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RESEARCH

Fluid resuscitation in children with severe infection and septic shock: a systematic review and meta-analysis

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Abstract

This study aimed to evaluate the current evidence on various aspects of fluid therapy such as type, volume, and timing of fluid bolus administration in children with septic shock. Systematic review and meta-analysis of clinical trials including children less than 18 years of age admitted to the pediatric emergency and intensive care unit with severe infection and shock requiring fluid resuscitation. The intervention included balanced crystalloids (BC) *vs* normal saline (NS), colloids *vs* NS, restricted *vs* liberal fluid bolus, and slow *vs* fast fluid bolus. The primary outcome was mortality rate. Of the 219 citations retrieved, 12 trials (3526 children with severe infection with or without malaria and shock) were included. The pooled results found no significant difference in the mortality rate between groups comparing balanced crystalloids (BC) *vs* normal saline (NS), colloids *vs* NS, restricted *vs* liberal fluid bolus, and slow *vs* fast fluid bolus. The risk of acute kidney injury (AKI) was significantly less in the BC group compared to the NS group. The certainty of evidence for mortality was of "moderate certainty" in the BC vs NS group, and was of "very low certainty" for the other two groups.
Conclusions: The current meta-analysis found no significant difference in the mortality rate between the types of resuscitation fluid, and their speed or volume of administration. However, a significantly decreased risk of AKI was found in the BC group. More evidence is needed regarding the speed and volume of administration of fluid boluses in critically ill children.
Prospero registration: CRD42020209066.

What is known:
• *Balanced crystalloids (BC) may be better than normal saline (NS) for fluid resuscitation in critically ill children.*
What is new:
• *BC are better than NS for fluid resuscitation in critically ill children as they decrease AKI and hyperchloremia.*

Keywords Sepsis · Septic shock · Fluid resuscitation · Balanced crystalloids · Normal saline · Mortality · Ventilation · Children

Introduction

Fluid bolus therapy (FBT) is the initial step and has been the cornerstone in the management of children with septic shock [1]. Improving the circulatory volume, the cardiovascular dysfunction and organ perfusion are the beneficial effects of fluid bolus therapy in these children [2]. The current surviving sepsis campaign guidelines for the management of septic shock in children (2020) recommend fluid bolus up to 40–60 mL/kg (10–20 mL/kg per bolus) in places with intensive care facilities and up to 40 mL/kg in places with no intensive care facilities of a crystalloid over the first hour in children with sepsis and sepsis-induced organ dysfunction with close monitoring for features of fluid overload after each bolus [3]. However, these guidelines are based on limited evidence available and several aspects of fluid therapy need further evaluation as highlighted by the guidelines.

There is growing body of evidence suggesting the adverse consequences of fluid overload in critically ill children [4,

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5] and also the effect of fluids containing higher chloride content on acute kidney injury (AKI) in children. Also, there is limited and evolving evidence on the other aspects of fluid therapy including volume, type, and speed of administration on various clinical outcomes and in varying pathological conditions [6–17]. Hence, we conducted the current systematic review and metanalysis to find out the current evidence on the various aspects of fluid bolus therapy in children with septic shock.

Methods

This systematic review is registered in the PROSPERO database (CRD42020209066).

Search methodology

We conducted a comprehensive search including the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE via PubMed (1980 to June 15, 2023), Embase (1980 to June 15, 2023), and SCOPUS (1980 to June 15, 2023) (for reference, the detail search strategy is attached as an online supplement (eTable 1 and 2)). We also searched clinical trial registries for ongoing and recently completed clinical trials (www.clinicaltrials.gov, ISRCTN Registry, www.who.int/ictrp/en). Two review authors independently performed search strategy to identify the potential studies (RRD, KKB).

Data collection and analysis

Selection of studies

Two review authors (RRD, KKB) independently screened the titles and abstracts of the articles identified by the searches for eligibility for inclusion in the study. Any discrepancy was resolved by discussion with the third author (JS).

