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Protocol for a systematic review and meta-analysis assessing conservative versus liberal intravenous fluid administration in patients with sepsis or septic shock at risk of fluid overload

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ABSTRACT

Introduction Intravenous crystalloid fluid resuscitation forms a crucial part of the early intervention bundle for sepsis and septic shock, with the Surviving Sepsis Campaign guidelines recommending a 30 mL/kg fluid bolus within the first hour. Compliance with this suggested target varies in patients with comorbidities such as congestive heart failure, chronic kidney disease and cirrhosis due to concerns regarding iatrogenic fluid overload. However, it remains unclear whether resuscitation with higher fluid volumes puts them at greater risk of adverse outcomes. Thus, this systematic review will synthesise evidence from existing studies to assess the effects of a conservative as compared with a liberal approach to fluid resuscitation in patients at greater perceived risk of fluid overload due to comorbid conditions.

Methods and analysis This protocol was registered on PROSPERO and has been drafted following the checklist of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. We will search MEDLINE, MEDLINE Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations, Embase, Embase Classic, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Web of Science Core Collection, CINAHL Complete and ClinicalTrials.gov. A preliminary search of these databases was performed from their inception to 30 August 2022. The risk of bias and random errors will be assessed using the revised Cochrane risk-of-bias tool for randomised clinical trials and the Newcastle-Ottawa Scale for case–control and cohort studies. If a sufficient number of comparable studies are identified, we will perform a meta-analysis applying random effects model. We will investigate heterogeneity using a combination of visual inspection of the funnel plot as well as the Egger's test.

Ethics and dissemination No ethics approval is required for this study since no original data will be collected. The findings will be disseminated through peer-reviewed publication and conference presentation.

PROSPERO registration number CRD42022348181.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A comprehensive systematic review of the management of patients with sepsis and comorbidities that may place them at greater risk of volume overload.
⇒ A search algorithm developed by an experienced medical librarian and customised for all databases.
⇒ Lack of language restrictions in the selection of the studies.
⇒ Quality of evidence dependent on the number of studies available and the variability in the intervention of interest (ie, time periods of interest and/or definitions of liberal vs conservative fluids).

INTRODUCTION

Timely intravenous fluid resuscitation has become one of the cornerstones in the management of patients with sepsis following studies that demonstrated that early, goal-directed therapy improves outcomes in sepsis and septic shock.[1] Subsequent versions of the Surviving Sepsis Campaign (SSC) guidelines have adopted 30 mL/kg bolus of intravenous crystalloid solution as one of the targets for initial fluid resuscitation goals,[2] although to varying degrees of recommendation strength. As such, fluid resuscitation has been adopted widely into clinical practice[3]; however, there has been marked variability with regard to the precise volume administered.[4]

Practice variability is especially pronounced in the management of patients with congestive heart failure (CHF), cirrhosis and chronic kidney disease (CKD).[5–7] The pathophysiology of these conditions typically dictates management principles that aim to reduce both preload and afterload, which is in stark contrast to aggressive fluid administration and the use of vasopressors in sepsis. Physicians therefore must weigh the possible risk

of intubation engendered by iatrogenic fluid overload against the need for higher doses of vasopressor support to maintain tissue perfusion in the face of distributive shock.[8] These patient populations thus present a unique challenge to healthcare providers. Due to concerns around precipitating volume overload and subsequent respiratory failure that warrants mechanical ventilation, these patients face a greater delay to fluid initiation as well as receive less volume.[6 7 9] Notably, the SSC guidelines do not make any special considerations for patient populations at potential risk of volume overload in their recommendations surrounding fluid resuscitation.

This dilemma has been the subject of a previous meta-analysis conducted by Pence *et al*[10]; however, this study was limited to patients with CHF and CKD, included five studies across two databases and may be limited in scope. By expanding search parameters across multiple databases using a customised search strategy developed by an experienced medical librarian, and by including additional comorbidities at risk of volume overload, our objective is to capture the full spectrum of available evidence to help guide management principles in such situations. Thus, the aim of this systematic review is to evaluate the effects of conservative versus liberal volumes in the resuscitation of patients with sepsis who are deemed to be at high risk of fluid overload.

