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Liberal versus conservative fluid therapy in adults and children with sepsis or septic shock (Review)

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[Intervention Review]

Liberal versus conservative fluid therapy in adults and children with sepsis or septic shock

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ABSTRACT

Background

Sepsis and septic shock are potentially life-threatening complications of infection that are associated with high morbidity and mortality in adults and children. Fluid therapy is regarded as a crucial intervention during initial treatment of sepsis. Whether conservative or liberal fluid therapy can improve clinical outcomes in patients with sepsis and septic shock remains unclear.

Objectives

To determine whether liberal versus conservative fluid therapy improves clinical outcomes in adults and children with initial sepsis and septic shock.

Search methods

We searched CENTRAL, MEDLINE, Embase, intensive and critical care conference abstracts, and ongoing clinical trials on 16 January 2018, and we contacted study authors to try to identify additional studies.

Selection criteria

We planned to include all randomized controlled trials (RCTs), quasi-RCTs, and cluster RCTs comparing liberal fluid therapy versus conservative fluid therapy for adults and children with sepsis or septic shock.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane. We assessed risk of bias of all included trials by using the Cochrane risk of bias tool. When appropriate, we calculated risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous outcomes, and mean differences (MDs) and 95% CIs for continuous outcomes. Our primary outcomes were all-cause mortality in hospital and at follow-up. Secondary outcomes included adverse events (organ dysfunction, allergic reaction, and neurological sequelae). We used GRADE to assess the quality of evidence for each outcome.

Main results

We identified no adult studies that met our selection criteria.

This review included three paediatric RCTs (N = 3402), but we were able to extract data from only two of the three trials (n = 3288). These trials were conducted in India (two studies) and Africa. Participants were children from one month to 12 years old with sepsis or septic

shock. All three included trials investigated liberal versus conservative fluid therapy, although definitions of liberal and conservative fluid therapy varied slightly across included studies. Results of the two trials included in the analyses show that liberal fluid therapy may increase risk of in-hospital mortality by 38% (2 studies; N = 3288; RR 1.38, 95% CI 1.07 to 1.77; number needed to treat for an additional harmful outcome (NNTH) = 34; moderate-quality evidence) and may increase risk of mortality at follow-up (at four weeks) by 39% (1 study; N = 3141; RR 1.39, 95% CI 1.11 to 1.74; NNTH = 29; high-quality evidence). The third study reported inconclusive results for in-hospital mortality (very low-quality evidence).

We are uncertain whether there is a difference in adverse events between liberal and conservative fluid therapy because the single-study results are imprecise (organ dysfunction - hepatomegaly: RR 0.95, 95% CI 0.60 to 1.50; n = 147; low-quality evidence; organ dysfunction - need for ventilation: RR 1.17, 95% CI 0.83 to 1.65; n = 147; low-quality evidence; allergic reaction: RR 1.74, 95% CI 0.36 to 8.37; n = 3141; low-quality evidence; neurological sequelae: RR 1.03, 95% CI 0.61 to 1.75; n = 2983; low-quality evidence). Results are also uncertain for other adverse events such as desaturation, tracheal intubation, increased intracranial pressure, and severe hypertension.

Authors' conclusions

No studies compared liberal versus conservative fluid therapy in adults. Low- to high-quality evidence indicates that liberal fluid therapy might increase mortality among children with sepsis or septic shock in hospital and at four-week follow-up. It is uncertain whether there are any differences in adverse events between liberal and conservative fluid therapy because the evidence is of low quality. Trials including adults, patients in other settings, and patients with a broader spectrum of pathogens are needed. Once published and assessed, three ongoing studies may alter the conclusions of this review.

PLAIN LANGUAGE SUMMARY

Different fluid therapy strategies for sepsis and septic shock

Review question

We aimed to investigate whether liberal fluid therapy can lead to more beneficial or harmful effects compared to conservative fluid therapy for adults and children with severe sepsis or septic shock. We mainly evaluated the different effects of these two interventions on risk of death and occurrence of adverse events.

Background

Sepsis and septic shock are complications of infection. Patients in the intensive care unit (ICU) are more likely than others to be affected by this condition. Once affected, patients experience organ dysfunction, which in some cases may lead to death. Fluid therapy is often used as an important intervention for initial treatment of sepsis in adults and children.

Results

We searched the electronic databases on 16 January 2018. We identified no adult trials that met our inclusion criteria. We included three trials involving 3402 children. We identified three 'ongoing' trials that have not yet been published. Pooled results from two trials (involving 3288 children) show that liberal fluid therapy may increase risk of in-hospital death by 38%, and risk of death at four-week follow-up by 39%. This means that for every 34 children receiving fluid therapy, one more in-hospital death will occur in the liberal fluid therapy group than in the conservative fluid therapy group. Similarly, at four-week follow-up, one more death will occur in the liberal fluid therapy group than in the conservative fluid therapy group for every 29 children receiving fluid therapy. One small study reported inconclusive results on risk of in-hospital death. We are uncertain whether there is a difference in adverse events (i.e. hepatomegaly, need for ventilation, allergic reaction, and neurological sequelae) between patients receiving liberal versus conservative fluid therapy.

One trial (involving 101 children) reported that conservative fluid therapy can shorten ICU stay and the duration of ventilation. However, we have very little confidence in this finding owing to the small sample size. We found no studies investigating adults with sepsis or septic shock.

Conclusion

Low- to high-quality evidence shows that liberal fluid therapy may increase the death rate for children with sepsis or septic shock. Except for this finding, we are uncertain about the effects of liberal versus conservative fluid therapy on the risk of adverse events. We are also uncertain about the effects of these two interventions for adults with sepsis or septic shock due to lack of data. Future trials focusing on adult sepsis or septic shock in other settings, with a wider range of pathogens, are expected. Once published and assessed, the three 'ongoing' studies identified may alter the conclusions of this review.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Liberal initial fluid versus conservative fluid therapy in adults and children with sepsis or septic shock

Patient or population: adults and children with initial sepsis and septic shock[a]
Settings: presentation to hospital emergency department or PICU
Intervention: liberal initial fluid therapy[b]
Comparison: conservative fluid therapy[c]

Outcomes		Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		Conservative fluid therapy	Liberal fluid therapy				
All-cause mortality	**All-cause mortality in hospital/ICU** Follow-up: 30 to 136.5 hours	**80 per 1000**	**110 per 1000** (85 to 141)	**RR 1.38** (1.07 to 1.77)	3288 (2 studies)	⊕⊕⊕⊖ **Moderate**[d]	
	All-cause mortality at follow-up Follow-up: 4 weeks	**87 per 1000**	**121 per 1000** (97 to 152)	**RR 1.39** (1.11 to 1.74)	3141 (1 study)	⊕⊕⊕⊕ **High**	
Adverse events	**Organ dysfunction - hepatomegaly** Follow-up: 1 hour	**342 per 1000**	**325 per 1000** (205 to 514)	**RR 0.95** (0.60 to 1.50)	147 (1 study)	⊕⊕⊖⊖ **Low**[e]	
	Organ dysfunction - need for ventilation Follow-up: 1 hour	**438 per 1000**	**513 per 1000** (364 to 723)	**RR 1.17** (0.83 to 1.65)	147 (1 study)	⊕⊕⊖⊖ **Low**[e]	
	Other - allergic reaction Follow-up: 48 hours	**2 per 1000**	**3 per 1000** (1 to 16)	**RR 1.74** (0.36 to 8.37)	3141 (1 study)	⊕⊕⊖⊖ **Low**[e]	
	Other - neurological sequelae	**20 per 1000**	**21 per 1000**	**RR 1.03**	2983 (1 study)	⊕⊕⊖⊖	

	Follow-up: 4 weeks	(12 to 35)	(0.61 to 1.75)	**Low**[e]

*The **corresponding risk** (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; ICU: intensive care unit; PICU: paediatric intensive care unit; RR: risk ratio.

GRADE Working Group grades of evidence.
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Only data from children were included in this analysis. Its application to resource-limited situations and the possible bias of data resources must be considered. All children received antibiotics, maintenance fluids, and supportive care according to standard guidelines.
[b]Maitland 2011 used intravenous maintenance fluids (20 to 40 mL/kg of 5% albumin solution or 0.9% saline solution), and Santhanam 2008 used 40 mL/kg of fluid over 15 minutes.
[c]Maitland 2011 used intravenous maintenance fluids (20 to 40 mL/kg, without bolus), and Santhanam 2008 used 20 mL/kg over 20 minutes up to a maximum of 60 mL/kg over 1 hour.
[d]Downgraded once for study limitation (high risk of attrition bias).
[e]Downgraded twice for imprecision due to wide 95% CIs, driven by small sample size or low event rates.

BACKGROUND

Sepsis and septic shock are potentially life-threatening complications of infection with high morbidity and mortality. Sepsis and septic shock are among the most common causes of death in non-coronary intensive care units (ICUs). Current management of septic shock includes initial resuscitation (first six hours), antibiotic therapy, administration of vasopressor agents (Gamper 2016; Rhodes 2016), and use of steroids in selected groups of patients (Annane 2003). Clinicians have tended to use liberal fluid such as fluid boluses for initial therapy for patients with sepsis. However, a multi-centre randomized controlled trial (RCT) suggested that conservative fluid (no bolus) decreased 48-hour and 28-day mortality compared to boluses of either 5% albumin or saline in children with severe febrile illness and impaired perfusion (Maitland 2011). Fluid therapy is an essential part of treatment for sepsis and septic shock. However, effects of liberal versus conservative fluid therapy in the initial phase of sepsis remain unclear.

Description of the condition

Sepsis is the systemic inflammatory response to infection. The definition of sepsis has changed over time. The 1991 consensus conference developed initial definitions of sepsis described as the presence or presumed presence of an infection accompanied by evidence of a systemic response, called the 'systemic inflammatory response syndrome' (Bone 1992). Pulmonary, gastrointestinal, genitourinary, and primary bloodstream infections account for the majority of infectious sources in patients with sepsis (Hodgin 2008). Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion (Bone 1992; Dellinger 2013). The exact mechanism by which sepsis produces multiple-organ dysfunction remains unknown, but it is thought to develop as the result of a dysregulated response of the immune system, which leads to systemic inflammation or an inflammatory response producing global tissue hypoxia and organ dysfunction (e.g. in the liver, lungs, heart, and kidneys). The ensuing sepsis can progress to multiple-organ failure and septic shock. Septic shock, which is defined as sepsis-induced hypotension that persists after adequate fluid resuscitation (Bone 1992; Dellinger 2008a), typically occurs in elderly patients; very young children; and patients with illnesses such as diabetes, cancer, or human immunodeficiency virus (HIV), or in those recovering from recent surgical or medical procedures. Septic shock is becoming an increasing health burden as incidence rates have increased owing to multi-resistant strains (Annane 2003). Patients with severe febrile illness and impaired perfusion were also eligible and are included in this review.

The epidemiology of sepsis and septic shock is poorly understood because population-based country-specific prospective cohort studies have been few. Historically, the diagnosis of sepsis and septic shock was based on hospital discharge records - not on the current consensus definition that was developed in 2001 (Levy 2003). The incidence of severe sepsis and septic shock in the European Union has been estimated at 90.4 cases per 100,000 population (Davies 2001). The incidence in Australia and New Zealand is estimated to be 77 per 100,000 (Finfer 2004), and in the USA, it is estimated to range from 81 in Martin 2003 to 300 in Angus 2001 per 100,000. It has been estimated that globally 1400 patients die each day as the result of sepsis and septic shock (Bone 1992). The population incidence rate was recently reported to be 288 cases of hospital-treated sepsis per 100,000 person-years (Fleischmann 2016). The incidence is increasing because of better recognition of sepsis and increasing numbers of morbid patients and multi-drug-resistant bugs. Most vulnerable are children younger than 12 months (Watson 2003), along with elderly patients, who have the highest incidence of sepsis and septic shock (Angus 2001).

The 1991 consensus conference developed initial definitions of sepsis. A 2001 task force expanded the list of diagnostic criteria but did not offer alternatives because supporting evidence was not available. Recently, the term 'sepsis' has been changed to 'sepsis-3', as defined in *JAMA* in 2016 (Singer 2016). According to this definition, sepsis is a life-threatening organ dysfunction (sequential (sepsis-related) organ failure assessment (SOFA) score ≥ 2 points) that is caused by a dysregulated host response to infection. Septic shock is defined as a subset of sepsis that is characterized by particularly profound circulatory, cellular, and metabolic abnormalities. Patients with septic shock can be clinically identified by the vasopressor requirement to maintain a mean arterial pressure ≥ 65 mmHg and a serum lactate level > 2 mmol/L (> 18 mg/dL) in the absence of hypovolaemia. However, we did not adopt these new definitions for sepsis and septic shock for this review because, on one hand, the new definition of sepsis was released post publication of the review protocol; and on the other hand, it was published in 2016, so very few studies have ever used this definition. We plan to adopt the new definitions for the next update of this review.

Description of the intervention

Fluid therapy is regarded as a crucial and effective intervention for initial treatment of children and adults with sepsis and septic shock. Fluid therapy is believed to improve clinical outcomes in patients with sepsis and septic shock. Fluid bolus therapy is widely adopted and is regarded as a key life-saving intervention in the management of sepsis. Its use is based mainly on expert opinion, as limited experimental evidence is available to guide decision-making.

The question of whether conservative or liberal fluid therapy can improve clinical outcomes in patients with sepsis and septic shock has not yet been resolved.

Conservative fluid therapy:

1. is defined for adults as no fluid bolus, titrated according to monitoring of heart rate, urine output, capillary refill, and level of consciousness (or total fluid amount less than that for liberal fluid therapy); and
2. is defined for children as no fluid bolus, titrated according to monitoring of heart rate, urine output, capillary refill, and level of consciousness (or total fluid amount less than that for liberal fluid therapy).

