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Associations Between Fluid Balance and Outcomes in Critically Ill Children: A Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Fluid therapy is a mainstay during the resuscitation of critically ill children. After initial stabilization, excessive fluid accumulation may lead to complications of fluid overload, which has been independently associated with increased risk for mortality and major morbidity in critically ill children.
Objectives: Perform an evidence synthesis to describe the methods used to measure fluid balance, define fluid overload, and evaluate the association between fluid balance and outcomes in critically ill children.
Design: Systematic review and meta-analysis.
Measurements: Fluid balance, fluid accumulation, and fluid overload as defined by authors.
Methods: We will search Ovid MEDLINE, Ovid EMBASE, Cochrane Library, and ProQuest, Dissertations and Theses. In addition, we will search www.clinicaltrials.gov, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and the proceedings of selected key conferences for ongoing and completed studies. Search strategy will be done in consultation with a research librarian. Clinical trials and observational studies (from database inception to present) in patients (<25 years) admitted to pediatric intensive care units (PICUs) reporting fluid balance, fluid accumulation, or fluid overload, and associated outcomes will be included. Language will not be restricted. Two reviewers will independently screen studies and extract data. Primary outcome is mortality, and secondary outcomes encompass critical care resource utilization. Quality of evidence and risk of bias will be assessed using the Newcastle-Ottawa Scale (NOS). Results will be synthesized qualitatively and pooled for meta-analysis if possible.
Limitations: Quality of the included studies; lack of randomized trials; high degrees of expected heterogeneity; and variations in definitions of fluid balance and fluid overload between studies.
Conclusion: We will comprehensively appraise and summarize the evidence of the association between fluid balance and outcomes in critically ill children, and in doing so attempt to harmonize definitions related to fluid balance, accumulation, and overload.
Systematic review registration: PROSPERO: CRD42016036209.

Abrégé

Mise en contexte: Une saine gestion des fluides est cruciale lors de la réanimation des enfants gravement malades puisqu'à la suite de la stabilisation du patient, l'accumulation excessive de liquides est susceptible de conduire à des complications. La surcharge liquidienne chez les enfants gravement malades a été associée de façon indépendante avec un risque accru de mortalité et à une morbidité plus importante.
Objectifs de l'étude: Cette étude vise à faire la synthèse des données probantes utilisées pour décrire les méthodes de mesure de l'équilibre hydrique, à mieux définir la surcharge liquidienne et à évaluer le rapport entre l'équilibre hydrique et les résultats observés chez les enfants gravement malades.
Type d'étude: L'étude s'effectuera sous la forme d'une revue systématique de la littérature suivie d'une méta-analyse.
Mesures: L'étude tiendra compte de l'équilibre hydrique, de l'accumulation de fluides et de la surcharge hydrique tels que ces termes sont définis par les auteurs.
Méthodologie: Les bases de données Ovid MEDLINE et Ovid EMBASE, de même que ProQuest, la Cochrane Library et les mémoires et thèses sur le sujet seront fouillés. Nous chercherons également sur le site internet www.clinicaltrials.gov, la plateforme WHO ICTRP (World Health Organization International Clinical Trials Registry Platform) et les comptes rendus

d'une sélection de conférences traitant d'études complétées ou en cours sur le sujet. La stratégie de recherche sera établie en collaboration avec un bibliothécaire de recherche. La revue colligera les essais cliniques et les études observationnelles répertoriés dans les bases de données qui font mention de l'équilibre hydrique, de l'accumulation de fluides, de surcharge liquidienne et des issues sur la santé associées à ceux-ci chez les patients de moins de 25 ans admis dans les unités de soins intensifs pédiatriques. La recherche ne sera pas restreinte à une langue en particulier. La sélection des études et l'extraction des données seront effectuées de manière indépendante par deux réviseurs. Le principal résultat observé sera la mortalité du patient, le second concernera l'utilisation des ressources en matière de soins critiques. La qualité des données retenues et le risque de biais seront évalués par la méthode de l'échelle de Newcastle-Ottawa. Les résultats seront synthétisés de façon qualitative et, si possible, regroupés en vue d'une méta-analyse.

Limites de l'étude: Les conclusions pourraient être limitées par la qualité inégale des études répertoriées, le manque d'essais cliniques randomisés, un fort degré d'hétérogénéité des données recueillies, et en raison de variations entre les études sélectionnées dans leur définition des termes équilibre hydrique et surcharge liquidienne.