Inclusion and exclusion criteria

The following criteria were used for inclusion in the study.

a. Types of studies
Randomized and quasi-randomized controlled trials.
b. Types of participants
Children less than 18 years of age admitted to the emergency or intensive care unit with severe infection and shock requiring fluid resuscitation. Children with shock due to other causes, severe dengue, underlying chronic diseases, and HIV were excluded.

c. Types of interventions
As per the study objectives, following interventions were reviewed.

Type of fluid:

a Balanced crystalloids (BC)

Different volumes of fluid boluses

a Volume of fluid bolus (restricted): up to 40 mL/kg
b Volume of fluid bolus: no bolus

Speed of administration: slow (> 15 min)
Timing of administration: early (≤ 1 h)

d. Types of control
As per the objectives, they are described below.

Type of fluid

a. Normal saline (NS) or unbalanced crystalloids (UBC)
b. Colloids

Different volumes of fluid boluses

iii. Volume of fluid bolus (liberal): ≥ 60 mL/kg
iv. Volume of fluid bolus (restricted): ≤ 40 mL/kg

Speed of administration: fast (≤ 15 min)
Timing of administration: late (> 1 h)

e. Types of outcome measures

Primary outcome

a. Mortality rate

Secondary outcomes

a. Risk of acute kidney injury (AKI)
b. Risk of intubation or mechanical ventilation
c. Duration of hospital stay
d. Duration of stay in intensive care unit (ICU)
e. Risk of hyperchloremia with/without acidosis
f. Risk of acidosis
g. Any adverse events

Data extraction and management

Two review authors independently extracted the data (RRD, KKB) from each included study using a pre-designed data

extraction form. We resolved disagreements through discussion with the third author (JS).

Assessment of risk of bias in included studies

We used the "risk of bias" assessment tool and criteria set out in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess risk of bias for included studies [18]. Two review authors independently assessed the risk of bias (RRD, KKB) and resolved disagreements through discussion (JS).

Measures of treatment effect

We performed statistical analysis according to statistical guidelines referenced in the *Cochrane Handbook for Systematic Reviews of Interventions* [18]. We did sub-group analyses to see the fluid responses based on patients with underlying conditions — sepsis and malaria.

Assessment of heterogeneity

We assessed statistical heterogeneity via visual inspection of forest plots of included trials, using the chi^2 test and the I^2 statistic. We used the following cut-offs for results of the I^2 test: < 50% low, 50 to 74% moderate, and ≥ 75% high heterogeneity. In case of high heterogeneity, we used both fixed as well as random effects model to see for any difference in the results. We tried to find out the reason for heterogeneity by doing either sub-group analyses or sensitivity analyses.

Assessment of reporting biases

We assessed reporting biases by trying to identify whether the study was included in a trial registry, whether a protocol is available, and whether the "Methods" section provides a list of outcomes.

Data synthesis

We used the Review Manager 5 software to combine in the meta-analysis data for outcomes from studies that met the inclusion criteria [19]. We performed statistical analyses according to statistical guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* [18].

Certainty of evidence

We used GRADE approach, as outlined in the GRADE Handbook, to assess the certainty of evidence [20]. We used GRADEproGDT (*GRADEpro 2016*) to create a "summary of findings" table to report the certainty of the evidence.

Results

Description of studies

The literature search identified 219 citations, of which 207 were excluded for various reasons (Fig. 1). Twelve RCTs were included in the quantitative data synthesis including 3526 children with severe sepsis and shock (intervention = 1758; control = 1768) [6–17] as shown in online supplement (eTable 3). The trials were conducted in both low-and-middle-income countries (LMICs) and high-income countries (India ($n = 4$), Africa ($n = 4$), Thailand ($n = 2$), USA ($n = 1$), and UK ($n = 1$)). However, largest proportions of children (96%) were included from LMICs.

Risk of bias in the included studies

The details have been provided in the online supplement (eTable 4). Of the 12 included trials, three had a high risk of bias [7, 11, 12] and the remaining eight trials had low to moderate risk of bias in different domains.

Effects of interventions

Objective 1: To compare different types of fluids.