Liberal fluid therapy:

1. is defined for adults as fluid challenge ≥ 1000 mL of crystalloids or 300 to 500 mL of colloids over 30 minutes before titration (or total fluid amount greater than that for conservative fluid therapy) (Dellinger 2008b); and
2. is defined for children as a fluid bolus of 20 mL/kg of crystalloids over 5 to 10 minutes before titration (or total fluid amount greater than that for conservative fluid therapy) (Dellinger 2008b).

How the intervention might work

Critical care doctors continue to debate the benefits of conservative versus liberal fluid therapy for clinical outcomes in patients with sepsis and septic shock. Too little fluid may cause tissue hypoperfusion and may worsen a person's condition, but over-prescription of fluid can cause or exacerbate oedema in the lungs, heart, gastrointestinal tract, skin, brain, and other tissues, leading to organ failure or cerebral oedema and herniation. No consensus has emerged among clinicians on the quantity of fluid that patients should receive.

Why it is important to do this review

Healthcare professionals frequently use fluid bolus therapy; they presently regard it as a key life-saving intervention in the management of sepsis. We are conducting this systematic review to explore uncertainty arising from conflicting results reported by studies on this topic.

OBJECTIVES

To determine whether liberal versus conservative fluid therapy improves clinical outcomes in adults and children with initial sepsis and septic shock.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) and quasi-RCTs in adults and children with sepsis and septic shock comparing liberal versus conservative fluid therapy. We planned to include cluster RCTs.

Types of participants

We included studies in adults and children with severe sepsis and septic shock comparing liberal versus conservative fluid therapy. Severe sepsis is defined as sepsis complicated by acute organ dysfunction. Septic shock is complicated by hypotension that is refractory to fluid, or by hyperlactataemia (Bone 1992). As described in the Background section, we noticed that the definition of sepsis has been recently changed to one provided for 'sepsis-3', which was published in *JAMA* in 2016 (Singer 2016). However, authors of this review did not adopt the new definition of sepsis for reasons stated in the previous section. We adopted the definitions for sepsis and septic shock developed in 1991 and plan to use the new definition in the update of this review. Adults and children with severe febrile illness and impaired perfusion were also eligible, thus we included them in this review.

We accepted study authors' definitions of severe sepsis and septic shock.

We excluded neonatal sepsis studies (both early and late).

Types of interventions

We defined conservative fluid therapy as follows.

1. For adults: no fluid bolus, titrated per clinical monitoring of cardiac output, including heart rate, pulse pressure, central venous pressure, urine output, capillary refill, and level of consciousness (or total fluid amount less than that for liberal fluid therapy).
2. For children: no fluid bolus, titrated per clinical monitoring of cardiac output, including heart rate, pulse pressure, central venous pressure, urine output, capillary refill, and level of consciousness (or total fluid amount less than that for liberal fluid therapy).

We defined liberal fluid therapy as follows.

1. For adults: fluid bolus greater than 1000 mL of crystalloids or 300 to 500 mL of colloids over 30 minutes before titration (or total fluid amount more than that for conservative fluid therapy) (Dellinger 2008b).
2. For children: fluid bolus 20 mL/kg of crystalloids over five to 10 minutes before titration (or total fluid amount more than that for conservative fluid therapy) (Dellinger 2008b).

Types of outcome measures

Primary outcomes

1. All-cause mortality
   a. All-cause mortality in hospital/ICU
   b. All-cause mortality at follow-up

Secondary outcomes

1. Vasoactive agent-free days in patients alive within 28 days
2. Pulmonary oedema
3. Adverse events
   a. Organ dysfunction (renal failure; respiratory failure, need for mechanical ventilation; central nervous system (CNS) dysfunction)
   b. Other adverse events: any other adverse events
4. Duration of organ dysfunction
5. Length of ICU stay
6. Ventilator-free days in patients alive within 28 days

Search methods for identification of studies

Electronic searches

We identified RCTs through literature searching using systematic and sensitive search strategies as outlined in Chapter 6.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not apply restrictions to language or publication status. We searched the following databases for relevant trials.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 12).
2. MEDLINE (Ovid SP 1966 to 16 January 2018).
3. Embase (Ovid SP 1988 to 16 January 2018).

We developed a subject-specific search strategy for MEDLINE and used that as the basis for search strategies applied to the other databases listed. When appropriate, we expanded the search strategy using search terms for identifying RCTs. We have provided all search strategies in Appendix 1, Appendix 2, and Appendix 3.

Searching other resources

We scanned the reference lists and citations of included trials and of any relevant systematic reviews identified to look for further

references to additional trials. When necessary, we contacted trial authors for additional information.

We also searched intensive and critical care conference abstracts and ongoing clinical trials up to January 2018 (www.clinicaltrials.gov). We developed the search strategy in consultation with the Information Specialist.

Data collection and analysis

Selection of studies

Two review authors (DL, XL) independently inspected the titles and abstracts of all study citations identified by the search. We resolved disagreements by discussion with a third review author (HZ).

Data extraction and management

Two review authors (DL, XL) independently extracted qualitative and quantitative data from all included studies onto a standardized data extraction form (see Appendix 4). We subsequently entered these data and analysed them in Review Manager 5.3.3 (RevMan 2014). We resolved disagreements through discussion. If we had required any additional information, we would have contacted study authors.

Assessment of risk of bias in included studies

Two review authors (DL, WC) independently assessed the risk of bias of all included studies using the Cochrane risk of bias tool, as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The 'risk of bias tool' encourages consideration of a series of domains of bias, including how the sequence was generated, how allocation was concealed, integrity of blinding, completeness of outcome data, selective reporting, and other biases. It should be noted that for these fluid management interventions, performance bias is inevitable. We employed assessment guidelines stated in Chapter 8 of the*Cochrane Handbook for Systematic Reviews of Interventions* and rated each of the bias domains described above as 'low risk', 'unclear risk', or 'high risk'. We resolved disagreements by discussion.

Measures of treatment effect

Binary data

Service users and clinicians generally find risk ratios (RRs) easier to understand than odds ratios (ORs) (Grimes 2008). ORs are often misinterpreted as RRs (Deeks 2000).

Therefore, for binary outcomes, we calculated RRs with 95% confidence intervals (CIs) using the random-effects model. If meta-analysed data were significant and non-heterogeneous (e.g. I^2 statistic < 50%), we would have calculated the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH).

Continuous data

In future updates, for continuous data, we would have calculated mean differences (MDs) with 95% CIs. For final point data (e.g. endpoint scale-derived data), we planned to meta-analyse only normally distributed data (non-skewed) by applying the following rule for positive measurements: the standard deviation (SD) when multiplied by two has to be less than the mean (Altman 1996). Had we obtained any skewed data from studies, we planned to not show these data graphically, but rather to add them to 'additional tables' and briefly comment on them in the text.

Unit of analysis issues

We considered that the individual participants in each trial arm represented the unit of analysis. Therefore, we anticipated that all trials had a parallel-group design. Had we included any cluster randomized clinical trials, we would have sought statistical advice as to how to process clustering effects.

Dealing with missing data

We followed the guidelines stated in the *Cochrane Handbook for Systematic Reviews of Interventions* for dealing with missing data (Higgins 2011). We contacted the original investigators when we encountered missing data. When data were missing from trial reports, we assumed that participants lost to follow-up did not show improvement, and that those lost participants were included as part of an intention-to-treat (ITT) analysis when possible. We made explicit the assumptions of any methods used to deal with missing data, for example, that the data were assumed missing at random. We performed sensitivity analyses to assess how sensitive results were to reasonable changes in the assumptions made. In the Discussion section, we addressed the potential impact of missing data on review findings (Higgins 2011).

Assessment of heterogeneity

For statistical heterogeneity, we used the I^2 statistic. We would have interpreted an I^2 statistical estimate of 50% or greater as evidence of high levels of heterogeneity (Higgins 2003). We evaluated clinical heterogeneity in selected studies by assessing the study population, the type of clinician involvement in the fluid strategy, the type of fluid selected (e.g. crystalloids vs colloids, saline vs Ringer's lactate), the type of vasopressor given, and the source of infection.

Assessment of reporting biases

Reporting biases occur when reporting of research findings is influenced by the nature and direction of results. These are described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Funnel plots may be useful for investigating reporting biases but are of limited power for detecting small-study effects (Egger 1997). We did not use funnel plots for outcomes, as we included fewer than 10 studies in this review.

Data synthesis

We performed random-effects model meta-analysis using the assumption that effects being estimated in the different studies were not identical but follow some distribution across studies.

Subgroup analysis and investigation of heterogeneity

Had we found any heterogeneity, we would have investigated sources of clinical heterogeneity using sensitivity analyses by removing trials with potentially higher risk of bias. We found no heterogeneity because of the sparse data.

Sensitivity analysis

Had we found sufficient data, we would have conducted sensitivity analyses for country-specific outcomes (i.e. comparing developing countries vs developed countries). In future updates of this review,

when data permit, we would like to examine the effects of more recently conducted trials (e.g. those conducted after the surviving sepsis campaign) on primary outcomes.

'Summary of findings' table and GRADE

We applied the principles of the GRADE system to assess the quality of the body of evidence associated with key outcomes of this review (Guyatt 2008), and we constructed Summary of findings for the main comparison by using GRADEpro software (GRADEpro GDT). Using the GRADE approach, we appraised the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed.

We have presented the following outcomes in Summary of findings for the main comparison.

1. All-cause mortality in hospital/ICU.
2. All-cause mortality at follow-up.
3. Adverse events including organ dysfunction and other adverse events.

RESULTS

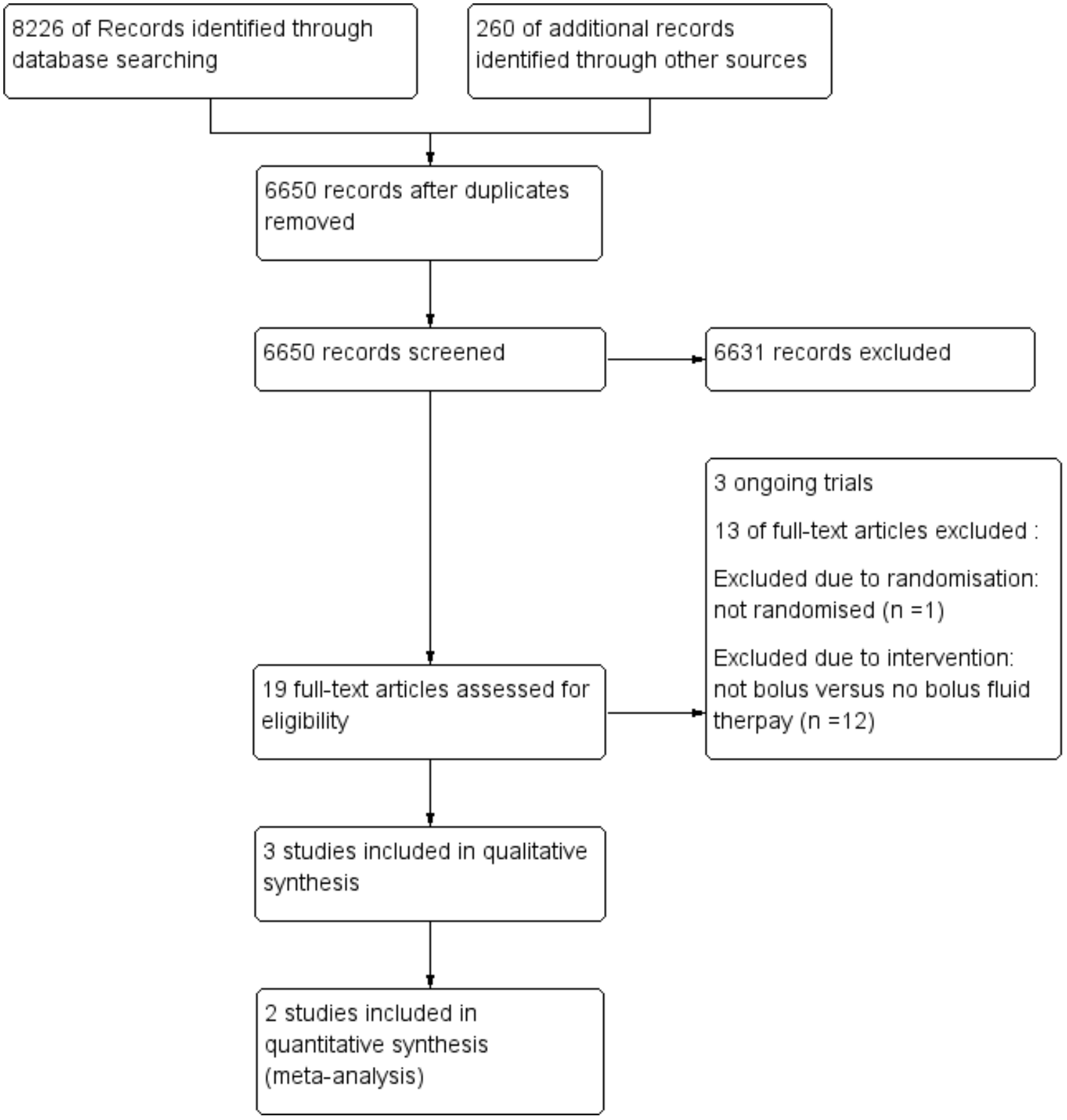
Description of studies

Please see Characteristics of included studies and Characteristics of excluded studies.

Results of the search

Through the electronic search, we retrieved 8226 references, and we identified a further 260 references by searching the ongoing clinical trials registry. Of these, 6650 references remained after we removed duplicates (see Figure 1). We excluded 6631 references through title and abstract screening. We obtained 19 full-text articles for further evaluation and subsequently included three trials (3402 children) (see Characteristics of included studies) and excluded 13 studies for the reasons given under Characteristics of excluded studies. Three studies were ongoing trials; we have presented these under Characteristics of ongoing studies.

Figure 1. Study flow diagram.



