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

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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 initiation of a 30ml/kg fluid bolus within the first hour of recognition. 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 the standard fluid volume in this patient population puts them at greater risk of adverse outcomes. Thus, this systematic review will synthesize evidence from existing studies to assess the effects of a conservative versus standardized approach to fluid resuscitation in patients at greater perceived risk of fluid overload.

Methods and analysis

This protocol was registered on PROSPERO and has been drafted following the checklist of Preferred Reporting Items for Systematic Reviews 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. The risk of bias and random errors will be assessed using the Revised Cochrane risk-of-bias tool (RoB2) for randomized clinical trials, and the Newcastle-Ottawa scale for case-control and cohort studies. If sufficient numbers 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

- A comprehensive systematic review of the management of patients with sepsis and comorbidities that place them at greater risk of volume overload using rigorous methodology.
- The search algorithm was developed by an experienced medical librarian and customized for all databases.
- Lack of language restrictions in the selection of the studies.
- The certainty of evidence is unclear as it will be dictated by the number of studies available, variability in the administration of the intervention (i.e., time periods of interest and/or definitions of standard versus restrictive fluids), as well as study quality.

## 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 30ml/kg bolus of IV crystalloid solution as one of the targets for initial fluid resuscitation goals [2], albeit 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 regards 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. However, physicians must weigh the 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. These patient populations thus present a challenge to healthcare providers. Given the existence of imperfect means of assessing intravascular volume status at bedside, there is marked hesitation in ordering the standard fluid bolus in these patients due to concern around precipitating volume overload and subsequent respiratory failure that warrants mechanical ventilation. This results in these patients receiving less fluid volume [6–8]. 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.[9]; however, this study was limited to patients with CHF and CKD, included five studies across two databases, and was thus limited in scope. By expanding search parameters across multiple databases using a customized 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 fluid resuscitation practices in patients with sepsis who are deemed to be at high risk of fluid overload and determine whether the volume of intravenous crystalloid fluid administered to these patient populations as part of the sepsis bundle impacts clinical outcomes.

## METHODS

Our systematic review protocol was registered in accordance with guidelines with the International Prospective Register of Systematic Reviews (PROSPERO) on September 1, 2022, registration number CRD42022348181. This systematic review will be reported following the checklist of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines[10]. 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 six 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 ICU and are diagnosed with sepsis or septic shock, along with a comorbidity that places them at greater risk of fluid overload: congestive heart failure, chronic kidney disease, cirrhosis, or pulmonary hypertension.

*Types of interventions*

We will include all studies that investigate outcomes related to restrictive intravenous fluid therapy, independent of the choice of crystalloid fluids. If the volume of intravenous fluid therapy is part of a multi-model intervention (e.g., bundle of sepsis care), the study will be excluded if the intravenous fluid attributable outcome cannot be ascertained.

*Types of control*

The comparison of interest will be usual care (i.e., standard intravenous fluid therapy).

*Types of outcomes*

The primary outcome of interest will be all-cause hospital mortality up to 30 days post-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) hypoxemic respiratory failure and (7) intravenous diuretic requirement.

**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 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. The MEDLINE search strategy is included in 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 (NIH).

*Data records and management*

Literature search results will be uploaded to Covidence (Version © 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 had 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, and illness severity covariates, and 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 standard deviation, or median and interquartile ranges 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% confidence

intervals (CI) 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 $Chi^2$ 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 0.1.

Subgroup analyses will be performed if a minimum of three included studies are identified that report on acute hospital mortality for a specific comorbidity (e.g., CHF), and reduced versus preserved ejection fraction heart failure. 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 to 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 (RoB2)[11]. 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 5 domains: (D1) arising from the randomization 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

[25]. The Newcastle-Ottawa Scale for case-control and for cohort studies will be used to determine study quality for non-RCTs[12].

*Confidence in cumulative evidence*

The final result of the systematic review will be condensed into an evidence profile that will contain the PECOS (population, exposure, comparator, and outcomes) question, the type and number of studies included, the number of participants in the studies, the effect size and their confidence intervals, and the grading of the quality of the evidence. The evidence quality for all outcomes will be judged 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.

## 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.

## PATIENT AND PUBLIC INVOLVEMENT

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

## DISCUSSION

Since the work of Rivers et al. (2001) nearly two decades ago[1], fluid resuscitation has formed one of the pillars of the surviving sepsis bundle. 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 emphasized early resuscitation with 30ml/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[6–8]. 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 septic patients is associated with increased mortality in the intensive care unit[13], 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 hemodynamic principles. This systematic review will therefore synthesize evidence from available RCTs and non-RCT studies in the literature to investigate whether the volume of

intravenous fluids administered in sepsis to patients diagnosed with comorbidities associated with volume overload impacts clinical outcomes.