Four RCTs reported the results comparing different types of crystalloids (BC versus NS) [6–9]. Five RCTs reported the results comparing colloids (human albumin solution, and gelatin polymer) versus crystalloids (NS) [10–14]. Of them, three trials included children with severe malaria [11–13], one trial included children with severe sepsis [10], and the other included children with both the conditions [14].

Primary outcome

(i) Mortality rate: The pooled data from four RCTs ($N = 841$) comparing various crystalloids found no significant difference in the mortality rate between the two groups (relative risk (RR) 0.99; 95% CI 0.81 to 1.22; moderate certainty of evidence) (Fig. 2). Similarly, there was no significant difference in the mortality rate between the colloid and NS groups either for severe sepsis (one RCT, $N = 60$) (RR 1.07; 95% CI 0.49 to 2.32; very low certainty of evidence) [10] (Fig. 3) or for combination of severe malaria and severe infections (five RCTs, $N = 2369$) (RR 0.94; 95% CI 0.76 to 1.17; low certainty of evidence) (Fig. 3) [10–14]. However, the mortality rate was significantly low (three

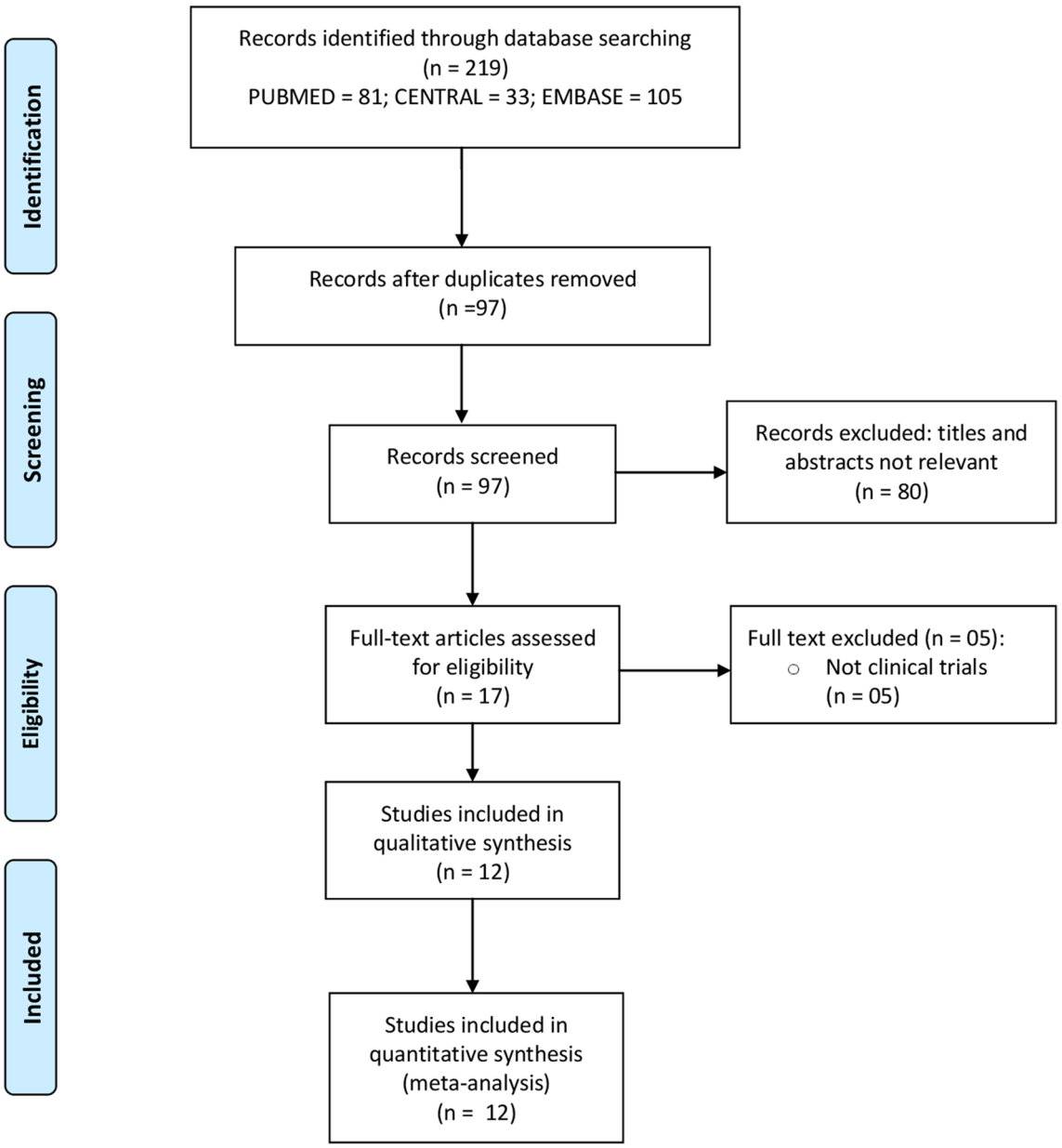


Fig. 1 PRISMA flow diagram. Legends: *n*, number of patients

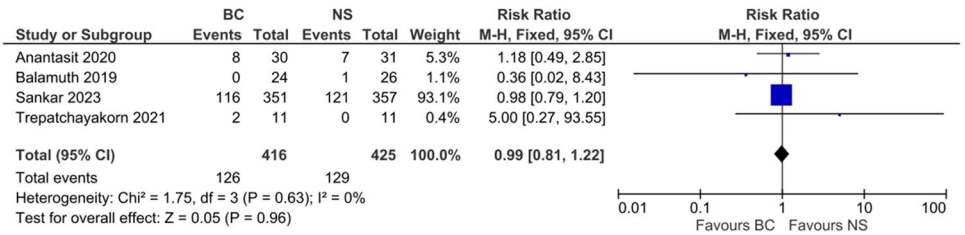


Fig. 2 Mortality rate (balanced crystalloid vs normal saline). Legends: BC, balanced crystalloid; NS, normal saline; CI, confidence interval; M-H, Mantel–Haenszel

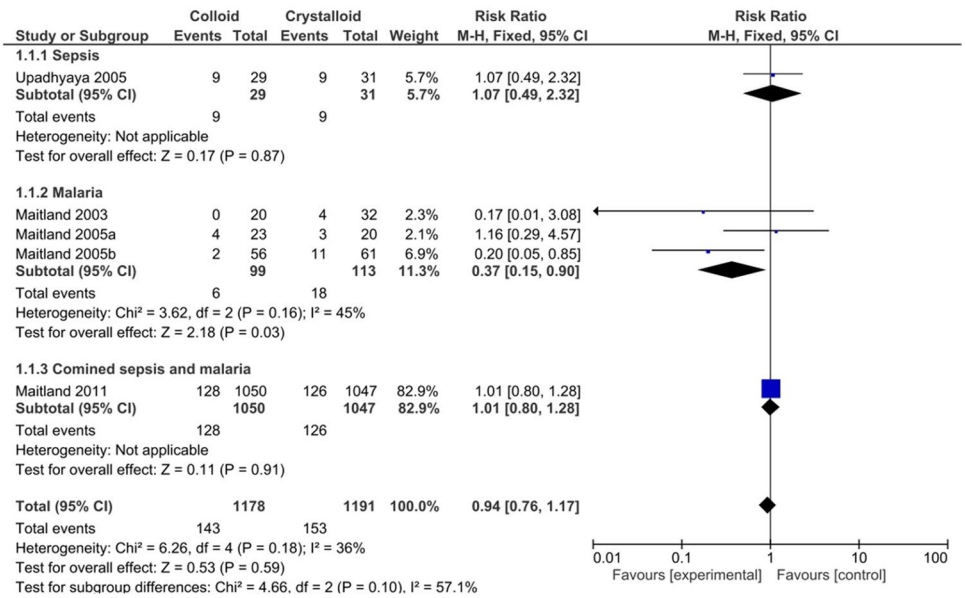


Fig. 3 Mortality rate (colloids vs crystalloids). Legends: CI, confidence interval; M-H, Mantel–Haenszel

RCTs, $N = 212$) (RR 0.37; 95% CI 0.15 to 0.9; very low certainty of evidence) in a subgroup of children with severe malaria (Fig. 3) [14].