Included studies

We did not identify any adult studies that met our selection criteria.

We included three eligible trials with 3402 paediatric participants (Benakatti 2014; Maitland 2011; Santhanam 2008). (See Characteristics of included studies.)

Settings

Benakatti 2014 was conducted in the paediatric ICU (PICU) of a hospital in India. Santhanam 2008, which was also conducted in India, enrolled children from the emergency department of a public hospital.

Maitland 2011 was a multi-centre study conducted in Africa; it involved six clinical centres distributed across the following countries: Kenya (one centre), Tanzania (one centre), and Uganda (four centres). Participants in this study were treated on general paediatric wards.

Participants

All included studies investigated children with sepsis and septic shock (Characteristics of included studies). Benakatti 2014 and Santhanam 2008 investigated children with septic shock. Maitland 2011 investigated children with severe febrile illness and impaired perfusion, 57% of whom suffered from malaria.

The age of children ranged from one month to 12 years. Only one included trial reported on proportions of male and female participants, including 1689 males and 1452 females (Maitland 2011). The other two trials did not offer details on patient gender (Benakatti 2014; Santhanam 2008).

Trial size

The total sample consisted of 3402 children. Sample sizes of the three trials were as follows: Benakatti 2014 (N = 101), Maitland 2011 (N = 3141), and Santhanam 2008 (N = 160).

Interventions

Types of interventions varied among the three trials.

Benakatti 2014 investigated effects of liberal and conservative fluid therapy for children with septic shock. The mean cumulative fluid balance in the conservative fluid therapy group was 42.6 (± 82.6) mL, and more fluid was administered in the other group: 339 (± 117) mL.

Maitland 2011 included three arms at the first eight hours and compared liberal fluid therapy including 20 mL/kg of 5% albumin bolus, 20 mL/kg 0.9% saline bolus, and conservative fluid therapy including 1.2 mL/kg no bolus control.

Santhanam 2008 compared effects of more intravenous fluid intake (i.e. liberal fluid therapy, 40 mL/kg of fluid over 15 minutes) versus less intravenous fluid intake (i.e. conservative fluid therapy, 20 mL/kg over 20 minutes) for children with septic shock. The total amount of fluid used in this trial was 72.5 mL/kg (interquartile range, 60 to 90 mL/kg) in the treatment group versus 60 mL/kg (interquartile range, 60 to 60 mL/kg) in the control group.

Outcomes

Researchers collected outcome data on mortality (Maitland 2011; Santhanam 2008), pulmonary oedema (Maitland 2011), organ dysfunction (Santhanam 2008), and other adverse events (Maitland 2011; Santhanam 2008).

Benakatti 2014 reported mortality, incidence of organ failure, other adverse events (e.g. acute kidney injury), and length of ICU stay; however, the study author did not report the number of participants in each group. Thus we were not able to pool these numbers in the meta-analysis. We narratively described these outcomes from Benakatti 2014 in the Results section of this review.

The included studies did not measure other prespecified outcomes mentioned in our protocol, including vasoactive-free days alive within 28 days and duration of organ dysfunction.

The included studies reported several other outcomes including proportion of recovery from organ failure, episodes of hypotensive shock within 48 hours, resolution of shock, length of hospital stay, and duration of ventilation, but because these are not outcomes of interest for this review (Li 2013), we did not analyse these data. We addressed these differences in the Differences between protocol and review section.

Excluded studies

We excluded 13 studies that did not meet the review inclusion criteria (Akech 2010; Bechir 2010; Boldt 1996a; Boldt 1996b; Chopra 2011; Dung 1999; McIntyre 2008; McIntyre 2012a; McIntyre 2012b; Ngo 2001; Rivers 2001; Wills 2005; Yealy 2014). Reasons for exclusion included non-randomized design and irrelevant interventions. Please refer to the Characteristics of excluded studies for further details.

Studies awaiting classification

We identified no studies awaiting classification.

Ongoing studies

We identified three ongoing studies (NCT02079402; NCT02159079; NCT02447042). Please refer to the Characteristics of ongoing studies section for details of these studies.

Risk of bias in included studies

We have described the risk of bias of the included studies in the 'Risk of bias table' for each included study (Characteristics of included studies). Visual representation of the summary of risk of bias is available in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

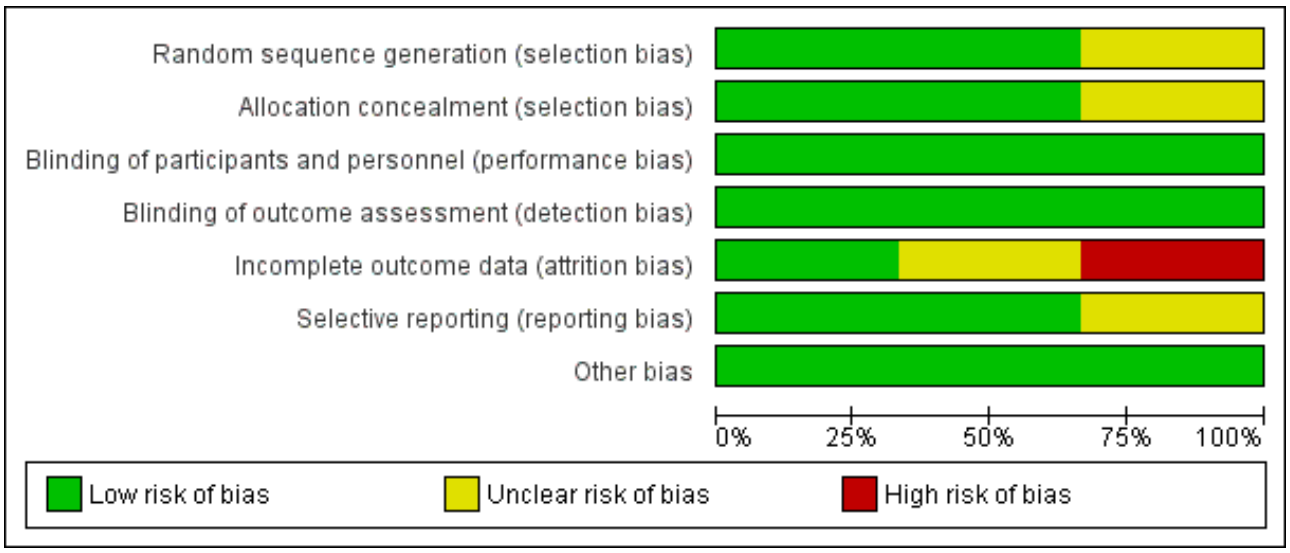
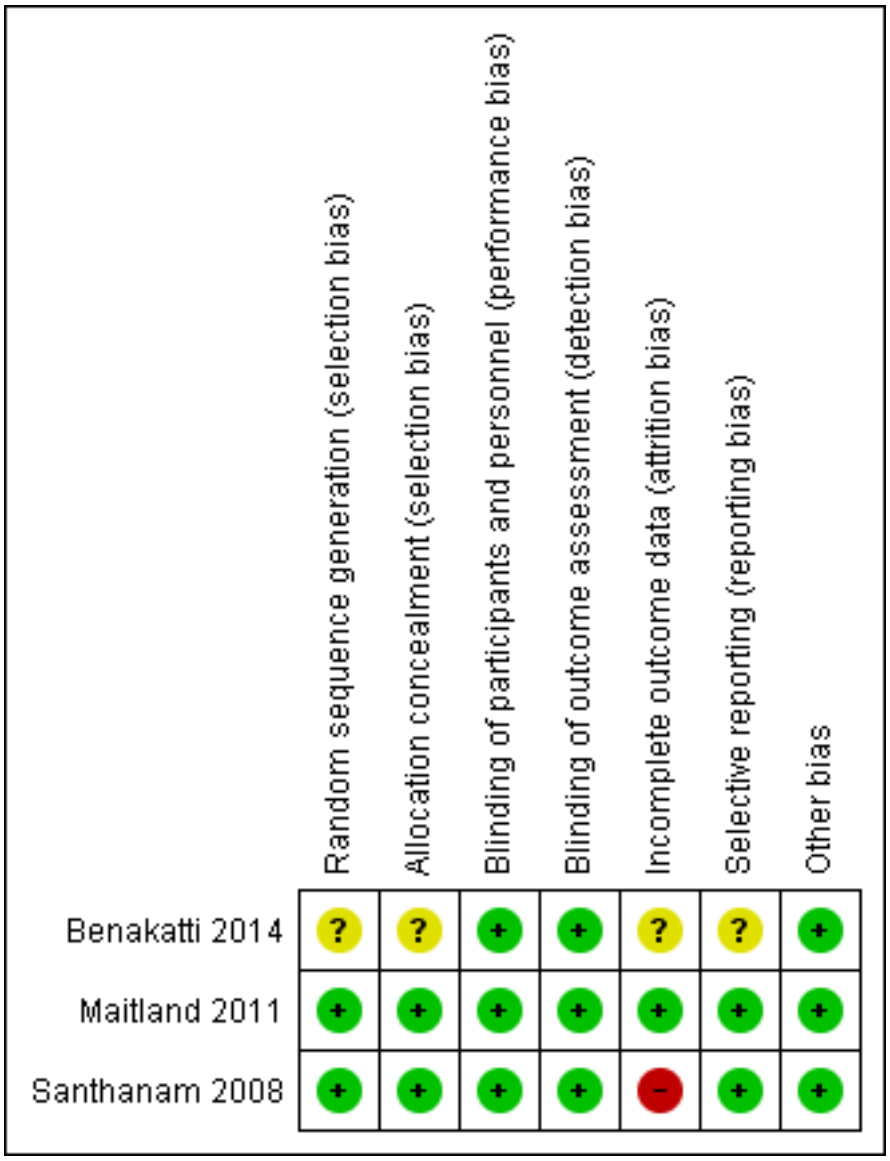


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We rated two trials as having 'low risk' of selection bias, as they employed adequate randomization procedures, including use of random numbers tables in Santhanam 2008, and block randomization based on permuted blocks of random sizes in Maitland 2011. We rated Benakatti 2014 as having unclear risk for selection bias based on insufficient descriptions of sequence generation.

We rated allocation concealment as having 'low risk' of bias in two trials, as study authors stated that the random sequence was placed in sealed, opaque envelopes (Maitland 2011; Santhanam 2008). The other trial did not provide any information on this domain, and we rated it as having unclear risk of bias (Benakatti 2014).

Blinding

Although most studies did not describe blinding of participants, personnel, or outcome assessors, all outcomes in this systematic review were objective outcomes (such as death and adverse events). Therefore, we rated all included studies as having low risk of performance bias and detection bias in that outcomes are not likely to be influenced by lack of blinding.

Incomplete outcome data

We do not have usable information on dropout from Benakatti 2014, but dropout was common in the two trials Maitland 2011 and Santhanam 2008. Santhanam 2008 enrolled 160 participants, 13 of whom left the trial early because of congenital heart disease, myeloid leukaemia, inborn error of metabolism, grade 3 malnutrition, or protocol violations. Although reasons for and proportions of dropout (< 10%) are balanced between groups, the missing data may have some impact on the overall estimate of the primary outcome (see Analysis 2.1); thus we rated this

domain as having high risk of bias in this study. In the largest randomized controlled trial, 69 children withdrew (6.6%) from the bolus albumin solution group, 64 (6.1%) from the bolus saline solution group, and 44 (4.2%) from the no bolus group (Maitland 2011). Researchers described the reasons for their withdrawal in detail and applied an ITT approach in the final analysis; therefore we rated this domain as having low risk of bias. Benakatti 2014 applied ITT analysis but did not report reasons for and numbers of participants leaving the study early. We do not have sufficient information to make a conclusive judgement; thus we rated this study as having unclear risk of bias.

Selective reporting

We rated two included trials as having low risk of bias for this domain, as we did not identify any obvious selective reporting when study authors compared the results versus prespecified outcome measures as listed in the Methods section of the paper (Maitland 2011; Santhanam 2008). Maitland 2011 provided registration data in the trial publication and reported all measured outcomes in the results section. Based on lack of full text, we rated Benakatti 2014 as having unclear risk of reporting bias.

Other potential sources of bias

We rated this domain as low risk for all three trials because we noted no other obvious bias.

Effects of interventions

See: **Summary of findings for the main comparison** Liberal initial fluid versus conservative fluid therapy in adults and children with sepsis or septic shock

Liberal initial fluid therapy versus conservative fluid therapy

1. All-cause mortality

1.1. All-cause mortality in hospital/ICU

We identified two relevant trials regarding all-cause mortality in the hospital/ICU (Maitland 2011; Santhanam 2008; N = 3288). We found a higher mortality rate among participants receiving liberal initial fluid therapy than among those given conservative fluid therapy (RR 1.38, 95% CI 1.07 to 1.77; NNTH = 34; Analysis 1.1). On average, risk of death was 1.38 times higher in the liberal fluid group than in the conservative fluid group. This means that if 34 children received liberal fluid therapy, one more death could be expected in the liberal fluid therapy group compared to the conservative fluid therapy group. We judged the quality of evidence for this outcome to be moderate. We downgraded the quality of evidence for serious study limitations (high risk of attrition bias) due to a pooled estimate effect that was not robust (Summary of findings for the main comparison; Analysis 2.1).

Benakatti 2014 also reported mortality rates in the PICU and revealed no clear differences between compared groups (18.5% vs 23.4%; P = 0.54). However, because several participants were absent from each group, we were unable to extract usable data for analysis.

1.2. All-cause mortality at follow-up

Maitland 2011 reported mortality rate at follow-up by four weeks (N = 3141) and noted a higher mortality rate among participants receiving liberal initial fluid therapy than among those given conservative fluid therapy (RR 1.39, 95% CI 1.11 to 1.74; NNTH = 29; Table 1). On average, risk of death was 1.39 times higher in the liberal fluid group than in the conservative fluid group. This means that if 29 children received liberal fluid therapy, one more death could be expected in the liberal fluid therapy group compared to the conservative fluid therapy group. We judged the quality of evidence for this outcome to be high (Summary of findings for the main comparison).