## AUTHOR CONTRIBUTIONS

AB wrote the first draft and revised the manuscript. All authors revised for critical content and approved the final version of the manuscript.

## FUNDING

This study received no funding.

## CONFLICTS

The authors have no conflicts of interest to declare.

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APPENDIX 1

# MEDLINE

Ovid MEDLINE(R) 1946 to July 26, 2022

| # | Searches | Results |
|---|---|---|
| 1 | Body Composition/ | 47184 |
| 2 | Body Fluid Compartments/ | 1250 |
| 3 | Body Water/ | 13737 |
| 4 | Capillary Permeability/ | 22007 |
| 5 | Colloids/ | 17071 |
| 6 | exp Crystalloid Solutions/ | 4162 |
| 7 | Dextrans/ | 24952 |
| 8 | exp Body Fluids/ | 341117 |
| 9 | exp Edema/ | 45439 |
| 10 | exp Fluid Therapy/ | 21718 |
| 11 | exp Indicator Dilution Techniques/ | 15200 |
| 12 | exp Intracellular Fluid/ | 52866 |
| 13 | exp Plasma Substitutes/ | 39641 |
| 14 | exp Water-Electrolyte Balance/ | 32513 |
| 15 | exp Water-Electrolyte Imbalance/ | 65637 |
| 16 | Extracellular Fluid/ | 4504 |
| 17 | Fluid Shifts/ | 648 |
| 18 | Hydrodynamics/ | 9038 |
| 19 | Hydroxyethyl Starch Derivatives/ | 3500 |
| 20 | Hypodermoclysis/ | 143 |
| 21 | Hypovolemia/ | 1697 |
| 22 | Isotonic Solutions/ | 8546 |
| 23 | Polygeline/ | 317 |
| 24 | Povidone/ | 7237 |
| 25 | Pulmonary Edema/ | 17768 |
| 26 | Rehydration Solutions/ | 1506 |
| 27 | Resuscitation/ and (fluid? or volume).mp. | 4979 |
| 28 | Ringer's Lactate/ | 1493 |
| 29 | Saline Solution/ | 991 |

| | | |
|---|---|---|
| 30 | (blood adj2 loss*).mp. | 63271 |
| 31 | (blood? adj2 (volum* or distribut*)).mp. | 51947 |
| 32 | (body adj2 water?).mp. | 19447 |
| 33 | (cardiogenic adj1 edema?).mp. | 112 |
| 34 | (cardiogenic adj1 oedema?).mp. | 27 |
| 35 | (dilution adj1 techni*).mp. | 15323 |
| 36 | (excess* adj2 fluid?).mp. | 1482 |
| 37 | (extracellular adj2 water?).mp. | 1911 |
| 38 | (fluid? adj1 accumulat*).mp. | 3226 |
| 39 | (fluid? adj2 administr*).mp. | 3209 |
| 40 | (fluid? adj1 balanc*).mp. | 5559 |
| 41 | (fluid? adj1 challeng*).mp. | 658 |
| 42 | (fluid? adj2 (dose or dosing)).mp. | 221 |
| 43 | (fluid? adj1 infus*).mp. | 2110 |
| 44 | (fluid? adj1 load*).mp. | 990 |
| 45 | (fluid? adj1 loss*).mp. | 1695 |
| 46 | (fluid? adj1 manag*).mp. | 2457 |
| 47 | (fluid? adj1 non-respon*).mp. | 16 |
| 48 | (fluid? adj1 nonrespon*).mp. | 15 |
| 49 | (fluid? adj1 overload*).mp. | 2749 |
| 50 | (fluid? adj1 replac*).mp. | 2398 |
| 51 | (fluid? adj1 respon*).mp. | 1316 |
| 52 | (fluid? adj1 restric*).mp. | 1930 |
| 53 | (fluid? adj1 resusci*).mp. | 5774 |
| 54 | (fluid? adj1 shift*).mp. | 1775 |
| 55 | (fluid? adj1 therap*).mp. | 23212 |
| 56 | (fluid? adj2 (distribut* or volume? or chang*)).mp. | 13100 |
| 57 | (infusion? adj2 volume?).mp. | 1319 |
| 58 | (intracellular adj2 water?).mp. | 1480 |
| 59 | (leg?? adj2 fluid?).mp. | 83 |
| 60 | (leg?? adj2 water?).mp. | 97 |
| 61 | (load* adj5 fluid?).mp. | 2269 |
| 62 | (lung? adj1 water?).mp. | 3022 |
| 63 | (neck?? adj2 fluid?).mp. | 41 |
| 64 | (neck?? adj2 water?).mp. | 50 |
| 65 | normal saline?.mp. | 20638 |
| 66 | (periop* adj2 intravenous fluid?).mp. | 51 |