Secondary outcomes

(i) Rate of acute kidney injury (AKI): The pooled data from four RCTs ($N = 841$) comparing various crystalloids found a significant decrease in the risk of AKI in the BC group (RR 0.67; 95% CI 0.53 to 0.85; moderate certainty of evidence) [6–9] (eFigure 1). The pooled data from a single RCT ($N = 60$) comparing colloids versus crystalloids did not find a significant difference in the risk of AKI between the two groups (RR 0.36; 95% CI 0.04 to 3.23; very low certainty of evidence) [10] (eFigure 2).

(ii) Risk of hyperchloremia (± acidosis): The pooled data from three RCTs ($N = 565$) comparing various crystalloids found a significant decrease in the risk of hyperchloremia (± acidosis) in the BC group (RR 0.69; 95% CI 0.58 to 0.82; moderate certainty of evidence) [6, 8, 9] (eTable 5). There was no heterogeneity (0%).

(iii) Duration of hospital stay (*d*): The pooled data from four RCTs ($N = 841$) comparing various crystalloids found a significant difference between the two groups (MD − 0.66; 95% CI − 1.09 to − 0.24; moderate certainty of evidence) with decrease in hospital stay duration of 16 h in the intervention group [6–9] (eTable 5). There was no heterogeneity (0%).

(iv) Duration of pediatric ICU stay (*d*): The pooled data from 3 RCTs ($N = 791$) comparing various crystalloids found a significant difference between the two groups (MD 0.31; 95% CI 0.09 to 0.53; moderate certainty of evidence) with the duration of stay being longer by 8 h in the intervention group [6, 7, 9] (eTable 5). There was no heterogeneity (0%).

(v) Other adverse events: Though the results could not be pooled, there was no significant difference between the two groups for any other reported adverse events (electrolyte disturbance, pulmonary edema, vaso-active infusion, cerebral edema) as reported in the included trials.

Objective 2: To compare different volumes of fluid boluses.

Three RCTs ($N = 2311$) reported the results comparing different volumes of fluid boluses [14, 16, 17]. Two RCTs compared restricted (≤ 40 mL/kg) versus liberal (≥ 60 mL/kg) fluid bolus in the first hour of resuscitation [16, 17]. One of them compared 10 mL/kg vs 20 mL/kg bolus after initial resuscitation [17]. The third trial compared no bolus versus normal fluid bolus [14].

Primary outcome

(i) Mortality rate: The data were pooled from two RCTs ($N = 220$) comparing restricted versus standard fluid bolus. There was no significant difference in the risk of mortality (RR 0.99; 95% CI 0.49 to 1.98; very low certainty of evidence) (Fig. 4) [16, 17]. One large trial compared no bolus versus fluid bolus of 20 mL/kg (maximum up to 40 mL/kg) and found a significant decrease in the risk of mortality in the no bolus group (RR 0.72;

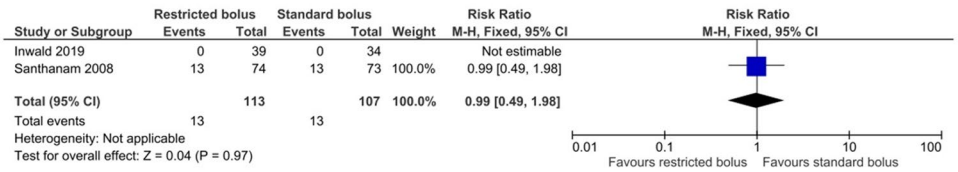


Fig. 4 Mortality rate (restricted vs liberal fluid bolus). Legends: CI, confidence interval; M-H, Mantel–Haenszel

95% CI 0.56 to 0.94; very low certainty of evidence) [14] (eTable 5).

Secondary outcomes

The detailed analysis is provided as online supplement (eTable 5).

