millilitres per kilogram; P: probability; pRBC:packed red blood cells; vs: versus; USD: USA dollars