| | | |
|---|---|---|
| 67 | (periop* adj2 iv fluid?).mp. | 13 |
| 68 | (physiolog* adj2 chang*).mp. | 18600 |
| 69 | (plasma adj1 substitu*).mp. | 7057 |
| 70 | (plasma adj1 volume?).mp. | 10725 |
| 71 | (pulmonary adj1 edema*).mp. | 24433 |
| 72 | (pulmonary adj1 oedema*).mp. | 3412 |
| 73 | (Ringer* adj2 acetat*).mp. | 426 |
| 74 | (Ringer* adj2 lactat*).mp. | 4743 |
| 75 | (Ringer* adj2 solution*).mp. | 9100 |
| 76 | saline solution?.mp. | 22259 |
| 77 | (segmental adj2 fluid?).mp. | 42 |
| 78 | (segmental adj2 water?).mp. | 12 |
| 79 | (third adj1 (space or spaces or spaced or spacing)).mp. | 361 |
| 80 | (total* adj1 body adj1 water?).mp. | 3413 |
| 81 | (total* adj1 fluid? adj1 volume?).mp. | 133 |
| 82 | (volume adj1 overload*).mp. | 4226 |
| 83 | (volume adj1 over-load*).mp. | 13 |
| 84 | (volume? adj1 respon*).mp. | 1194 |
| 85 | (volume? adj1 resuscitat*).mp. | 1132 |
| 86 | (wet adj1 lung?).mp. | 1648 |
| 87 | anasarca.mp. | 853 |
| 88 | body water?.mp. | 16804 |
| 89 | colloid?.mp. | 34016 |
| 90 | crystalloid?.mp. | 6999 |
| 91 | de-resuscitat*.mp. | 17 |
| 92 | deresuscitat*.mp. | 14 |
| 93 | edema*.mp. | 157498 |
| 94 | electrical imped*.mp. | 4325 |
| 95 | EVLW.mp. | 489 |
| 96 | Extravascular lung water?.mp. | 2116 |
| 97 | Hyperhydrat*.mp. | 680 |
| 98 | Hyper-hydrat*.mp. | 32 |
| 99 | itbv.mp. | 75 |
| 100 | oedema*.mp. | 28297 |
| 101 | overhydrat*.mp. | 944 |
| 102 | over-hydrat*.mp. | 113 |
| 103 | rehydrat*.mp. | 9850 |

| | | |
|---|---|---|
| 104 | (resuscit* and (fluid? or volume)).mp. | 13821 |
| 105 | TBW.mp. | 1701 |
| 106 | thermodilut*.mp. | 5278 |
| 107 | thermo-dilut*.mp. | 37 |
| 108 | vascular permeabilit*.mp. | 11550 |
| 109 | Albumins/ | 21426 |
| 110 | (albumin or albumins).mp. | 189851 |
| 111 | "Plasmalyte A".mp. | 75 |
| 112 | "Plasma-lyte A".mp. | 57 |
| 113 | "Plasmalyte R".mp. | 12 |
| 114 | "Plasma-lyte R".mp. | 5 |
| 115 | plasmalyte??.mp. | 152 |
| 116 | plasma-lyte??.mp. | 178 |
| 117 | or/1-116 [ Body Fluids or Fluid Responsiveness ] | 1190027 |
| 118 | exp Sepsis/ | 137287 |
| 119 | Shock, Septic/ | 24409 |
| 120 | Acute Lung Injury/ | 7877 |
| 121 | Candidemia/ | 1484 |
| 122 | Candidiasis/ and 1967:2010.dt. [ historical ] | 128 |
| 123 | Candidiasis/bl [Blood] | 575 |
| 124 | Capillary Leak Syndrome/ | 664 |
| 125 | Cytokine Release Syndrome/ | 1873 |
| 126 | Endotoxemia/ | 4659 |
| 127 | Fungemia/ | 3137 |
| 128 | exp Bacteremia/ | 32080 |
| 129 | exp Shock/ | 83720 |
| 130 | exp Systemic Inflammatory Response Syndrome/ | 144556 |
| 131 | Hemorrhagic Septicemia/ | 234 |
| 132 | Multiple Organ Failure/ | 11855 |
| 133 | Respiratory Distress Syndrome, Adult/ | 23558 |
| 134 | Sepsis-Associated Encephalopathy/ [ MeSH 2015 ] | 195 |
| 135 | Vasoplegia/ | 235 |
| 136 | (acute adj2 ill*).mp. | 10766 |
| 137 | (acute adj2 injur*).mp. | 93840 |
| 138 | (acute adj2 lung* adj2 injur*).mp. | 16256 |
| 139 | (acute adj2 respira* adj2 fail*).mp. | 8224 |
| 140 | (acute adj2 respiratory distress syndrome*).mp. | 16714 |