(ii) Risk of intubation/mechanical ventilation: The data were pooled from a single RCT ($N=73$), and there was no significant difference between the two groups (RR 0.44; 95% CI 0.15 to 1.34; very low certainty of evidence) [17].
(iii) Duration of hospital stay (*d*): The data were pooled from two RCTs ($N=220$), and there was no significant difference between the two groups (MD − 0.23; 95% CI − 1.01 to 0.55; very low certainty of evidence) [16, 17].
(iv) Duration of ICU stay (*d*): The data were pooled from a single RCT ($N=21$), and there was no significant difference between the two groups (MD − 2.64; 95% CI − 7.25 to 1.97; very low certainty of evidence] [17].
(v) Rate of acute kidney injury (AKI), risk of hyperchloremia (± acidosis), and other adverse events: These were not reported by restricted versus standard volume of bolus [16, 17]. However, the trial comparing no bolus versus bolus reported about other adverse events (raised intracranial pressure, pulmonary edema, allergic reaction, and neurological sequelae), but found no difference between the two groups [14].

Objective 3: To compare fast (≤ 15 min) versus slow (> 15 min) administration of fluids.

Two RCTs ($N=243$) from India reported the results of their studies comparing fast (≤ 15 min) versus slow (> 15 min) administration of fluids in children with septic shock [15, 16].

Primary outcome

(i) Mortality rate: The data were pooled from two RCTs ($N=243$), and there was no significant difference in the risk of mortality between the two groups (RR 0.9; 95% CI 0.59 to 1.37; very low certainty of evidence) (Fig. 5) [15, 16].

Secondary outcomes

The detailed analysis is provided as online supplement (eTable 5).

(ii) Risk of intubation/mechanical ventilation: The data were pooled from two RCTs ($N=243$). There was significantly increased risk of intubation/mechanical ventilation (RR 1.34; 95% CI 1.03 to 1.75; very low certainty of evidence) in the fast bolus group [15, 16].
(iii) Duration of ICU stay (*d*): The data were pooled from a single RCT ($N=96$), and there was no significant difference between the two groups (MD 0.6; 95% CI − 1.1 to 2.3; very low certainty of evidence) [15].
(iv) Duration of hospital stay (*d*), rate of acute kidney injury (AKI), risk of hyperchloremia (± acidosis), and other adverse events: These were not reported by any of the trials.

Objective 4: To compare early (≤ 1 h) versus late (> 1 h) administration of fluids.

We could not find any trial comparing early vs late administration of fluids.

Sensitivity analysis and sub-group analysis

As there were few studies with limited sample size, and no or low heterogeneity among the included trials, we did not carry out either sensitivity analyses or sub-group analyses.

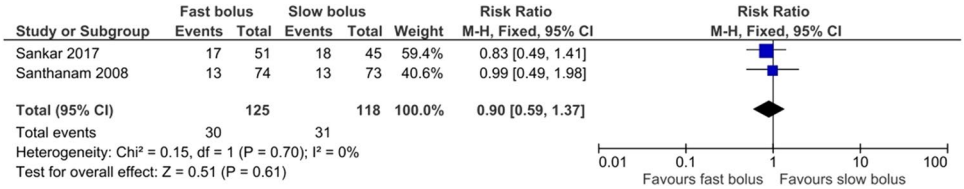


Fig. 5 Mortality rate (fast vs slow fluid bolus). Legends: CI, confidence interval; M-H, Mantel–Haenszel

Publication bias

Because of an insufficient number of trials (less than 10) included in this meta-analysis for the primary outcome data, we could not assess publication bias by constructing a funnel plot.

GRADE evidence

A detailed analysis of the summary of evidence is provided as online supplements (eTables 6, 7 and 8).