2. Vasoactive agent-free days in patients alive within 28 days

No study reported this outcome.

3. Pulmonary oedema at over 24 hours

One large RCT (N = 3141) reported data on this outcome (Maitland 2011), revealing no clear differences between liberal fluid and conservative fluid groups in the incidence of pulmonary oedema by 48 hours (RR 1.66, 95% CI 0.67 to 4.12; Table 1). We judged the quality of evidence for this outcome to be low. We downgraded the quality of evidence for serious imprecision due to small numbers of events.

4. Adverse events

4.1. Organ dysfunction

4.1.1. Hepatomegaly

One relevant trial (N = 147) reported this outcome (Santhanam 2008). Results showed no clear differences in the incidence of hepatomegaly between the two therapy groups by 60 minutes after infusion (RR 0.95, 95% CI 0.60 to 1.50; Table 1).

4.1.2. Need for ventilation

One relevant trial (N = 147) reported this outcome (Santhanam 2008), showing no clear differences between the two therapy groups (RR 1.17, 95% CI 0.83 to 1.65; Table 1).

We judged the quality of these outcomes to be low. We downgraded the quality of evidence for very serious imprecision due to small sample size and small numbers of events (Summary of findings for the main comparison).

4.2. Other adverse events

Maitland 2011 reported that by 48 hours after resuscitation, data showed no clear differences between liberal initial fluid and conservative fluid therapy in the incidence rate of adverse events, including allergic reactions (N = 3141; RR 1.74, 95% CI 0.36 to 8.37), neurological sequelae (N = 2983; RR 1.03, 95% CI 0.61 to 1.75), increased intracranial pressure (N = 3141; RR 1.54, 95% CI 0.78 to 3.02), and severe hypotension (N = 3141; RR 0.50, 95% CI 0.10 to 2.46; Table 1). We judged the quality of these outcomes to be low. We downgraded the quality of evidence for serious imprecision due to small numbers of events (Summary of findings for the main comparison).

Santhanam 2008 (N = 147) contributed data for other adverse events at 60 minutes. We found no clear differences between the two therapy groups for occurrence of desaturation (RR 1.81, 95% CI 0.97 to 3.38) and tracheal intubation (RR 1.30, 95% CI 0.90 to 1.89; Table 1). We judged the quality of these outcomes to be low. We downgraded the quality of evidence for very serious imprecision due to small sample size and small numbers of events (Summary of findings for the main comparison).

5. Duration of organ dysfunction

No study reported this outcome.

6. Length of ICU stay

Only Benakatti 2014 (N = 101) reported this outcome by measuring duration of PICU-free days. Results show that children in the liberal initial fluid group had fewer PICU-free days (mean ± SD: 12.7 ± 9.5 days) than those in the conservative fluid therapy group (mean ± SD: 17.2 ± 9 days; P = 0.015). However, the number of participants in each group was not reported in this abstract and the data were skewed; we did not perform parameter testing.

7. Ventilator-free days in patients alive within 28 days

Only Benakatti 2014 (N = 101) reported this outcome. Results show that liberal initial fluid therapy could lead to fewer ventilation-free days (mean ± SD: 6.3 ± 5.8 days) when compared with conservative fluid therapy (mean ± SD: 9.9 ± 5.2 days; P = 0.012). However, study authors did not report in this abstract the number of participants in each group and the data were skewed; we did not perform parameter testing.

Sensitivity analysis (assumption for missing data): liberal initial fluid therapy versus conservative fluid therapy

Data were sparse; therefore we did not perform sensitivity analysis for country-specific outcomes. We performed sensitivity analysis only for assumptions of missing data.

Two studies reported missing data at follow-up (Maitland 2011; Santhanam 2008). We made an assumption regarding missing data for all-cause mortality and adverse events according to the protocol (see Dealing with missing data).

For all-cause mortality in hospital, results based on data from completers are different from those based on assumption (Analysis 1.1). When we analysed the data based on assumption for missing data (with ITT analysis), results showed no clear differences between liberal initial fluid therapy and conservative fluid therapy in risk of death (2 studies; N = 3301; RR 1.26, 95% CI 0.85 to 1.86; Analysis 2.1). This indicated that missing data may have had some impact on study findings.

For other outcomes of adverse events (Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6), the sensitivity analysis showed consistent results whether or not data were based on assumptions for missing data. These results were not influenced by missing data.

DISCUSSION

Summary of main results

All included studies investigated the effects of liberal fluid therapy for children with septic shock. Moderate-quality evidence from two randomized controlled trials (RCTs) (N = 3288) indicates that liberal fluid therapy may increase in-hospital mortality risk by 38% compared with conservative fluid therapy. When approximately 34 children received liberal fluid therapy, one more in-hospital death could be expected in the liberal fluid therapy group compared to the conservative fluid therapy group. High-quality evidence from one RCT (N = 3141) also shows that liberal fluid therapy may increase mortality risk by 39% compared with conservative fluid therapy at four-week follow-up, and very low-quality evidence from Benakatti 2014 suggests no clear differences in in-hospital mortality between the compared groups. Researchers identified similar effects with liberal and conservative fluid therapy for pulmonary oedema and adverse events, for instance, hepatomegaly, need for ventilation, allergic reaction, and neurological sequelae (low-quality evidence).

One small RCT enrolling children with septic shock reported that conservative fluid therapy reduced intensive care unit (ICU) stay and duration of ventilator use (N = 101; Benakatti 2014). However, this evidence is weakened by its small sample size and by the fact that no data were available for meta-analysis. We did not identify any benefit of liberal fluid therapy. Because relevant data are sparse, we are uncertain about the effects of liberal fluid therapy for vasoactive agent-free days; other organ dysfunction such as renal failure, respiratory failure, and central nervous system (CNS) dysfunction; and duration of organ dysfunction.

Overall completeness and applicability of evidence

Findings of this review are applicable to children between one month and 12 years of age (Benakatti 2014; Maitland 2011; Santhanam 2008). The absence of adult data limits the external validity and applicability of review findings. Participants were mainly from India and Africa, which might present racial and geographical limitations to the applicability of evidence. Furthermore although all included participants received the diagnosis of sepsis and septic shock, other key differences may contribute to clinical heterogeneity (e.g. Maitland 2011 included more participants with malaria and participants had no access to advanced ICU care, Benakatti 2014 enrolled participants admitted to the paediatric intensive care unit (PICU) after resuscitation). The included studies seemed insufficient in addressing the predefined objective of this review, as only a small number of included studies contributed data for the primary outcomes. Completeness of evidence is also poor due to lack of data on some important secondary outcomes, such as vasoactive agent-free days, renal failure, and duration of organ dysfunction. Studies reported on other secondary outcomes such as pulmonary oedema, length of ICU stay, and ventilator-free days, but the sparse data give rise to uncertainty in the findings. All of this, coupled with lack of data on adults, has compromised the completeness of evidence.

Quality of the evidence

Overall, the risk of bias of individual included studies was moderate, as all three studies showed appropriate study design and reliable conduct (Benakatti 2014; Maitland 2011; Santhanam 2008). Randomization and allocation concealment were generally well conducted and described (Maitland 2011; Santhanam 2008), hence selection bias was at low risk. For measurement of objective outcomes, risk of performance and detection bias was low as well. Dropouts had some impact on the stability of overall estimates of primary outcomes (such as mortality rate in hospital), nevertheless regarding adverse events, the estimates were robust.

Evidence for the key outcomes was of low to high quality because we had to downgrade the quality of evidence for study limitations due to high risk of attrition bias and imprecision associated with wide 95% confidence intervals (CIs).

Potential biases in the review process

We strictly complied with the *Cochrane Handbook for Systematic Reviews of Interventions* throughout key stages of the review to

minimize any potential bias (Higgins 2011). Two review authors screened studies, extracted data, and assessed the quality of studies independently. We discussed disagreements and made final decisions with the help of a third methodologist when necessary. The amount of fluid intake and the definitions of liberal and conservative fluid therapy varied among included studies. This variation may have induced some clinical heterogeneity, although this is not evident in the current data set, as only one meta-analysis was performed. However, variation in definitions may prove to be a stumbling block for inclusion screening and synthesis in future updates. The limited number of databases searched and the insufficient search for grey literature may have led to missing studies and may consequently bias review results. Finally, incomplete correspondence with Benakatti 2014 led to involuntary exclusion of data from this study, which may have altered the effect estimates that would have been obtained for some outcomes had these data been included in the analysis.

Agreements and disagreements with other studies or reviews

Ford 2012 conducted a systematic review to evaluate the effects of fluid resuscitation for children with septic shock or sepsis. Ford planned to include randomized, quasi-randomized controlled trials, as well as controlled before-after trials. Ford and colleagues included 13 studies in their review (Akech 2006; Akech 2010; Akech 2010a; Chopra 2011; Cifra 2003; Dung 1999; Maitland 2005a; Maitland 2005b; Maitland 2011; Ngo 2001; Santhanam 2008; Upadhyay 2005; Wills 2005). However, we did not include most of those studies in the current review because the intervention of interest in our review was different from that explored by Ford 2012. The 12 studies in Ford 2012 compared not only use of liberal versus conservative fluid therapy, but also use of different types of fluid. One study was not eligible for inclusion in our review because participants were ineligible (Akech 2010). Four studies compared effects of colloids versus crystalloids for children with dengue shock (Cifra 2003; Dung 1999; Ngo 2001; Wills 2005). We did not include these four studies due to ineligible participants and interventions. Four trials investigated interventions in children with malarial infection; we excluded these studies because of ineligible participants or different study aims such as selection of different fluids (Akech 2006; Akech 2010a; Maitland 2005; Maitland 2005a). Finally, only four trials in Ford 2012 assessed interventions in children with septic shock (Chopra 2011; Maitland 2011; Santhanam 2008; Upadhyay 2005). Two of these did not compare effects of liberal and conservative fluid therapy for septic shock, and we considered them as ineligible for inclusion in the present review (Chopra 2011; Upadhyay 2005). To demonstrate effects of liberal versus conservative fluid therapy for children with septic shock, Ford and colleagues presented data from only one trial and did not conduct meta-analysis (Maitland 2011). Conclusions of the Ford 2012 review are consistent with those of the current review, but we regard the results of the Ford review to be less robust when missing data are taken into account (in-hospital mortality rate was no longer significant after missing data were considered).

AUTHORS' CONCLUSIONS

Implications for practice

Sepsis and septic shock are serious conditions with a high mortality rate, and fluid therapy is a first-line treatment. Many guidelines for sepsis published between 2004 and 2012 point out that sufficient fluid resuscitation is very important in the early period of shock (Dellinger 2004; Dellinger 2008a; Dellinger 2013). This review found that liberal fluid intake in children with septic shock may lead to higher risk of death than is seen with conservative fluid intake. Effects on other outcomes such as in-hospital/ICU mortality and adverse events are uncertain due to the low and moderate quality of available evidence. This review did not find sufficient evidence to confidently conclude any beneficial effect of liberal fluid therapy compared to conservative fluid therapy. Very low-quality evidence derived from one small study suggests that conservative fluid therapy can shorten ICU stay and duration of ventilation (N = 101; Benakatti 2014). Three ongoing studies, once published and assessed, may alter the conclusions of this review.

Implications for research

We did not identify any trial involving adults or patients from developed countries; this limits generalization of our results, which should be interpreted with caution. Review authors identified only three paediatric studies from limited resource countries with specific pathogens (Benakatti 2014; Maitland 2011; Santhanam 2008). Further studies including adults, patients in other settings, and patients with a broader spectrum of pathogens are expected. Also expected are studies providing fluid replacement consistent with physiological considerations of euvolaemia, which might provide more clinically relevant and accurate results than are obtained when fluid replacement is targeted to fixed-dose regimen . A standardized definition of liberal fluid needs to be established in future studies to help reduce clinical heterogeneity and improve the consistency and applicability of findings. Data on long-term mortality rate and adverse events (at and beyond four weeks) should be collected, especially for pulmonary oedema and renal dysfunction. More data on vasoactive agent-free days, duration of organ dysfunction, and length of hospital/ICU stay are also needed. The time points of measurements for these outcomes should be standardized in future studies.

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REFERENCES

References to studies included in this review

Benakatti 2014 *{published data only}*

Benakatti G, Singhi S, Jayshree M, Bansal A. Conventional vs. restrictive maintenance fluid regime in children with septic shock after initial resuscitation: a randomized open label controlled pilot trial. *Pediatric Critical Care Medicine* 2014;**15**(4 Suppl):1-30.

* Benakatti G, Singhi S, Muralidharan J, Bansal A. Conventional vs. restrictive maintenance fluid regime in children with septic shock after initial resuscitation: a randomized open label controlled trial. *Archives of Disease in Childhood* 2012;**97**:A5.

Maitland 2011 *{published data only}*

* Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. *New England Journal of Medicine* 2011;**364**(26):2483-95. [PUBMED: 21615299]

Olupot-Olupot P. Fluid expansion as supportive therapy (FEAST) trial: mortality after fluid bolus in African children. *Tropical Medicine and International Health* 2012;**17**:43.

Rossi Gabriele. The FEAST trial of fluid bolus in African children with severe infection. *Lancet* 2012;**379**:614-5.