| | | |
|---|---|---|
| 141 | (adult adj2 respiratory distress syndrome*).mp. | 4347 |
| 142 | (bacteri* adj2 blood*).mp. | 7415 |
| 143 | (bacter* adj2 shock).mp. | 943 |
| 144 | (blood* adj2 poison*).mp. | 277 |
| 145 | (Candid* adj2 blood*).mp. | 919 |
| 146 | (capillar* adj2 leak*).mp. | 2155 |
| 147 | cytokine release? syndrome?.mp. | 3045 |
| 148 | (cytokine? adj2 storm*).mp. | 3931 |
| 149 | (endotox* adj2 shock).mp. | 4352 |
| 150 | (fung* adj2 blood*).mp. | 334 |
| 151 | (hemorrhag* adj2 septic*).mp. | 1145 |
| 152 | (lung* adj2 shock).mp. | 603 |
| 153 | (multi* adj2 organ* adj2 dysfunction).mp. | 5084 |
| 154 | (multi* adj2 organ* adj2 fail*).mp. | 19547 |
| 155 | (sep*3 adj2 associated adj2 deliri*).mp. | 17 |
| 156 | (sep*3 adj2 associated adj2 encephalopath*).mp. | 361 |
| 157 | (septic adj2 disease?).mp. | 645 |
| 158 | (septic adj2 shock).mp. | 35067 |
| 159 | (shock adj2 syndrom*).mp. | 6095 |
| 160 | (sever* adj2 infect*).mp. | 31660 |
| 161 | (toxi* adj2 shock).mp. | 5058 |
| 162 | bacteraemi*.mp. | 6837 |
| 163 | bacteremi*.mp. | 40879 |
| 164 | candidaemia?.mp. | 658 |
| 165 | candidemia?.mp. | 3045 |
| 166 | endotoxaemi*.mp. | 1101 |
| 167 | endotoxemi*.mp. | 9572 |
| 168 | fungaemia?.mp. | 384 |
| 169 | fungemia?.mp. | 4047 |
| 170 | hypercytokinemia?.mp. | 407 |
| 171 | hypercytokinaemia?.mp. | 34 |
| 172 | parasitemi*.mp. | 10135 |
| 173 | pyaemia*.mp. | 56 |
| 174 | pyemia*.mp. | 68 |
| 175 | pyohemia*.mp. | 12 |
| 176 | sepses.mp. | 31 |
| 177 | sepsis*.mp. | 128461 |

| | | |
|---|---|---|
| 178 | septic*.mp. | 86877 |
| 179 | septicaemi*.mp. | 6469 |
| 180 | septicemi*.mp. | 15350 |
| 181 | sirs.mp. | 5593 |
| 182 | systemic inflammatory response syndrome.mp. | 9816 |
| 183 | uroseps#s.mp. | 1228 |
| 184 | uro-seps#s.mp. | 6 |
| 185 | urosept*.mp. | 50 |
| 186 | uro-sept*.mp. | 0 |
| 187 | vasoplegi*.mp. | 561 |
| 188 | viremi??.mp. | 19503 |
| 189 | or/118-188 [ Sepsis and Related Terms ] | 472684 |
| 190 | exp Heart Failure/ or exp Cardio-Renal Syndrome/ or exp Dyspnea, Paroxysmal/ or exp Edema, Cardiac/ or exp Heart Failure, Diastolic/ or exp Heart Failure, Systolic/ or (cardiac failure or congestive heart failure or heart decompensation or heart failure or left sided heart failure or left-sided heart failure or myocardial failure or right sided heart failure or right-sided heart failure).mp. | 225113 |
| 191 | exp Ventricular Dysfunction/ or exp Ventricular Dysfunction, Left/ or exp Ventricular Dysfunction, Right/ or ventricular dysfunction?.mp. | 51402 |
| 192 | exp Liver Cirrhosis/ or exp Liver Cirrhosis, Alcoholic/ or exp Liver Cirrhosis, Biliary/ or exp Liver Cirrhosis, Experimental/ or (cirrho* or liver fibrosis).mp. | 139718 |
| 193 | exp Kidney Failure, Chronic/ or exp Frasier Syndrome/ or (chronic kidney failure or chronic renal failure or esrd or end stage kidney disease or end stage renal disease or eskd).mp. | 122381 |
| 194 | 190 or 191 or 192 or 193 | 513064 |
| 195 | 194 [ Selected Diseases ] | 513064 |
| 196 | 117 and 189 and 195 [ Fluids + Sepsis + Selected Diseases ] | 3440 |
| 197 | Clinical Trial, Phase III/ | 20884 |
| 198 | exp Clinical Trial/ | 949066 |
| 199 | Clinical Trials, Phase III as Topic/ | 10905 |
| 200 | Comparative Study/ | 1911363 |
| 201 | Controlled Clinical Trial/ | 94969 |
| 202 | Controlled Clinical Trials as Topic/ | 5637 |
| 203 | Cross-Sectional Studies/ | 438332 |
| 204 | Double-Blind Method/ | 172836 |
| 205 | Equivalence Trial/ | 1039 |
| 206 | Equivalence Trials as Topic/ | 589 |
| 207 | exp Case-Control Studies/ | 1346545 |
| 208 | exp Cohort Studies/ | 2385601 |