Discussion

We found that in four RCTs comprising of 841 children, although there was no significant difference in mortality rate, children in the balanced fluid group had less risk of acute kidney injury and hyperchloremia (moderate certainty of evidence). However, the majority of children are from one study from a developing nation. A recent systematic review including 162 children found that use of balanced fluids is associated with improvement in blood pH and bicarbonate levels [21]. In adults, in a recent systematic review, it was observed that the use of crystalloids is associated with high probability of decreasing mortality [22]. The decreased risk of AKI with balanced fluids is due to low chloride content in the balanced fluids leading to less hyperchloremia, less hyperchloremia related inflammation, renal blood flow velocity, and decreased GFR [6, 23]. With beneficial effects in both adults and children, it is time for us to shift to balanced fluids during initial resuscitation and the recent "Survival Sepsis Campaign Guideline (SSG)" have recommended balanced fluids over NS in the initial fluid resuscitation in children as well as adults [3, 24] and the results of our systematic review add strength to this recommendation.

When comparing crystalloids with colloids in septic shock, in the only available study with a small sample size, there was no significant difference in mortality or AKI. From three RCTs, in children with malaria, it was found that there is decreased mortality in children receiving albumin instead of crystalloids. However, the results were not significant when all studies on use of colloids were combined. With limited availability, associated cost, and paucity of evidence, colloids may not be useful in children with sepsis and may be more useful in children with malaria, malnutrition, or third spacing, and further research is needed in these specific subgroups of populations.

The initial American College of Critical Care Medicine (ACCM) and SSG guidelines has recommended fluid boluses up to 60 mL/kg in the initial resuscitation of hemodynamically unstable children [25]. However, with the vast data on the adverse effects of fluid overload in critically ill children including mortality [26], aggressive fluid resuscitation is being closely monitored. The FEAST trial has questioned the aggressive fluid resuscitation approach being followed in children with shock. Although it showed mortality benefit in children with no fluid bolus, there were caveats including greater proportion of children with malaria and severe anemia. From the two studies included in our systematic review comparing restrictive fluid therapy during resuscitation, there was no significant difference in mortality or need for mechanical ventilation with restrictive fluid strategy. This limited evidence on restrictive fluid approach during resuscitation further highlights the need for more studies with large number of children for evaluating the best fluid strategy in children with septic shock.

The initial guidelines have recommended administering fluid bolus as rapidly as possible by push pull technique in children with decreased perfusion [24]. A trial including children with septic shock observed that with liberal fluids during the first hour of resuscitation, there was greater hepatomegaly at 20 min, although other parameters were not significantly different [16]. In the current systematic review, we found that from the two RCTs included, children in the rapid fluid bolus group had increased requirement of mechanical ventilation as compared to the slow fluid bolus therapy, although there was no difference in mortality. This has a great clinical significance as with high prevalence of malnutrition and sepsis-induced myocardial dysfunction, the speed of fluid administration may have to be curtailed to prevent the adverse consequences especially in resource limited settings. With evolving literature and pros and cons of fluid administration, the principles of fluid therapy need to be revisited.

Strengths and limitations

Current systematic review is the first systematic review in critically ill children to evaluate and summarize the various aspects of fluid therapy including type of fluids, restrictive versus liberal approach, and fast versus slow bolus. We included studies from both LMIC and developed nations which makes the results more generalizable. Our review has few limitations. First, the numbers of included studies are less. Second, some included studies were old considering the change in the fluid management in critically ill children over time.

Conclusions

The current systematic review highlights that the use of balanced crystalloids is associated with lower risk of hyperchloremia and acute kidney injury. No conclusive evidence on the use of colloids in sepsis. However, there is significantly decreased mortality in children with malaria with use of colloids. Faster administration of fluid boluses is associated with higher risk of

mechanical ventilation. There is limited evidence on the use of restrictive fluid strategy during initial resuscitation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-024-05653-w.

Author's contributions Conceptualization: JS, RRD; Methodology and carrying out of the experiment: RRD, JS, KKB; Formal analysis and investigation: RRD, KKB; Writing of initial draft: JS, RRD; Review and editing: JS, RRD, KKB; Guarantor: JS. All the authors have seen and approved this version for publication.

Data Availability All the data are published with this manuscript and there are no unpublished data. For any additional information, the corresponding author can be contacted.

Declarations

Ethics approval Not required for this study.

Competing interests The authors declare no competing interests.

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