Santhanam 2008 *{published data only}*

Santhanam I, Sangareddi S, Venkataraman S, Kissoon N, Thiruvengadamudayan V, Kasthuri RK. A prospective randomized controlled study of two fluid regimens in the initial management of septic shock in the emergency department. *Pediatric Emergency Care* 2008;**24**(10):647-55. [PUBMED: 19242131]

References to studies excluded from this review

Akech 2010 *{published data only}*

Akech SO, Karisa J, Nakamya P, Boga M, Maitland K. Phase II trial of isotonic fluid resuscitation in Kenyan children with severe malnutrition and hypovolaemia. *BMC Pediatrics* 2010;**71**:1186/1471-2431-10-71. [PUBMED: 20923577]

Bechir 2010 *{published data only}*

Bechir M, Puhan MA, Neff SB, Guggenheim M, Wedler V, Stover JF, et al. Early fluid resuscitation with hyperoncotic hydroxyethyl starch 200/0.5 (10%) in severe burn injury. *Critical Care* 2010;**14**:R123. [PUBMED: 20584291]

Boldt 1996a *{published data only}*

Boldt J, Mueller M, Menges T, Papsdorf M, Hempelmann G. Influence of different volume therapy regimens on regulators of the circulation in the critically ill. *British Journal of Anaesthesia* 1996;**77**(4):480-7.

Boldt 1996b *{published data only}*

Boldt J, Müller M, Heesen M, Heyn O, Hempelmann G. Influence of different volume therapies on platelet function in the critically ill. *Intensive Care Medicine* 1996;**22**(10):1075-81.

Chopra 2011 *{published data only}*

Chopra A, Kumar V, Dutta A. Hypertonic versus normal saline as initial fluid bolus in pediatric septic shock. *Indian Journal of Pediatrics* 2011;**78**(7):833-7. [PUBMED: 21290201]

Dung 1999 *{published data only}*

Dung NM, Day NP, Tam DT, Loan HT, Chau HT, Minh LN, et al. Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous-fluid regimens. *Clinical Infectious Diseases* 1999;**29**(4):787-94. [PUBMED: 10589889]

McIntyre 2008 *{published data only}*

McIntyre LA, Fergusson D, Cook DJ, Rankin N, Dhingra V, Granton J, et al. Canadian Critical Care Trials Group. Fluid resuscitation in the management of early septic shock (FINESS): a randomized controlled feasibility trial. *Canadian Journal of Anaesthesia* 2008;**55**(12):819-26. [PUBMED: 19050085]

McIntyre 2012a *{published data only}*

McIntyre L, Fergusson DA, Rowe B, Cook DJ, Arabi Y, Bagshaw SM, et al. Canadian Critical Care Trials Group. The PRECISE RCT: evolution of an early septic shock fluid resuscitation trial. *Transfusion Medication Reviews* 2012;**26**(4):333-41. [PUBMED: 22222146]

McIntyre 2012b *{published data only}*

McIntyre LA, Fergusson DA, Cook DJ, Rowe BH, Bagshaw SM, Easton D, et al. Canadian Critical Care Trials Group. Fluid resuscitation with 5% albumin versus normal saline in early septic shock: a pilot randomized, controlled trial. *Journal of Critical Care* 2012;**27**(3):317. [PUBMED: 22176806]

Ngo 2001 *{published data only}*

Ngo NT, Cao XT, Kneen R, Wills B, Nguyen VM, Nguyen TQ, et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. *Clinical Infectious Diseases* 2001;**32**:204-13. [PUBMED: 11170909]

Rivers 2001 *{published data only}*

Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine* 2001;**345**:1368-77. [PUBMED: 11794169]

Wills 2005 *{published data only}*

Wills BA, Nguyen MD, Ha TL, Dong TH, Tran TN, Le TT, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *New England Journal of Medicine* 2005;**353**(9):877-89. [PUBMED: 16135832]

Yealy 2014 *{published data only}*

ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, et al. A randomized trial of protocol-based care for early septic shock. *New England Journal of Medicine* 2014;**370**(18):1683-93. [24635773]

References to ongoing studies

NCT02079402 *{unpublished data only}*

NCT02079402. Conservative vs. liberal approach to fluid therapy of septic shock in intensive care. clinicalTrials.gov/show/NCT02079402 (date first received 5 March 2014).

NCT02159079 *{unpublished data only}*

NCT02159079. A randomized controlled trial of a conservative fluid balance strategy for patients with sepsis and cardiopulmonary dysfunction. clinicaltrials.gov/ct2/show/NCT02159079 (date first received 9 June 2014).

NCT02447042 *{unpublished data only}*

NCT02447042. Minimal volume for a fluid challenge in septic patients. clinicaltrials.gov/ct2/show/NCT02447042 (date first received 18 May 2015).

Additional references

Akech 2006

Akech S, Gwer S, Idro R, Fegan G, Eziefula AC, Newton CR, et al. Volume expansion with albumin compared to gelofusine in children with severe malaria: results of a controlled trial. *PLoS Clinical Trials* 2006;**1**(5):e21.

Akech 2010a

Akech SO, Jemutai J, Timbwa M, Kivaya E, Boga M, Fegan G, et al. Phase II trial on the use of Dextran 70 or starch for supportive therapy in Kenyan children with severe malaria. *Critical Care Medicine* 2010;**38**(8):1630-6.

Altman 1996

Altman DG, Bland JM. Detecting skewness from summary information. *BMJ* 1996;**313**:1200. [PUBMED: 8916759]

Angus 2001

Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Critical Care Medicine* 2001;**29**(7):1303-10. [PUBMED: 11445675]

Annane 2003

Annane D, Aegerter P, Jars-Guincestre MC, Guidet B. Current epidemiology of septic shock: the CUB-Rea Network. *American Journal of Respiratory and Critical Care Medicine* 2003;**168**(2):165-72. [PUBMED: 12851245]

Bone 1992

Bone RC, Balk RA, Cerra FB. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. *Chest* 1992;**101**:1644-55. [PUBMED: 1303622]

Cifra 2003

Cifra H, Velasco J. A comparative study of the efficacy of 6% Haes-Steril and Ringer's lactate in the management of dengue shock syndrome 555. *Critical Care and Shock* 2003;**6**:95–100.

Davies 2001

Davies A, Green C, Hutton J. Severe sepsis: a European estimate of the burden of disease in ICU. *Intensive Care Medicine* 2001;**27**:S284.

Deeks 2000

Deeks J. Issues in the selection for meta-analyses of binary data. Proceedings of the 8th International Cochrane Colloquium, 2000 Oct 25-28; Cape Town: South Africa. The Cochrane Collaboration, 2000.

Dellinger 2004

Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign Management Guidelines Committee. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Critical Care Medicine* 2004;**32**:858-73. [PUBMED: 18158437]

Dellinger 2008a

Spoelstra-de Man AME, Girbes ARJ. Comment on "Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008". *Intensive Care Medicine* 2008;**34**:17-60. [PUBMED: 18415078]

Dellinger 2008b

Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. International Surviving Sepsis Campaign Guidelines Committee, American Association of Critical-Care Nurses, American College of Chest Physicians, American College of Emergency Physicians, Canadian Critical Care Society, European Society of Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Respiratory Society, International Sepsis Forum, Japanese Association for Acute Medicine, Japanese Society of Intensive Care Medicine, Society of Critical Care Medicine, Society of Hospital Medicine, Surgical Infection Society, World Federation of Societies of Intensive, Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Critical Care Medicine* 2008;**36**:296-327. [PUBMED: 18158437]

Dellinger 2013

Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Intensive Care Medicine 2013; Vol. 39:165–228. [PUBMED: 23361625]

Egger 1997

Egger M, Davey-Smith G, Schneider M, Minder CSO. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**13**:629-34. [PUBMED: 9310563]

Finfer 2004

Finfer S, Bellomo R, Lipman J, French C, Dobb G, Myburgh J. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. *Intensive Care Medicine* 2004;**6**:1252. [PUBMED: 14963646]

Fleischmann 2016

Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T Schlattmann P, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *American Journal of Respiratory and Critical Care Medicine* 2016;**193**(3):259-72. [PUBMED: 26414292]

Ford 2012

Ford N, Hargreaves S, Shanks L. Mortality after fluid bolus in children with shock due to sepsis or severe infection: a systematic review and meta-analysis. *PLoS One* 2012;**7**(8):e43953. [PUBMED: 22952819]

Gamper 2016

Gamper G, Havel C, Arrich J, Losert H, Pace NL, Müllner M, et al. Vasopressors for hypotensive shock. *Cochrane Database of Systematic Reviews* 2016, Issue 2. [DOI: 10.1002/14651858.CD003709.pub4]

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 6 November 2016. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Grimes 2008

Grimes DA, Schulz KF. Making sense of odds and odds ratios. *Obstetrics and Gynecology* 2008;**111**(2):423-6. [PUBMED: 18238982]

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed.)* 2008;**336**(7650):924-6. [PUBMED: 18436948]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60. [PUBMED: 12958120]

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hodgin 2008

Hodgin KE, Moss M. The epidemiology of sepsis. *Current Pharmaceutical Design* 2008;**14**(19):1833-9. [PUBMED: 18691094]

Levy 2003

Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Critical Care Medicine* 2003;**31**(4):1250-6. [PUBMED: 12682500]

Maitland 2005a

Maitland K, Pamba A, English M, Peshu N, Marsh K, Newton C, et al. Randomized trial of volume expansion with albumin or saline in children with severe malaria: preliminary evidence of albumin benefit. *Clinical Infectious Diseases* 2005;**40**(4):538-45. [PUBMED: 15712076]

Maitland 2005b

Maitland K, Pamba A, English M, Peshu N, Levin M, Marsh K, et al. Pre-transfusion management of children with severe malarial anaemia: a randomised controlled trial of intravascular volume expansion. *British Journal of Haematology* 2005;**128**(3):393-400. [PUBMED: 15667544]

Martin 2003

Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *New England Journal of Medicine* 2003;**348**(16):1546-54. [PUBMED: 12700374]

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rhodes 2016

Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Medicine* 2017;**43**(3):304-77.

Singer 2016

Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;**315**(8):801-10. [PUBMED: 26903335]

Upadhyay 2005

Upadhyay M, Singhi S, Murlidharan J, Kaur N, Majumdar S. Randomized evaluation of fluid resuscitation with crystalloid (saline) and colloid (polymer from degraded gelatin in saline) in pediatric septic shock. *Indian Pediatrics* 2005;**42**(3):223-31. [PUBMED: 15817970]

Watson 2003

Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. *American Journal of Respiratory and Critical Care Medicine* 2003;**167**(5):695-701. [PUBMED: 12433670]

References to other published versions of this review

Li 2013

Li D, Li X, Cui W, Shen H, Zhu H, Xia Y. Conservative versus liberal fluid therapy for initial severe sepsis and septic shock. *Cochrane Database of Systematic Reviews* 2013, Issue 7. [DOI: 10.1002/14651858.CD010593]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Benakatti 2014

Methods	Study design: prospective randomized trial Blinding: not reported Settings: not reported Duration: 12 months Dropouts: not stated. Intention-to-treat analysis was conducted
Participants	Diagnosis: children with septic shock N = 101 Age: 3 to 144 months Sex: not reported **Inclusion criteria** 1. Not reported **Exclusion criteria** 1. Not reported
Interventions	1. **Group A:** conventional fluid regimen; n = not reported 2. **Group B:** restrictive maintenance fluid regimen; n = not reported
Outcomes	**Could not be used, as the number of participants in each group is not reported** 1. Mortality in ICU 2. Organ failure 3. Incidence of acute kidney injury (AKI) 4. Length of ICU stay 5. Duration of ventilation (days) 6. Recovery from organ failure
Notes	No information provided on funding or declaration of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comments: prospective randomized trial
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not reported; however, all measured outcomes are objective outcomes, which are less likely to be affected by blinding

Benakatti 2014 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported; however, all measured outcomes are objective outcomes, which are less likely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comments: although intention-to-treat analysis was conducted, reasons for and proportions of dropouts in each group remain unclear
Selective reporting (reporting bias)	Unclear risk	Comments: all measured outcome were reported in the abstract; however, whether selective reporting is evident in the full report remains unclear
Other bias	Low risk	Comments: none

Maitland 2011

Methods	Study design: parallel-group randomized trial Blinding: blind to assessor Settings: general paediatric wards at 6 clinical centres in Kenya, Tanzania, and Uganda Duration: 24 weeks; 13 January 2009 to 13 January 2011 Drop-outs: 69 children withdrew from group A, 64 children from group B, and 44 from the control group
Participants	Diagnosis: "children with severe febrile illness and impaired perfusion" (p. 2483) N = 3141 Age: 60 days to 12 years old, median age 23 months, interquartile range 14 to 37 months Sex: female 1452, male 1689 **Inclusion criteria** 1. Children between 60 days and 12 years of age, presenting with a severe febrile illness complicated by impaired consciousness (prostration or coma), respiratory distress (increased work of breathing), or both, and with impaired perfusion **Exclusion criteria** 1. Severe malnutrition 2. Gastroenteritis 3. Non-infectious causes of shock (e.g. trauma, surgery, burns) 4. Conditions for which volume expansion is contraindicated
Interventions	1. **Group A:** 20 mL of 5% albumin solution per kilogram of body weight; n = 1050 2. **Group B:** 20 mL of 0.9% saline solution per kilogram of body weight; n = 1047 3. **Control group:** no bolus; n = 1044
Outcomes	1. All-cause mortality in hospital/ICU (within 48 hours) 2. All-cause mortality at follow-up (4 weeks) 3. Pulmonary oedema 4. Other adverse events: neurological sequelae, increased intracranial pressure, severe hypotension, and allergic reaction **Could not be used, as these were not prespecified in the protocol**

Maitland 2011 *(Continued)*

	1. Episodes of hypotensive shock within 48 hours
Notes	The author did not include the children with severe hypotension in the analysis. Funded by the Medical Research Council, UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was performed in permuted blocks of random sizes and was stratified according to clinical centre" (p. 2485) Comments: study author provided sufficient information on the generation of randomization
Allocation concealment (selection bias)	Low risk	Quote: "trial numbers were kept inside opaque, sealed envelopes, which were numbered consecutively and opened in numerical order by a study clinician" (p. 2485) Comments: study author provided sufficient information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comments: not reported; we suspect a potential performance bias in ICU settings; however, all measured outcomes are objective outcomes, which are less likely to be affected by blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "an end-point review committee, whose members were unaware of the treatment assignments, reviewed all deaths, neurologic sequelae, and adverse events" (p. 2485) Comments: the outcome assessor was blinded and was unable to know group assignments. In addition, all measured outcomes are objective outcomes, which are less likely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comments: 69 children withdrew from group A, 64 children from group B, and 44 children from group C. ITT analysis was applied
Selective reporting (reporting bias)	Low risk	Comments: registration data available (ISRCTN69856593); http://www.controlled-trials.com/ All outcomes are available in the trial publication and are reported in the results
Other bias	Low risk	Quote: "the study was funded by the Medical Research Council, UK; Baxter Healthcare donated the 5% albumin and 0.9% saline solutions" (p. 2485) Comments: none