METHODS

Our systematic review protocol was registered in accordance with guidelines with the International Prospective Register of Systematic Reviews (PROSPERO) on 1 September 2022 (registration number: CRD42022348181). This systematic review will be reported following the checklist of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.[11] In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

Eligibility criteria

Types of studies

This study will include randomised controlled trials (RCTs), cluster RCTs and controlled clinical trials, as well as prospective and retrospective cohort and case–control studies. Conference abstracts published within the last 6 years (2016 onwards) will be included. We will include studies without language restrictions.

Types of participants

Studies will be considered for inclusion if they included adults (aged 18 years and over) who present to the emergency department or are admitted to the ward or intensive care unit (ICU) and are diagnosed with sepsis or septic shock, along with a comorbidity that places them at greater risk of fluid overload: CHF, CKD, cirrhosis or pulmonary hypertension.

Types of interventions

We will include all studies that compare outcomes related to different volumes of intravenous fluid therapy administered during the resuscitation stage or initial management, as defined in the original study. The exact cut-offs that comprise 'conservative' versus 'liberal' volume will also be as defined in the original study. If the volume of intravenous fluid therapy is part of a multimodel intervention (eg, bundle of sepsis care), the study will be excluded if the intravenous fluid attributable outcome cannot be ascertained. We will limit our search to studies comparing the volume of crystalloid solutions independent of the choice of crystalloid solutions.

Types of control

The comparison of interest will be usual care (ie, liberal intravenous fluid therapy), as defined by the original study.

Types of outcomes

The primary outcome of interest will be all-cause mortality up to 30 days after hospital discharge. Secondary outcomes of interest will include: (1) need for intubation during admission following fluid resuscitation, (2) duration of mechanical ventilation, (3) ICU and hospital length of stay, (4) ICU mortality, (5) vasopressor requirement, (6) hypoxaemic respiratory failure, including use of non-invasive positive pressure ventilation, (7) intravenous diuretic requirement and (8) need for any renal replacement therapy.

Search strategy

Literature search strategies were developed in collaboration with a medical librarian with expertise in systematic reviews using controlled vocabulary and text word search elements for each of the following concept blocks: (fluids or fluid resuscitation) AND (sepsis or septic shock) AND (selected diseases, including heart failure, ventricular dysfunction, liver cirrhosis, kidney failure) AND (quantitative studies). We used 10 potentially relevant test articles to test and build the search. These articles were identified using the function similar articles in PubMed and by reviewing the references of selected articles. The first 100 articles from each search were reviewed to ensure the sensitivity of the developed search strategies. The final strategy was reached through an iterative process. A preliminary search was performed from the inception of the aforementioned databases to 30 August 2022. An example of the search strategy specific to MEDLINE is included in online supplemental appendix 1.

Information sources

We will search the following databases: MEDLINE, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase, Embase Classic, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews (all via the Ovid platform), Web of Science Core Collection (Clarivate Analytics), CINAHL

Complete (EbscoHost) and ClinicalTrials.gov (National Institutes of Health).

Data records and management

Literature search results will be uploaded to Covidence (Version Copyright 2022, Melbourne, Australia), a web-based software program that facilitates abstract and full-text screening. The titles and abstracts of filtered studies will be screened by two reviewers against inclusion criteria to determine whether they move to the next stage in the selection process. The full text of these studies will then be screened independently by two reviewers. All disagreements will be resolved through discussion, and if resolution cannot be reached then a third reviewer will be consulted. Reasons for exclusion of studies will be collected during the full-text screening phase.

Data collection process

Two authors will independently extract data from eligible studies using a standardised data extraction form that comprises information regarding study design, patient characteristics such as age, sex, illness severity covariates, and the number of patients who have the comorbidities of interest, as well as intervention descriptions. For outcome data, we will extract the number of patients in each intervention arm and the number of patients experiencing the outcome of interest. For length of stay outcomes, we will extract the mean and SD, or median and IQRs for each group. An Excel spreadsheet will be used for data recording purposes.