| | | |
|---|---|---|
| 209 | exp Randomized Controlled Trial/ | 576830 |
| 210 | exp Randomized Controlled Trials as Topic/ | 161270 |
| 211 | Longitudinal Studies/ | 160155 |
| 212 | Meta-Analysis as Topic/ | 21680 |
| 213 | Meta-Analysis/ | 165842 |
| 214 | Multicenter Studies as Topic/ | 21624 |
| 215 | Multicenter Study/ | 324974 |
| 216 | Observational Study/ | 131500 |
| 217 | Observational Studies as Topic/ | 8109 |
| 218 | Placebos/ | 35921 |
| 219 | Pragmatic Clinical Trial/ | 2137 |
| 220 | Pragmatic Clinical Trials as Topic/ | 806 |
| 221 | Prospective Studies/ | 636831 |
| 222 | Retrospective Studies/ | 1051976 |
| 223 | Systematic Review/ [ New MeSH 2019 ] | 199603 |
| 224 | Systematic Reviews as Topic/ [ New MeSH 2019 ] | 8984 |
| 225 | Validation Studies/ | 109085 |
| 226 | ("phase 1" or "phase1" or "phase I").mp. | 68092 |
| 227 | ("phase 2" or "phase2" or "phase II").mp. | 92901 |
| 228 | ("phase 3" or "phase3" or "phase III").mp. | 62507 |
| 229 | ((multicenter* or multicentre* or multicentric) adj2 (trial? or study or studies)).mp. | 366072 |
| 230 | ((noninferiority or non-inferiority) adj4 (trial? or study or studies)).mp. | 5685 |
| 231 | ((single or double or triple or treble) adj3 (blind* or mask*)).mp. | 245537 |
| 232 | (case control* adj2 (study or studies)).mp. | 349305 |
| 233 | (comparative adj2 (trial? or study or studies)).mp. | 1971101 |
| 234 | (conceal* adj2 allocat*).mp. | 3002 |
| 235 | (controlled adj1 clinical adj2 (trial? or study or studies)).mp. | 130583 |
| 236 | (cross-sectional* adj2 (study or studies)).mp. | 463061 |
| 237 | (equivalen* adj4 (trial? or study or studies)).mp. | 5961 |
| 238 | (evaluation adj1 (study or studies)).mp. | 389411 |
| 239 | (longitudinal* adj2 (study or studies)).mp. | 199829 |
| 240 | (meta-anal* or metanal* or metaanal*).mp. | 237511 |
| 241 | (observational adj2 (trial? or study or studies)).mp. | 218289 |
| 242 | (overview? adj4 (review or reviews)).mp. | 20267 |
| 243 | (pragmatic adj2 (trial? or study or studies)).mp. | 5417 |
| 244 | (prospective* adj2 (study or studies)).mp. | 730026 |
| 245 | (retrospective* adj2 (study or studies)).mp. | 1087989 |