Santhanam 2008

Methods	Study design: parallel-group randomized trial Blinding: blind to participants and personnel Settings: emergency department of a public hospital in India

Santhanam 2008 *(Continued)*

	Duration: November 2003 and December 2004 Dropouts: 6 participants from intervention group, 7 from control group
Participants	Diagnosis: "healthy children aged between 1 month and 12 years who were triaged as septic shock at the outpatient department" (p. 648) N = 160 Age: 1 month to 12 years old (p. 648) Sex: not stated **Inclusion criteria** 1. "Healthy children aged between 1 month and 12 years triaged as septic shock at the outpatient department" (p. 648) **Exclusion criteria** 1. "Age younger than 30 days, shock due to hypovolaemia, haemorrhage, anaphylaxis, envenomation, diabetic ketoacidosis, inborn errors, of metabolism, drug toxicity, trauma, burns, stridor, near fatal asthma, pre-hospital fluid resuscitation, grade 3 malnutrition, chronic systemic co-morbidities, genetic disorders, malignancies, immunocompromised conditions, human immunodeficiency virus, do not resuscitate orders, physician's decision not to treat, and cardiopulmonary arrest before arrival or within the first hour of resuscitation" (p. 647)
Interventions	1. 40 mL/kg of fluid over 15 minutes followed by dopamine and further titration of therapy to achieve therapeutic goals (study protocol); n = 80 2. 20 mL/kg over 20 minutes up to a maximum of 60 mL/kg over 1 hour followed by dopamine (control protocol) in septic shock; n = 80
Outcomes	1. All-cause mortality in hospital 2. Organ dysfunction: hepatomegaly, need for ventilation 3. Other adverse events: desaturation and tracheal intubation **Could not be used, as these were not prespecified in the protocol** 1. Resolution of shock 2. Length of hospital stay 3. Duration of ventilation
Notes	No information provided on funding or declaration of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random numbers were generated using randomization tables of blocks of eight" (p. 652) Comments: study author provided sufficient information on the generation of randomization
Allocation concealment (selection bias)	Low risk	Quote: "sealed, opaque, randomly assorted envelopes were opened by a registered nurse who was not part of the study team" (p. 652) Comment: study author provided sufficient information on allocation concealment

Santhanam 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "participants were unaware of the study group assignments. The nurse who administered fluids was aware of the study assignment but did not assess patients or influence therapeutic decisions. The residents in the ED and the physicians in the wards were not aware that a study was in progress or the study-group assignments. The principal investigator was not blinded but did not influence patient management after transfer" (p. 652) Comments: patients and personnel were blinded, and all measured outcomes are objective outcomes, which are less likely to be affected by blinding; risk of performance bias is low
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comments: although the paper did not describe blinding of outcome assessment, we rated this domain as low risk because all measured outcomes are objective outcomes, which are less likely to be affected by blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Comments: 6 participants in the intervention group left the study early because of inborn errors of metabolism (n = 1), congenital heart disease (n = 1), acute myeloid leukaemia (n = 1), violation of protocol (n = 1), and grade 3 malnutrition (n = 2) 7 participants in the control group left the study early because of portal hypertension with gastrointestinal bleed (n = 1), violation of protocol (n = 2), intracranial bleed due to coagulation disorder (n = 1), grade 3 malnutrition (n = 2), and non-accidental injury (n = 1) (p. 650, Figure 3). Data from 147 participants were analysed. Although reasons for and proportions (< 10%) of dropout are balanced between groups, the missing data may have some impact on the overall estimate of the primary outcome (see Analysis 2.1)
Selective reporting (reporting bias)	Low risk	Comments: it appears that all measured outcomes were reported
Other bias	Low risk	Comments: none

AKI = acute kidney injury; ED = emergency department; ICU = intensive care unit; ITT = Intention-to-treat; n/N = number.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akech 2010	Study design: randomized controlled trial Participants: Kenyan children aged over 6 months with severe malnutrition and shock Intervention: comparison focused on different kinds of fluid
Bechir 2010	Study design: randomized controlled trial Participants: patients with severe burn injury Intervention: comparison focused on different kinds of fluid
Boldt 1996a	Study design: randomized controlled trial Participants: those with trauma and sepsis Intervention: comparison focused on different kinds of fluid

Study	Reason for exclusion
	Notes: this article is being retracted following an investigation by the Justus-Liebig Universität Giessen of the work done by Joachim Boldt during his time there, as there is significant doubt regarding the veracity of this publication
Boldt 1996b	Study design: randomized controlled trial Participants: traumatized participants and non-traumatized surgical participants with sepsis Intervention: comparison focused on different kinds of fluid
Chopra 2011	Study design: randomized controlled trial Participants: children between 2 and 12 years of age with septic shock Intervention: comparison focused on different kinds of fluid
Dung 1999	Study design: randomized controlled trial Participants: children with dengue haemorrhagic fever and dengue shock syndrome Intervention: comparison focused on different kinds of fluid
McIntyre 2008	Study design: randomized controlled trial Participants: those with severe sepsis or septic shock Intervention: comparison focuses on different kinds of fluid
McIntyre 2012a	Study design: review
McIntyre 2012b	Study design: randomized controlled trial Participants: adults with early suspected septic shock Intervention: comparison focused on different kinds of fluid
Ngo 2001	Study design: randomized controlled trial Participants: children with dengue shock syndrome Intervention: comparison focused on different kinds of fluid
Rivers 2001	Study design: randomized controlled trial Participants: those with severe sepsis and septic shock Intervention: comparison focused on early goal-directed therapy or no goal-directed therapy. We excluded this study because it focused on different kinds of therapy: one group received bundled therapy, and another did not receive bundled therapy. Fluid therapy is only an element of the intervention in this study; thus we will not be able to attribute any differential treatment effect to fluid therapy
Wills 2005	Study design: randomized controlled trial Participants: children with dengue shock syndrome Intervention: comparison focused on different kinds of fluid
Yealy 2014	Study design: randomized controlled trial Participants: children with dengue shock syndrome

Study	Reason for exclusion
	Intervention: comparison focused on protocol-based early goal-directed therapy vs protocol-based standard therapy

Characteristics of ongoing studies *[ordered by study ID]*

NCT02079402

Trial name or title	Conservative vs liberal approach to fluid therapy of septic shock in intensive care (CLASSIC)
Methods	Randomized open-label study
Participants	Patients with septic shock or sepsis **Inclusion criteria** 1. Adult intensive care patients (age ≥ 18 years) with sepsis defined as 2 of 4 SIRS criteria fulfilled within 24 hours and suspected or confirmed site of infection or positive blood culture 2. Suspected or confirmed circulatory impairment (hypotension/hypoperfusion/hypovolaemia) for no longer than 12 hours, including the hours preceding ICU admission 3. At least 30 mL/kg ideal body weight (IBW) fluid (colloids, crystalloids, or blood products) given in the last 6 hours 4. Shock defined as ongoing infusion of norepinephrine (any dose) to maintain blood pressure **Exclusion criteria** 1. Use of any form of renal replacement therapy (RRT) 2. RRT deemed imminent by the ICU doctor (i.e. RRT will be initiated within 6 hours) 3. Severe hyperkalaemia (p-K > 6 mm) 4. Plasma creatinine > 350 µmol/L 5. Invasively ventilated with FiO_2 > 0.80 and PEEP > 10 cmH_2O 6. Life-threatening bleeding 7. Kidney or liver transplant during current admission 8. Burns > 10% body surface area (BSA) 9. Previously enrolled in the CLASSIC trial and has finished the 90-day observation period 10. Patient for whom it has been decided not to give full life support including mechanical ventilation and RRT Consent could not be obtained
Interventions	**Group 1:** liberal (target-guided) fluid resuscitation **Group 2:** conservative (trigger-guided) fluid resuscitation
Outcomes	**Primary outcome measures** 1. Resuscitation volume **Secondary outcome measures** 1. Fluid balance 2. Total fluid input 3. Number of patients with protocol violations 4. Major protocol violation defined as ≥ 1 resuscitation fluid boluses given without fulfilment of ≥ 1 of the CLASSIC criteria in the conservative (trigger-guided) group 5. Accumulated serious adverse reactions (SARs)

NCT02079402 *(Continued)*

	Other outcome measures 1. All-cause mortality 2. Days alive without use of mechanical ventilation 3. Days alive without use of renal replacement therapy 4. Worsening of acute kidney injury according to KDIGO criteria 5. Ischaemic events 6. Delta-creatinine
Starting date	28 February 2014
Contact information	Anders Perner, MD PhD; Rigshospitalet, Denmark
Notes	None

NCT02159079

Trial name or title	A randomized controlled trial of a conservative fluid balance strategy for patients with sepsis and cardiopulmonary dysfunction (BALANCE study)
Methods	Randomized open-label study
Participants	Patients with sepsis **Inclusion criteria** 1. ICU patients 2. Adults 3. Sepsis as defined by ≥ 2 systemic inflammatory response syndrome criteria and receipt of antimicrobial therapy 4. Cardiopulmonary dysfunction defined as shock or respiratory failure **Exclusion criteria** 1. Inability to obtain consent 2. Greater than 48 hours since inclusion criteria initially met 3. Allergy to furosemide and bumetanide 4. Rhabdomyolysis with creatinine kinase > 5000 U/L 5. Hypercalcaemia with calcium > 11 mg/dL 6. Diabetic ketoacidosis requiring continuous insulin infusion 7. Tumor lysis syndrome diagnosed clinically 8. Pancreatitis diagnosed clinically 9. Chronic hypoxic respiratory failure with home oxygen use of $FiO_2 \geq 0.3$ 10. Chronic ventilator dependence 11. Cervical spinal cord injury at level C5 (C5 denotes a rating level of spinal injury according to the American Spinal Injury Association (ASIA) impairment scale) or higher 12. Amyotrophic lateral sclerosis 13. Guillain-Barré syndrome 14. Myasthenia gravis 15. Renal failure requiring renal replacement therapy 16. Burns > 20% of body surface area 17. Pregnancy 18. Preexisting pulmonary hypertension with PAP mean > 40 on RHC 19. Severe chronic liver disease with Childs-Pugh score > 11

NCT02159079 *(Continued)*

	20.Moribund and not expected to survive an additional 24 hours 21.Active withdrawal of life support or transition to comfort measures only 22.Unwillingness of treating physician to employ conservative fluid strategy
Interventions	**Group 1:** usual care **Group 2:** conservative fluid management strategy
Outcomes	**Primary outcome measures** 1. ICU-free days to 14 days after enrolment **Secondary outcome measures** 1. Ventilator-free days 2. In-hospital mortality 3. ICU-free days 4. Cardiovascular and renal failure-free days 5. Incidence of cardiovascular failure 6. Incidence of renal failure 7. Time to resolution of shock 8. Days alive and free of delirium/coma and ICU residency in the first 14 days
Starting date	3 June 2014
Contact information	Matthew W. Semler, MD Tel: (615) 802-8428 Email: matthew.semler@gmail.com
Notes	None

NCT02447042

Trial name or title	Minimal volume for a fluid challenge in septic patients
Methods	Randomized open-label study
Participants	Patients with sepsis **Inclusion criteria** 1. Fulfil 2 of 4 criteria of the systemic inflammatory response syndrome (SIRS) due to known or suspected infection within the previous 24 hours. SIRS criteria include the following. a. Core temperature > 38°C or < 36°C b. Tachycardia (heart rate > 90 beats per minute) c. Tachypnoea (respiratory rate > 20 breaths per minute or $PaCO_2$ < 4.3 kPa or need for mechanical ventilation) d. Abnormal white cell count (> 12,000 cells/mm^3 or < 4000 cells/mm^3, or > 10% immature (band cells) forms) **Exclusion criteria** 1. Extensive peripheral arterial occlusive disease in upper limbs 2. Postoperative valvular insufficiency 3. Aortic valve regurgitation

NCT02447042 *(Continued)*

	4. Tachyarrhythmia 5. Cardiac assist device (intra-aortic balloon pump) 6. Previously known right ventricular failure 7. Known vasospastic diseases, systemic sclerosis, or Raynaud's phenomenon 8. Requiring aggressive fluid resuscitation due to life-threatening cardiovascular instability 9. Known pregnant women
Interventions	**Group 1: 2 mL/kg fluid challenge** 1. Fluid challenge with crystalloids (2 mL/kg) infused in 5 minutes; measurement of Pmsf arm before and after the fluid challenge **Group 2: 3 mL/kg fluid challenge** 1. Fluid challenge with crystalloids (3 mL/kg) infused in 5 minutes; measurement of Pmsf-arm before and after the fluid challenge **Group 3: 4 mL/kg fluid challenge** 1. Fluid challenge with crystalloids (4 mL/kg) infused in 5 minutes; measurement of Pmsf-arm before and after the fluid challenge **Group 4: 5 mL/kg fluid challenge** 1. Fluid challenge with crystalloids (5 mL/kg) infused in 5 minutes; measurement of Pmsf-arm before and after the fluid challenge
Outcomes	**Primary outcome measures** 1. Change in Pmsf-arm (expressed in percentage from baseline value) **Secondary outcome measures** 1. Change in cardiac output (expressed in percentage from baseline value) 2. Proportion of responders in each group
Starting date	November 2014
Contact information	Hollmann D Aya, MD Tel: +44(0)2087250399. Email: hollmann.aya@nhs.net
Notes	None.