Conclusions: Nous proposons de résumer et d'évaluer de manière globale les preuves rapportées dans la littérature d'une association entre l'équilibre hydrique et les issues sur la santé des enfants gravement malades. Parallèlement, nous souhaitons contribuer à harmoniser les définitions des termes équilibre hydrique, accumulation de fluides et surcharge liquidienne.

Keywords
fluid balance, fluid overload, resuscitation, pediatric, critical illness, mortality

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What was known before

Positive fluid balance is common in critically ill children and independently associated with worse outcomes.

What this adds

This systematic review will comprehensively appraise and summarize the evidence evaluating the association between fluid balance and outcomes in critically ill children

Background

Fluid therapy is the cornerstone of resuscitation in critically ill children. Reestablishment of adequate intravascular volume using early aggressive fluid administration is lifesaving.[1-3] Moreover, beyond fluid therapy directed at resuscitation, critically ill children often receive variable amounts of obligatory fluid intake (ie, medications, nutrition, transfusions).[4,5] This cumulative fluid delivery often exceeds net fluid loss, leading to a positive fluid balance. Growing body of circumstantial evidence suggests that the accumulation of fluid beyond the initial resuscitation phase may exert an incremental risk for major morbidity and mortality.[4-10] These observations highlight the importance of monitoring fluid status and evaluating for the degree of fluid accumulation. As a consequence, fluid balance is routinely measured in critically ill children using several methods such as recorded daily intake-output and serial body weight measurements. However, the precision of such methods in accurately reflecting intravascular volume status or reliably correlating with the clinical manifestations of fluid accumulation is questionable.[11-14]

The concept of "fluid overload" has been described in the literature using various definitions. Although some of the proposed definitions have been shown to correlate with outcomes, it is unclear how generalizable some of these findings are in light of study size and design limitations. The majority of prior studies were small, single center, and often evaluated fluid overload in specific clinical settings (such as bone marrow

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transplant or post–cardiac surgery patients). Significant discrepancy in fluid overload estimation can occur, depending on the definition used.[15] Furthermore, none of these definitions integrated the rate of fluid accumulation and the time frame in which it occurred in relation to different phases of critical illness. There is no broad consensus on how to precisely and reliably define the terms fluid accumulation and fluid overload, and we believe this may be hindering progress in the field.

In view of these limitations, we aim to conduct a systematic review and meta-analysis to appraise and synthesize the evidence describing the methods to measure fluid balance, define fluid overload, and evaluate the association between the various fluid-related metrics and outcomes in critically ill children. Synthesis of the available evidence is an important step in providing a foundation that will harmonize the various definitions of fluid metrics and help develop future interventional strategies to prevent or mitigate avoidable fluid accumulation and overload.

Objectives

- Describe the methods used to measure fluid balance in critically ill children
- Describe the definitions for fluid balance, fluid accumulation, and fluid overload in critically ill children
- Evaluate the association between fluid balance and mortality in critically ill children
- Evaluate the association between fluid balance and organ dysfunction and resource utilization in critically ill children.

Methods

Study Design

We will perform a systematic review and meta-analysis focused on critically ill children exploring the methods used to assess fluid balance, define fluid overload, and evaluate the association between fluid balance and outcomes. Our review will follow the format recommended by the Cochrane and Center for Reviews and Dissemination, and described according to the PRISMA-P guideline[16,17] (Additional file 1).

Study Registration

This systematic review has been registered with PROSPERO (CRD42016036209) in March 2016.

Criteria for Considering Studies for This Review

Inclusion criteria. All included studies will fulfill each of these criteria:

1. Population: studies enrolling patients below 25 years of age, admitted to a pediatric critical care setting.
2. Design: studies reporting original data incorporating interventional (randomized controlled trials or quasi-randomized controlled trials), cohort or case-control studies.
3. Exposure: studies describe a measure of fluid balance, fluid accumulation, and/or fluid overload.
4. Outcome: studies describe at least one of the following outcomes of interest:

Primary outcome

- 28-day mortality

Secondary outcomes

- Severity of illness scores (eg, Pediatric Risk of Mortality [PRISM])
- Organ failure scores (eg, Pediatric Logistic Organ Dysfunction [PELOD])
- Specific organ system dysfunction:
    - PaO_2/FiO_2 ratio and/or oxygenation index
    - Receipt and duration of mechanical ventilation
    - Receipt and duration of renal replacement therapy
- Receipt and duration of extracorporeal life support (ECLS)
- Duration of pediatric intensive care unit (PICU) and hospital length of stay

Exclusion criteria

1. Adult studies (age ≥25 years)
2. Neonatal studies inclusive of premature infants or infants younger than 4 weeks of age
3. Case reports, case series, or observational studies that do not include a control/comparator
4. Studies conducted in noncritical care settings

Search Strategy for Identification of Studies

The search strategy was developed in consultation with an experienced research librarian and independently peer-reviewed by a second librarian.[18] The search will be inclusive of all publications from database inception to present. We will search Ovid MEDLINE In-Process & Other Non-indexed Citations and Ovid MEDLINE, Ovid EMBASE, Cochrane Library via Wiley, and ProQuest Dissertations and Theses Global. In addition, www.clinicaltrials.gov and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) will be searched for ongoing and completed clinical trials. We will perform a search of selected conference proceedings held within the last 3 years for the Society of Critical Care Medicine (SCCM), Canadian Critical Care Society, the European Society of Intensive Care Medicine (ESICM), the International Symposium on Intensive Care and Emergency Medicine (ISICEM), the World Federation of Pediatric Intensive and Critical Care Societies, American

Society of Nephrology (ASN), International Society of Nephrology (ISN), International Symposium on AKI in Children, and International Conference on Paediatric Continuous Renal Replacement Therapy (pCRRT). There will be no language restriction. Authors will be contacted by email to request additional data not described in a primary publication or data from unpublished studies if applicable. Our search strategy will use a combination of subject headings and text words for concepts related to children, critical illness, and fluid balance (Additional file 2). Finally, we will manually search for relevant studies using reference lists of retrieved citations and prior reviews of similar topics. Search results will be organized using EndNote X7 citation management software (Thomson Reuters, Philadelphia, Pennsylvania).

Data Extraction and Analysis

All identified titles and abstracts of studies examining the association between fluid balance and outcomes in pediatric population will be initially assessed independently by 2 reviewers for potential relevance. Selected studies will be retrieved and then be subjected to a second phase of screening for eligibility, as determined by the eligibility criteria listed above. Reason(s) for ineligibility will be documented for all studies excluded in the second phase of screening. Disagreements will be resolved through discussion or by a third reviewer if necessary.

A standardized data extraction form (Additional file 3) will be piloted and then used to extract data from the reports of all included studies in duplicate, and independently by 2 reviewers. Discrepancies in extracted data will be resolved by consensus, and if consensus cannot be reached, decisions will be left to the senior author (S.M.B).

Abstracted data from each study will include the details on the following:

- Study design, methodology, analysis, funding source, registration, and publication details.
- Aggregate participant demographic characteristics (eg, age, sex, and race).
- Aggregate participant clinical characteristics (eg, comorbid diseases, admission diagnostic category, and surgical status).
- Operational definitions for fluid balance, accumulation, and fluid overload, data on daily and cumulative fluid balance, and proportion and timing of occurrence of fluid accumulation and fluid overload.
- All primary and secondary outcomes reported, with their effect size and confidence intervals.
- Study quality features (see below).

Assessment of Methodological Quality and Risk of Bias

Studies selected for retrieval will be assessed by 2 independent reviewers for methodological quality and risk of bias. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer (S.M.B.). The Newcastle-Ottawa Scale (NOS) will be used to assess the methodological quality of the included study.

Data Synthesis/Analysis Plan

The results of our search will be reported in a PRISMA flowchart. We will present tables outlining (1) study characteristics, (2) risk of bias for each study, and (3) study results and their effect measures. Quantitative studies will, where possible, be pooled in statistical meta-analysis. We will use random effects model to pool effect sizes for each outcome; study weights will be measured using the inverse variance method. Dichotomous outcomes will be reported, where possible, as pooled odd ratios and 95% confidence intervals based on the random effects model. Continuous outcomes will be reported using calculated weighted mean differences with their 95% confidence intervals. We will use the DerSimonian and Laird method to compute between-studies variance.[19] Results will be presented in forest plot using Review Manager (RevMan 5.3) software. We will contact authors for missing data, and if not possible, the potential impact of missing data on the results will be reported in the "Discussion" section. If statistical pooling is not possible, or if there are data from only 1 study for an outcome, the findings will be presented in narrative form. A priori, we have not defined a degree of heterogeneity that would preclude meta-analytic pooling.