| | | |
|---|---|---|
| 246 | (superiority adj4 (trial? or study or studies)).mp. | 3892 |
| 247 | (systematic adj4 (review or reviews or overview or overviews)).mp. | 242401 |
| 248 | (validation adj1 (study or studies)).mp. | 123222 |
| 249 | cohort*.mp. | 784345 |
| 250 | placebo*.mp. | 233244 |
| 251 | quasirandom*.mp. | 130 |
| 252 | random*.mp. | 1396764 |
| 253 | semiquantitative.mp. | 19431 |
| 254 | quantitativ*.mp. | 712863 |
| 255 | or/197-254 [ Quantitative Studies ] | 7125796 |
| 256 | 196 and 255 [ Fluids + Sepsis + Selected Diseases + Studies ] | 1320 |
| 257 | 256 not (exp animals/ not (exp animals/ and exp humans/)) | 1260 |
| 258 | limit 256 to humans | 1260 |
| 259 | 257 or 258 | 1260 |
| 260 | limit 259 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") | 219 |
| 261 | 259 not 260 | 1041 |
| 262 | limit 259 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") | 934 |
| 263 | 261 or 262 | 1173 |
| 264 | remove duplicates from 263 [ removal of internal database duplicates ] | 1168 |

# Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Title** | | | |
| Identification | #1a | Identify the report as a protocol of a systematic review | 1 |
| Update | #1b | If the protocol is for an update of a previous systematic review, identify as such | N/A |

| | | | |
|---|---|---|---|
| **Registration** | | | |
| | #2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 4 |
| **Authors** | | | |
| Contact | #3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contribution | #3b | Describe contributions of protocol authors and identify the guarantor of the review | 14 |
| **Amendments** | | | |
| | #4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | 7 |
| **Support** | | | |
| Sources | #5a | Indicate sources of financial or other support for the review | 14 |
| Sponsor | #5b | Provide name for the review funder and / or sponsor | N/A |
| Role of sponsor or funder | #5c | Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol | N/A |
| **Introduction** | | | |
| Rationale | #6 | Describe the rationale for the review in the context of what is | 6 |

| | | | |
|---|---|---|---|
| | | already known | |
| Objectives | #7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 7 |
| **Methods** | | | |
| Eligibility criteria | #8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 7 |
| Information sources | #9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 9 |
| Search strategy | #10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 9 |
| Study records - data management | #11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 10 |
| Study records - selection process | #11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | 10 |
| Study records - data collection | #11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any | 10 |

| | | | |
|---|---|---|---|
| process | | processes for obtaining and confirming data from investigators | |
| Data items | #12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 10 |
| Outcomes and prioritization | #13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 8 |
| Risk of bias in individual studies | #14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 11 |
| Data synthesis | #15a | Describe criteria under which study data will be quantitatively synthesised | 10 |
| Data synthesis | #15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ) | 11 |
| Data synthesis | #15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 11 |
| Data synthesis | #15d | If quantitative synthesis is not appropriate, describe the type of summary planned | N/A |
| Meta-bias(es) | #16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within | 11 |

| | | | |
|---|---|---|---|
| | | studies) | |
| Confidence in cumulative evidence | #17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 12 |

BMJ Open

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



| | |
|---|---|
| Journal: | *BMJ Open* |
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| Primary Subject Heading: | Intensive care |
| Secondary Subject Heading: | Intensive care, Medical management |
| Keywords: | Chronic renal failure < NEPHROLOGY, Heart failure < CARDIOLOGY, INTENSIVE & CRITICAL CARE, GENERAL MEDICINE (see Internal Medicine) |
| | |

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

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**Abstract word count:** 298

**Word count:** 2091

**Key words:** sepsis; congestive heart failure; chronic kidney disease; cirrhosis; fluid resuscitation

**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 synthesize evidence from existing studies to assess the effects of a conservative as compared to 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 Reviews 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 was performed of these databases was performed from their inception to August 30, 2022. The risk of bias and random errors will be assessed using the Revised Cochrane risk-of-bias tool (RoB2) for randomized 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

- 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 customized for all databases.
- Lack of language restrictions in the selection of the studies.
- Quality of evidence dependent upon the number of studies available and the variability in the intervention of interest (i.e., time periods of interest and/or definitions of liberal versus 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 IV crystalloid solution as one of the targets for initial fluid resuscitation goals [2], albeit 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 regards 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 customized 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 September 1, 2022, registration number CRD42022348181. This systematic review will be reported following the checklist of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 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 six 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 ICU and are diagnosed with sepsis or septic shock, along with a comorbidity that places them at greater risk of fluid overload: congestive heart failure, chronic kidney disease, 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 multi-model intervention (e.g., 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 (i.e., 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 post-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) hypoxemic respiratory failure, including use of non-invasive positive pressure ventilation (NIPPV), (7) intravenous diuretic requirement, and (8) need for any for of renal replacement therapy (RRT).

**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 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 August 30, 2022. An example of the search strategy specific to MEDLINE is included in 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 (NIH).