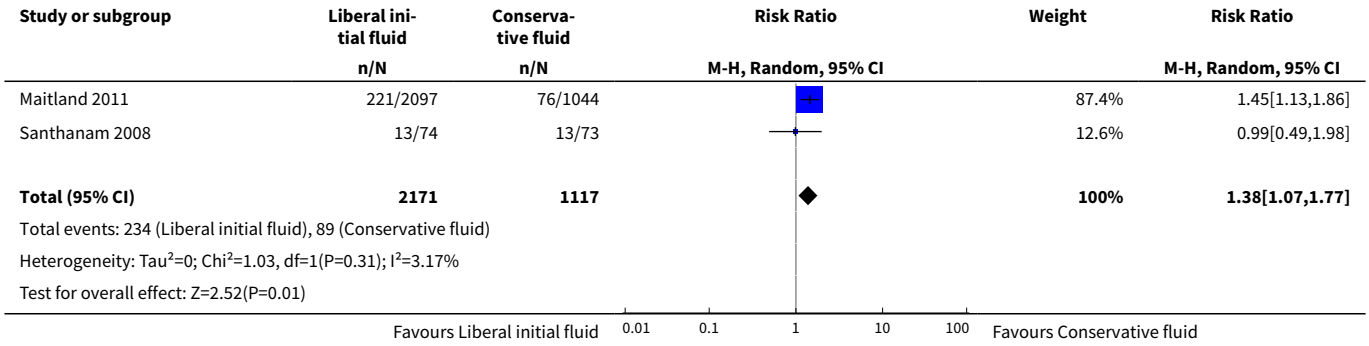
ASIA = American Spinal Injury Association; BSA = body surface area; FiO_2 = fraction of inspired oxygen; IBW = ideal body weight; ICU = Intensive care unit; KDIGO = Kidney Disease Improving Global Outcomes; kPa = kilopascal; PAP = pulmonary arterial pressure; PEEP = positive end-expiratory pressure; p-K = plasma kalium; Pmsf = mean systemic filling pressure (mean pressure in the cardiovascular system); RHC = right heart catheterization; RRT = renal replacement therapy; SARs = serious adverse reactions; SIRS = systemic inflammatory response syndrome

DATA AND ANALYSES

Comparison 1. Liberal initial fluid versus conservative fluid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality in hospital	2	3288	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.07, 1.77]

Analysis 1.1. Comparison 1 Liberal initial fluid versus conservative fluid, Outcome 1 All-cause mortality in hospital.

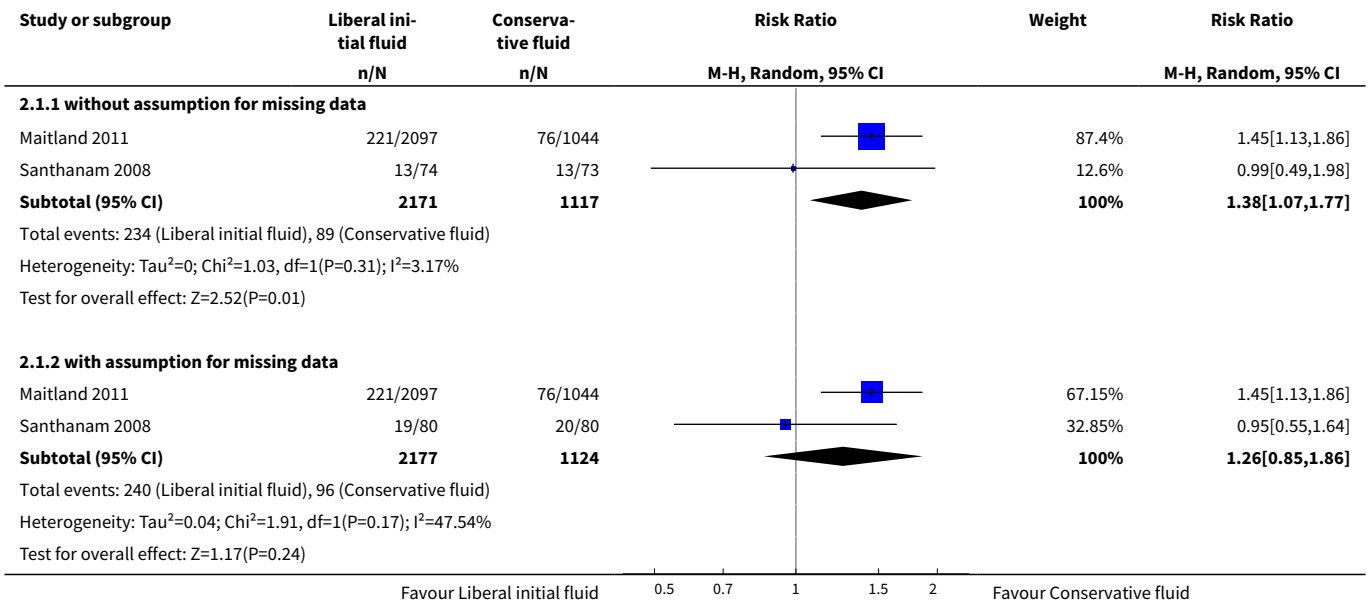


Comparison 2. Sensitivity analysis: liberal initial fluid versus conservative fluid

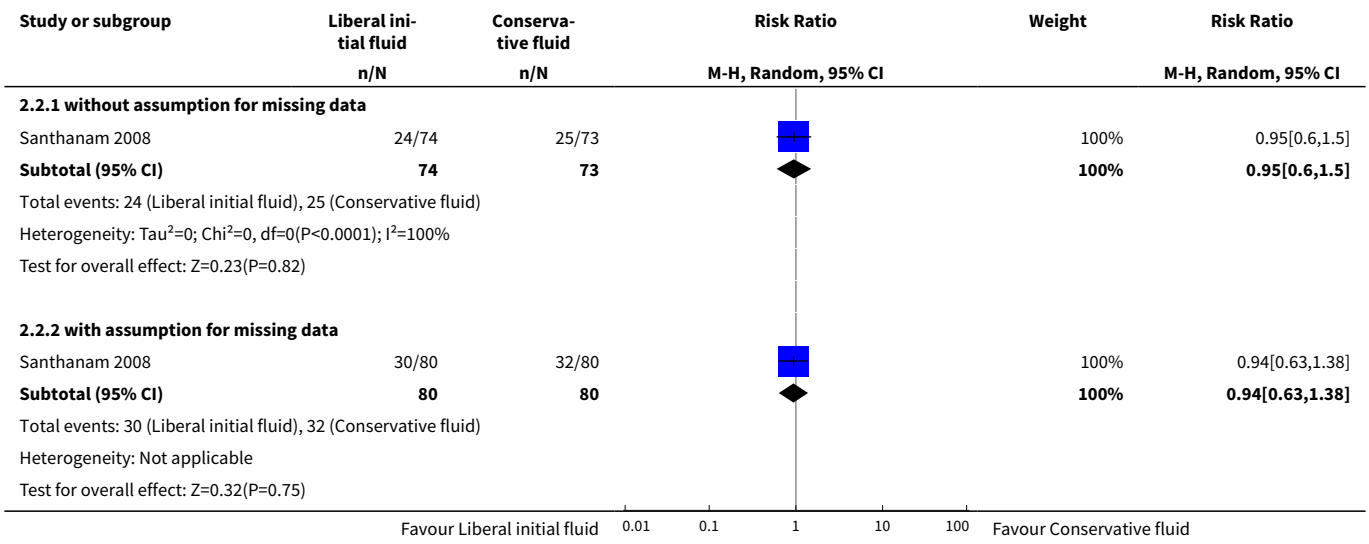
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality in hospital	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 without assumption for missing data	2	3288	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.07, 1.77]
1.2 with assumption for missing data	2	3301	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.85, 1.86]
2 Adverse events: organ dysfunction - hepatomegaly	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 without assumption for missing data	1	147	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.60, 1.50]
2.2 with assumption for missing data	1	160	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.63, 1.38]
3 Adverse events: organ dysfunction - need for ventilation	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 without assumption for missing data	1	147	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.83, 1.65]
3.2 with assumption for missing data	1	160	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.85, 1.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Adverse events: other - desaturation	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 without assumption for missing data	1	147	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.97, 3.38]
4.2 with assumption for missing data	1	160	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.90, 2.41]
5 Adverse events: other - tracheal intubation	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 without assumption for missing data	1	147	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.90, 1.89]
5.2 with assumption for missing data	1	160	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.89, 1.69]
6 Adverse events: other - neurological sequelae	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 without assumption for missing data	1	2983	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.61, 1.75]
6.2 with assumption for missing data	1	3141	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.86, 1.49]

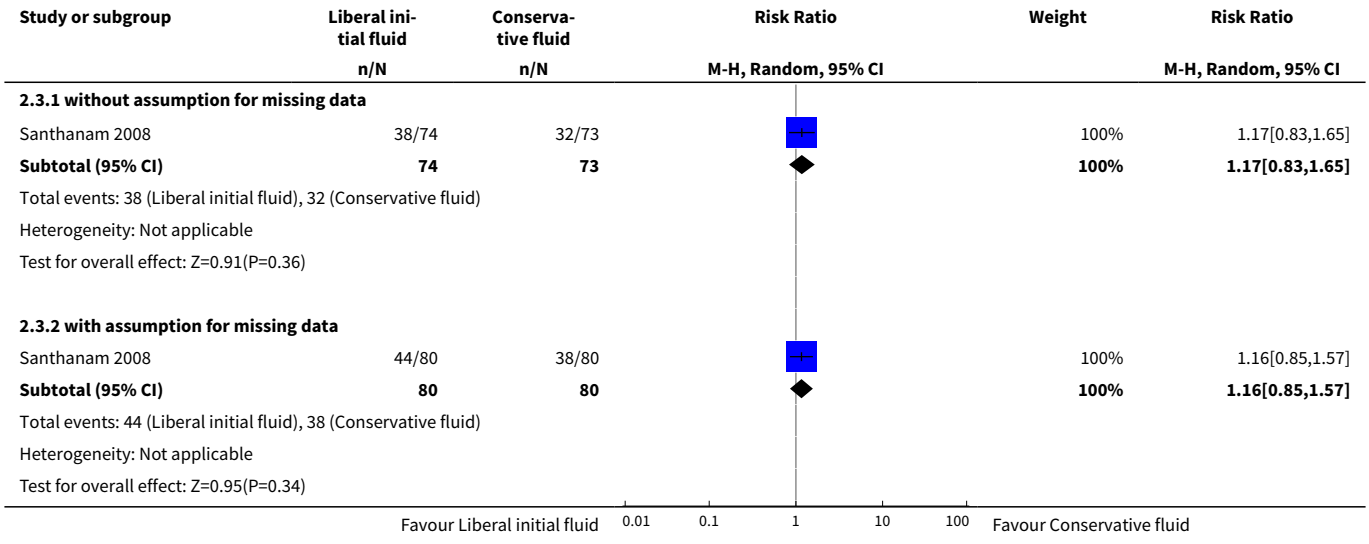
Analysis 2.1. Comparison 2 Sensitivity analysis: liberal initial fluid versus conservative fluid, Outcome 1 All-cause mortality in hospital.



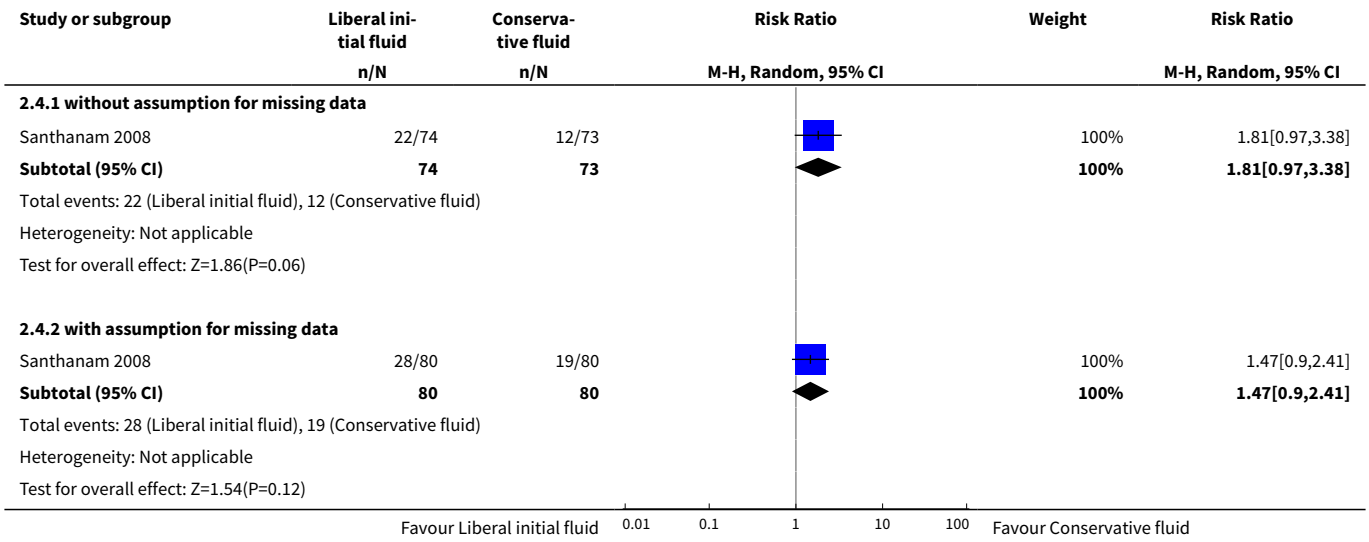
Analysis 2.2. Comparison 2 Sensitivity analysis: liberal initial fluid versus conservative fluid, Outcome 2 Adverse events: organ dysfunction - hepatomegaly.