Assessment of Heterogeneity

Clinical heterogeneity will be assessed by comparing the populations, exposures, and outcome measurements in all included studies. We will address clinical heterogeneity using subgroup and sensitivity analyses. Heterogeneity will be assessed statistically using I^2 statistics and categorized as <25%, 25% to 50%, 50% to 75%, and >75%.[20] Heterogeneity will also be evaluated using forest plots and sensitivity analyses based on the different study designs included in the review.

Assessment of Reporting Bias

We will assess potential reporting bias using a funnel plot if a sufficient number of studies are identified (>10 studies). Visual assessment and variance-stabilizing regression method will be used to test funnel plot asymmetry.

Subgroup Analysis

Depending on the number of studies included in the final analysis, the following subgroup analyses will be performed:

1. Infants (<1 year of age) and older children.
2. Children with primary cardiac and noncardiac diagnosis.

3. Sepsis and nonsepsis diagnosis.
4. Surgical and nonsurgical admissions.

Discussion

While timely fluid administration can be lifesaving, it has been suggested that the accumulation of fluid after initial resuscitation and hemodynamic stabilization can contribute to potentially avoidable adverse consequences and less favorable outcomes. Available studies of fluid balance in pediatric critical illness show that positive fluid balance potentially exerts an independent increased risk for mortality and adverse events, including worsening pulmonary and kidney function, longer duration of mechanical ventilation, and longer duration of PICU stay. While provocative, current evidence is largely derived from small, single-center, retrospective cohort studies, where variable definitions for fluid overload have been applied. The prevention or attenuation of fluid accumulation could improve patient-centered outcomes and health resource utilization.

Expected Limitations

The review may be limited by the quality of the included studies and a lack of pediatric interventional studies focused on this subject. Differences in definitions of fluid balance and fluid overload between studies may restrict the ability to synthesize the study findings. It also may be limited because of significant clinical or statistical heterogeneity between studies. The absence of specific fluid metrics data in some studies may limit our ability to include them in the meta-analysis. The number of studies included in the final analysis, their sample size, and access to individual data will determine the ability to conduct the proposed subgroup analyses.

Conclusion

We will perform a systematic review and evidence synthesis of fluid balance, accumulation, and overload among critically ill children and its association with patient-centered and health services outcomes. We expect our review will describe the broad impact of fluid accumulation and provide a foundation that will harmonize the various definitions for fluid metrics. This will help the development of future interventional strategies to prevent or mitigate avoidable fluid accumulation with the goal of improving outcomes for critically ill children at high risk of adverse events.

List of Abbreviations

AKI, acute kidney injury; CPB, cardiopulmonary bypass; CRRT, continuous renal replacement therapy; ECLS, extracorporeal life support; NOS, Newcastle-Ottawa Scale; PELOD, Pediatric Logistic Organ Dysfunction; %FO, percent fluid overload; PICU, pediatric intensive care unit; PRISM, Pediatric Risk of Mortality; RRT, renal replacement therapy.

Ethics Approval and Consent to Participate

As this is a protocol for a systematic review ethics approval and consent to participate is not required.

Availability of Data and Supporting Materials

Additional file 1: Preferred Reporting Items for Systematic review and Meta-analysis Protocols (PRISMA-P) 2015 checklist: recommended items to address in a systematic review protocol.
Additional file 2: MEDLINE search strategy.
Additional file 3: Data extraction form.

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Author Contributions

RA was responsible for the preparation of the protocol and drafting the early manuscript. CM, ES, RKB, and SRM provided content expertise and assisted with preparation of the protocol and manuscript. SMB and RA were responsible for finalizing the protocol, and completion of the final manuscript. RF developed the search strategy in consultation with RA and SMB. All authors provided critical revision of the protocol and final manuscript. SMB will guarantee the content of the protocol. All authors approved the final manuscript and consented for publication.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: S.M.B. has received consulting fees and honoraria from Baxter Healthcare Corp.

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