*Data records and management*

Literature search results will be uploaded to Covidence (Version © 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 had 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 standard deviation, or median and interquartile ranges 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% confidence intervals (CI) 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 $Chi^2$ 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 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 (e.g., 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 hours, 6 hours, and greater than 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 to 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 (RoB2)[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 5 domains: (D1) arising from the randomization 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 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.

## 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.

## PATIENT AND PUBLIC INVOLVEMENT

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

## 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 emphasized 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 septic patients is associated with increased mortality in the intensive care unit[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 hemodynamic 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.

**AUTHOR CONTRIBUTIONS**

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.

**FUNDING**

This study received no funding.

**CONFLICTS**

The authors have no conflicts of interest to declare.

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APPENDIX 1

# MEDLINE

Ovid MEDLINE(R) 1946 to July 26, 2022

| # | Searches | Results |
|---|---|---|
| 1 | Body Composition/ | 47184 |
| 2 | Body Fluid Compartments/ | 1250 |
| 3 | Body Water/ | 13737 |
| 4 | Capillary Permeability/ | 22007 |
| 5 | Colloids/ | 17071 |
| 6 | exp Crystalloid Solutions/ | 4162 |
| 7 | Dextrans/ | 24952 |
| 8 | exp Body Fluids/ | 341117 |
| 9 | exp Edema/ | 45439 |
| 10 | exp Fluid Therapy/ | 21718 |
| 11 | exp Indicator Dilution Techniques/ | 15200 |
| 12 | exp Intracellular Fluid/ | 52866 |
| 13 | exp Plasma Substitutes/ | 39641 |
| 14 | exp Water-Electrolyte Balance/ | 32513 |
| 15 | exp Water-Electrolyte Imbalance/ | 65637 |
| 16 | Extracellular Fluid/ | 4504 |
| 17 | Fluid Shifts/ | 648 |
| 18 | Hydrodynamics/ | 9038 |
| 19 | Hydroxyethyl Starch Derivatives/ | 3500 |
| 20 | Hypodermoclysis/ | 143 |
| 21 | Hypovolemia/ | 1697 |
| 22 | Isotonic Solutions/ | 8546 |
| 23 | Polygeline/ | 317 |
| 24 | Povidone/ | 7237 |
| 25 | Pulmonary Edema/ | 17768 |
| 26 | Rehydration Solutions/ | 1506 |
| 27 | Resuscitation/ and (fluid? or volume).mp. | 4979 |
| 28 | Ringer's Lactate/ | 1493 |
| 29 | Saline Solution/ | 991 |

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|---|---|---|
| 30 | (blood adj2 loss*).mp. | 63271 |
| 31 | (blood? adj2 (volum* or distribut*)).mp. | 51947 |
| 32 | (body adj2 water?).mp. | 19447 |
| 33 | (cardiogenic adj1 edema?).mp. | 112 |
| 34 | (cardiogenic adj1 oedema?).mp. | 27 |
| 35 | (dilution adj1 techni*).mp. | 15323 |
| 36 | (excess* adj2 fluid?).mp. | 1482 |
| 37 | (extracellular adj2 water?).mp. | 1911 |
| 38 | (fluid? adj1 accumulat*).mp. | 3226 |
| 39 | (fluid? adj2 administr*).mp. | 3209 |
| 40 | (fluid? adj1 balanc*).mp. | 5559 |
| 41 | (fluid? adj1 challeng*).mp. | 658 |
| 42 | (fluid? adj2 (dose or dosing)).mp. | 221 |
| 43 | (fluid? adj1 infus*).mp. | 2110 |
| 44 | (fluid? adj1 load*).mp. | 990 |
| 45 | (fluid? adj1 loss*).mp. | 1695 |
| 46 | (fluid? adj1 manag*).mp. | 2457 |
| 47 | (fluid? adj1 non-respon*).mp. | 16 |
| 48 | (fluid? adj1 nonrespon*).mp. | 15 |
| 49 | (fluid? adj1 overload*).mp. | 2749 |
| 50 | (fluid? adj1 replac*).mp. | 2398 |
| 51 | (fluid? adj1 respon*).mp. | 1316 |
| 52 | (fluid? adj1 restric*).mp. | 1930 |
| 53 | (fluid? adj1 resusci*).mp. | 5774 |
| 54 | (fluid? adj1 shift*).mp. | 1775 |
| 55 | (fluid? adj1 therap*).mp. | 23212 |
| 56 | (fluid? adj2 (distribut* or volume? or chang*)).mp. | 13100 |
| 57 | (infusion? adj2 volume?).mp. | 1319 |
| 58 | (intracellular adj2 water?).mp. | 1480 |
| 59 | (leg?? adj2 fluid?).mp. | 83 |
| 60 | (leg?? adj2 water?).mp. | 97 |
| 61 | (load* adj5 fluid?).mp. | 2269 |
| 62 | (lung? adj1 water?).mp. | 3022 |
| 63 | (neck?? adj2 fluid?).mp. | 41 |
| 64 | (neck?? adj2 water?).mp. | 50 |
| 65 | normal saline?.mp. | 20638 |