Data synthesis

For dichotomous data, we will use the pooled estimate of risk ratio (RR) with 95% CIs using a random effects model. For all other continuous data, the pooled estimate of standardised mean difference with 95% CI will be calculated using a random effects model. Heterogeneity will be analysed using the χ^2 test; statistical significance level will be set at 0.1, while the I^2 value will be used to determine the extent of heterogeneity, with I^2 greater than 50% representing substantial heterogeneity. If 10 or greater studies are reporting on our primary outcome, the risk of publication bias will be assessed using a funnel plot and Egger's test on asymmetry at alpha level of 0.1. If statistical aggregation is limited and not possible due to the available number of studies, then a narrative approach will be employed to describe the results.

Subgroup analyses will be performed if a minimum of three included studies are identified that report on all-cause mortality for a specific comorbidity (eg, CHF), and reduced versus preserved ejection fraction heart failure. We will also complete a subgroup analysis of the primary outcome in studies that specifically use 30 mL/kg as the cut-off for conservative versus liberal fluid therapy, as well as comparing studies in which patients receive fluid resuscitation within 3, 6 and >6 hours. To test for a subgroup effect, pooled RRs for each subgroup will be compared using a z-test. A sensitivity analysis of study quality (high as compared with low) will be performed for the primary outcome.

Risk of bias in individual studies

The risk of bias will be assessed for all included RCTs using the revised Cochrane risk-of-bias tool.[12] Two authors will independently and in duplicate assess the risk of systematic errors (bias) in the included trials, with discrepancies resolved by consensus. We will assess the risk of bias across five domains: (D1) arising from the randomisation process; (D2) due to deviation from intended interventions (effect of adhering to intervention); (D3) in missing outcome data; (D4) in measurement of the outcome; and (D5) in selection of the reported result. If one or more domains are adjudicated as 'high risk' in at least one domain or 'some concerns' for multiple domains, we will classify the trial as having an overall high risk of bias. The Newcastle-Ottawa Scale for case–control and for cohort studies will be used to determine the study quality for non-RCTs.[13]

Confidence in cumulative evidence

The final result of the systematic review will be condensed into an evidence profile using an adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology across the domains of risk of bias, consistency, directness, precision and publication bias. The GRADE assessment will be employed for all studies that undergo meta-analyses; however, some studies included in the systematic review that could not be included in the meta-analysis may also be used for developing conclusions.

Patient and public involvement

Patients nor the public were or will be involved in the design, or conduct, or reporting, or dissemination plans of our research.

ETHICS AND DISSEMINATION

Given the nature of the study, no ethics committee approval is required. The results of this analysis will be published in a peer-reviewed journal after completion.

DISCUSSION

Although strict compliance to many of the components of the early goal-directed therapy bundle has fallen out of favour,[3] subsequent revisions of the SSC guidelines have emphasised early resuscitation with 30 mL/kg bolus of intravenous crystalloid fluid along with the use of dynamic measures to predict fluid responsiveness.[2] However, actual practice widely varies and is further complicated in patients with CHF, cirrhosis and CKD who often pose a challenge due to imperfect means of assessing intravascular volume status at the bedside. The view that these patients are at acute risk of volume overload, despite presenting with reduced effective circulating volume from vasoplegia-induced fluid redistribution,

has presented a major barrier to early resuscitation and effective management of sepsis. For instance, patients with these comorbidities receive less volume of fluid resuscitation and experience greater delays to the initiation of fluid resuscitation.[6 7 9] This is despite a paucity of evidence that specifically links fluid resuscitation in sepsis with adverse outcomes in these patients. Although a positive fluid balance in patients with sepsis is associated with increased mortality in the ICU,[14] this is distinct from the management principles advocated for by the SSC guidelines, which place emphasis on the initial resuscitation in sepsis and septic shock. Such variability in guideline adherence may engender disparities in patient management and influence clinical outcomes, and it is therefore necessary to provide clarity around management of such clinical scenarios with possibly competing haemodynamic principles. This systematic review will therefore provide crucial data on how the volume of intravenous fluids administered for resuscitation in sepsis impacts clinical outcomes in patients with comorbidities associated with volume overload.

Contributors AB conceptualised and planned the study with MEW, MLP, ME, TSM, AP and PS. AB and ME designed the search terms with input from MEW. AB wrote the first draft with input from MEW and revised the manuscript with feedback from MLP, ME, TSM, AP and PS. All authors approved the final version of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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