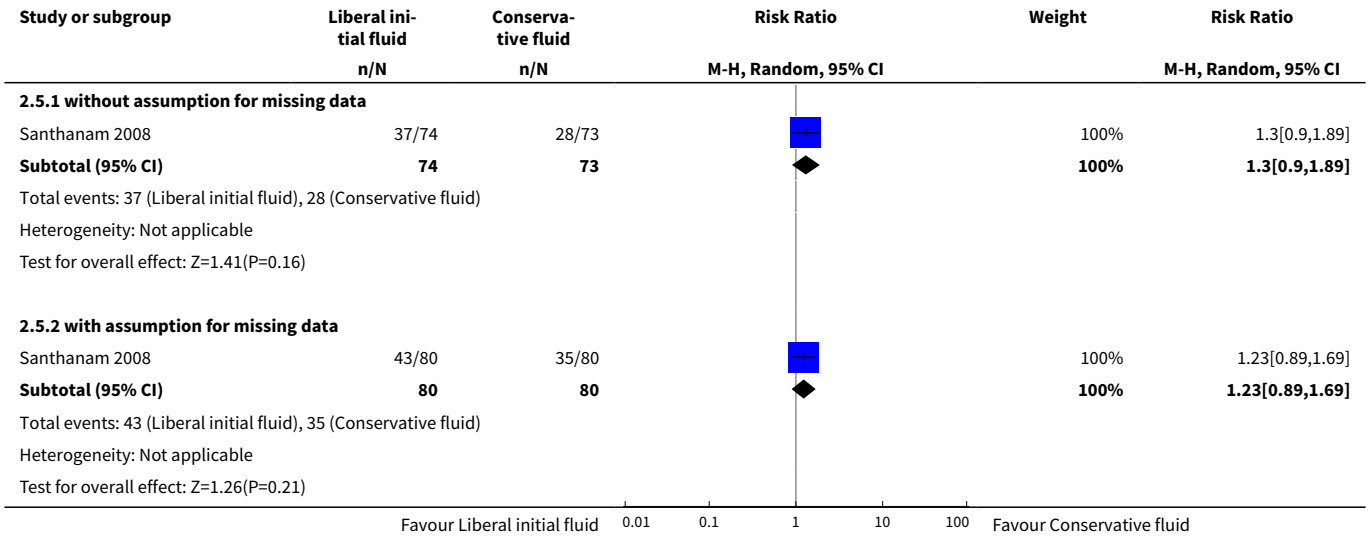
Analysis 2.3. Comparison 2 Sensitivity analysis: liberal initial fluid versus conservative fluid, Outcome 3 Adverse events: organ dysfunction - need for ventilation.



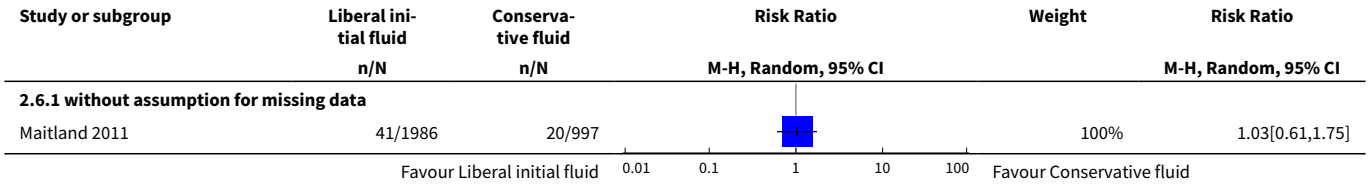
Analysis 2.4. Comparison 2 Sensitivity analysis: liberal initial fluid versus conservative fluid, Outcome 4 Adverse events: other - desaturation.

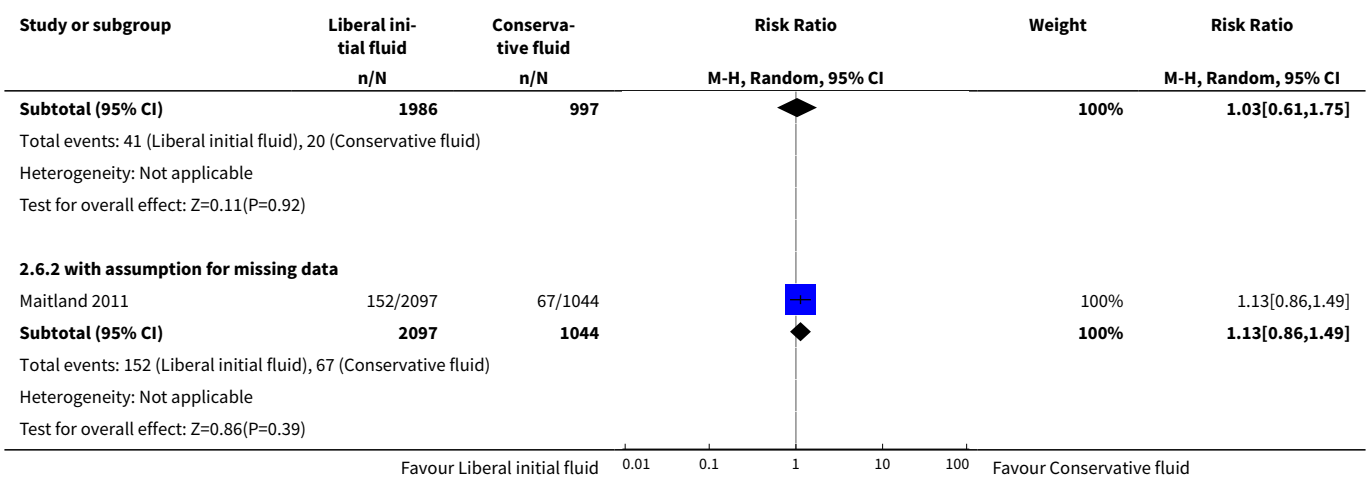


Analysis 2.5. Comparison 2 Sensitivity analysis: liberal initial fluid versus conservative fluid, Outcome 5 Adverse events: other - tracheal intubation.



Analysis 2.6. Comparison 2 Sensitivity analysis: liberal initial fluid versus conservative fluid, Outcome 6 Adverse events: other - neurological sequelae.





ADDITIONAL TABLES

Table 1. Single study data (dichotomous data)

Liberal fluid therapy vs conservative fluid therapy

Outcome		Time point	Study	Liberal fluid therapy		Conservative fluid therapy		Effect measure	Statistical test
				Events	Total	Events	Total	RR (95% CI)	P value
All-cause mortality at follow-up (4 weeks)		4 weeks	Maitland 2011	254	2097	91	1044	1.39 (1.11 to 1.74)	0.005 (NNTH = 29)
Pulmonary oedema		48 hours	Maitland 2011	20	2097	6	1044	1.66 (0.67 to 4.12)	0.27
Adverse events: organ dysfunction	Hepatomegaly	1 hour	Santhanam 2008	24	74	25	73	0.95 (0.60 to 1.50)	0.82
	Need for ventilation	< 6 hours	Santhanam 2008	38	74	32	73	1.17 (0.83 to 1.65)	0.36
Adverse events: other	Allergic reaction	48 hours	Maitland 2011	7	2097	2	1044	1.74 (0.36 to 8.37)	0.49
	Neurological sequelae	4 weeks	Maitland 2011	41	1986	20	997	1.03 (0.61 to 1.75)	0.92
	Increased intracranial pressure	48 hours	Maitland 2011	34	2097	11	1044	1.54 (0.78 to 3.02)	0.21
	Severe hypotension	48 hours	Maitland 2011	3	2097	3	1044	0.05 (0.10 to 2.46)	0.39
	Desaturation	1 hour	Santhanam 2008	22	74	12	73	1.81 (0.97 to 3.38)	0.06
	Tracheal intubation	1 hour	Santhanam 2008	37	74	28	73	1.30 (0.90 to 1.89)	0.16

CI: confidence interval; NNTH: number needed to treat for an additional harmful outcome; RR: risk ratio.

APPENDICES

Appendix 1. CENTRAL, the Cochrane Library search strategy

#1 MeSH descriptor: [Sepsis] explode all trees
#2 MeSH descriptor: [Shock, Septic] explode all trees
#3 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees
#4 MeSH descriptor: [Multiple Organ Failure] explode all trees
#5 (search sepsis* or septic* or sirs or infection* or mods or mof):ti,ab
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Fluid Therapy] explode all trees
#8 fluid therapy*
#9 #7 or #8
#10 #6 and #9

Appendix 2. MEDLINE (Ovid SP) search strategy

1. Sepsis/ or Shock, Septic/ or Infection/ or (sepsis* or septic* or sirs or infection* or shock* or mods or mof).ti,ab. or exp Systemic Inflammatory Response Syndrome/ or Multiple Organ Failure/
2. Fluid Therapy/ or fluid.ti,ab.
3. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
4. 1 and 2 and 3

Appendix 3. Embase (Ovid SP) search strategy

1. sepsis/ or septic shock/ or (sepsis* or septic* or sirs or infection* or shock* or mods or mof).ti,ab. or systemic inflammatory response syndrome/ or multiple organ failure/
2. fluid therapy/ or fluid.ti,ab.
3. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab.) not (animals not (humans and animals)).sh.
4. 1 and 2 and 3

Appendix 4. Data extraction form

Trial ID
Title
Author
Country
Citation (journal, year, volume, page)
Study type
Study quality
Participants
Diagnosis
n =
Age
Sex

(Continued)

History		
Included		
Excluded		
Intervention		
Definition of conservative fluid therapy		
Definition of liberal fluid therapy		
Outcomes		
	Intervention	Control
n =		
Mortality at 28 days		
Vasoactive agent-free days		
Pulmonary oedema		
Duration of organ dysfunction		
Number of organ dysfunctions		
Notes		

CONTRIBUTIONS OF AUTHORS

Danyang Li (DL), Xueyang Li (XL), Wei Cui (WC), Huahao Shen (HS), Hong Zhu (HZ), and Yi Xia (YX).

Conceiving the review: DL.

Co-ordinating the review: WC.

Undertaking manual searches: DL.

Screening search results: DL, WC.

Organizing retrieval of papers: WC, HS.

Screening retrieved papers against inclusion criteria: DL, WC.

Appraising quality of papers: HZ, YX.

Abstracting data from papers: DL, XL.

Writing to authors of papers for additional information: XL.

Providing additional data about papers: XL.

Obtaining and screening data on unpublished studies: DL, WC.

Managing data for the review: DL.

Entering data into Review Manager: DL.

Managing RevMan statistical data: DL.

Interpreting data: DL, WC.

Making statistical inferences: DL.

Writing the review: DL.

Securing funding for the review: none.

Performing previous work that was the foundation of the present study: none.

Serving as guarantor for the review: DL.

Reading and checking the review before submission: WC, DL, HS.

DECLARATIONS OF INTEREST

Danyang Li: no known conflict of interest.

Xueyang Li: no known conflict of interest.

Wei Cui: no known conflict of interest.

Huahao Shen: no known conflict of interest.

Hong Zhu: no known conflict of interest.

Yi Xia: no known conflict of interest.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol (Li 2013).

a. Liberal fluid therapy was regarded as the intervention and conservative fluid therapy was the control in the review. Therefore, we changed the title of the published protocol - "Liberal versus conservative fluid therapy in adults and children with sepsis or sepsis or septic shock".
b. The description of the condition/diagnosis was unclear in the previous protocol and led to confusion for readers. In the full review, we tried to clarify the definition of the condition by elaborating on the diagnosis (i.e. by clarifying what sepsis shock is and is not). The first paragraph of Types of participants now reads: "We included studies in adults and children with severe sepsis and septic shock comparing liberal versus conservative fluid therapy. Severe sepsis is defined as sepsis complicated by acute organ dysfunction. Septic shock is complicated by hypotension that is refractory to fluid, or by hyperlactataemia (Bone 1992). As described in the Background section, we noticed that the definition of sepsis has been recently changed to one provided for 'sepsis-3', which was published in *JAMA* in 2016 (Singer 2016). However, authors of this review did not adopt the new definition of sepsis for reasons stated in the previous section. We adopted the definitions for sepsis and septic shock developed in 1991 and plan to use the new definition in the update of this review. Adults and children with severe febrile illness and impaired perfusion were also eligible, thus we included them in this review."
c. The protocol states that we did not plan to undertake subgroup analysis. We made this statement because we anticipated few studies. We removed this sentence from the review.
d. We improved the presentation structure of the Types of outcome measures section in an effort to improve clarity. The changes are mostly structural, with a few minor changes made to the content. We list these changes here.
    i. We replaced "death, all-cause mortality in hospital/ICU (28 days mortality)" with "all-cause mortality (at follow-up)", as the length of follow-up is not limited to 28 days. Collecting data on the rate of mortality at follow-up is a more comprehensive approach than focusing only on 28 days.
    ii. Adverse events were not well defined in the published protocol as it did not capture all potentially important adverse events (Li 2013). The protocol states that outcomes would be grouped according to the following time points: 6, 12, and 24 hours. We removed the time points. Instead we created the outcome "other adverse events" and grouped those adverse events into two categories: organ dysfunction and other adverse events. This section now reads as follows.

Primary outcomes

a. All-cause mortality
    i. All-cause mortality (in hospital/ICU)
    ii. All-cause mortality (at follow-up)

Secondary outcomes

1. Vasoactive agent-free days in patients alive within 28 days
2. Pulmonary oedema
3. Adverse events
   a. Organ dysfunction (renal failure; respiratory failure, need for mechanical ventilation; central nervous system (CNS) dysfunction)
   b. Other adverse events: any other adverse events
4. Duration of organ dysfunction
5. Length of ICU stay
6. Ventilator-free days in patients alive within 28 days

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Fluid Therapy [adverse effects] [*methods]; Hospital Mortality; Randomized Controlled Trials as Topic; Sepsis [mortality] [*therapy]; Shock, Septic [therapy]

MeSH check words

Adult; Child; Child, Preschool; Humans; Infant