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|---|---|---|
| 66 | (periop* adj2 intravenous fluid?).mp. | 51 |
| 67 | (periop* adj2 iv fluid?).mp. | 13 |
| 68 | (physiolog* adj2 chang*).mp. | 18600 |
| 69 | (plasma adj1 substitu*).mp. | 7057 |
| 70 | (plasma adj1 volume?).mp. | 10725 |
| 71 | (pulmonary adj1 edema*).mp. | 24433 |
| 72 | (pulmonary adj1 oedema*).mp. | 3412 |
| 73 | (Ringer* adj2 acetat*).mp. | 426 |
| 74 | (Ringer* adj2 lactat*).mp. | 4743 |
| 75 | (Ringer* adj2 solution*).mp. | 9100 |
| 76 | saline solution?.mp. | 22259 |
| 77 | (segmental adj2 fluid?).mp. | 42 |
| 78 | (segmental adj2 water?).mp. | 12 |
| 79 | (third adj1 (space or spaces or spaced or spacing)).mp. | 361 |
| 80 | (total* adj1 body adj1 water?).mp. | 3413 |
| 81 | (total* adj1 fluid? adj1 volume?).mp. | 133 |
| 82 | (volume adj1 overload*).mp. | 4226 |
| 83 | (volume adj1 over-load*).mp. | 13 |
| 84 | (volume? adj1 respon*).mp. | 1194 |
| 85 | (volume? adj1 resuscitat*).mp. | 1132 |
| 86 | (wet adj1 lung?).mp. | 1648 |
| 87 | anasarca.mp. | 853 |
| 88 | body water?.mp. | 16804 |
| 89 | colloid?.mp. | 34016 |
| 90 | crystalloid?.mp. | 6999 |
| 91 | de-resuscitat*.mp. | 17 |
| 92 | deresuscitat*.mp. | 14 |
| 93 | edema*.mp. | 157498 |
| 94 | electrical imped*.mp. | 4325 |
| 95 | EVLW.mp. | 489 |
| 96 | Extravascular lung water?.mp. | 2116 |
| 97 | Hyperhydrat*.mp. | 680 |
| 98 | Hyper-hydrat*.mp. | 32 |
| 99 | itbv.mp. | 75 |
| 100 | oedema*.mp. | 28297 |
| 101 | overhydrat*.mp. | 944 |

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| 102 | over-hydrat*.mp. | 113 |
| 103 | rehydrat*.mp. | 9850 |
| 104 | (resuscit* and (fluid? or volume)).mp. | 13821 |
| 105 | TBW.mp. | 1701 |
| 106 | thermodilut*.mp. | 5278 |
| 107 | thermo-dilut*.mp. | 37 |
| 108 | vascular permeabilit*.mp. | 11550 |
| 109 | Albumins/ | 21426 |
| 110 | (albumin or albumins).mp. | 189851 |
| 111 | "Plasmalyte A".mp. | 75 |
| 112 | "Plasma-lyte A".mp. | 57 |
| 113 | "Plasmalyte R".mp. | 12 |
| 114 | "Plasma-lyte R".mp. | 5 |
| 115 | plasmalyte??.mp. | 152 |
| 116 | plasma-lyte??.mp. | 178 |
| 117 | or/1-116 [ Body Fluids or Fluid Responsiveness ] | 1190027 |
| 118 | exp Sepsis/ | 137287 |
| 119 | Shock, Septic/ | 24409 |
| 120 | Acute Lung Injury/ | 7877 |
| 121 | Candidemia/ | 1484 |
| 122 | Candidiasis/ and 1967:2010.dt. [ historical ] | 128 |
| 123 | Candidiasis/bl [Blood] | 575 |
| 124 | Capillary Leak Syndrome/ | 664 |
| 125 | Cytokine Release Syndrome/ | 1873 |
| 126 | Endotoxemia/ | 4659 |
| 127 | Fungemia/ | 3137 |
| 128 | exp Bacteremia/ | 32080 |
| 129 | exp Shock/ | 83720 |
| 130 | exp Systemic Inflammatory Response Syndrome/ | 144556 |
| 131 | Hemorrhagic Septicemia/ | 234 |
| 132 | Multiple Organ Failure/ | 11855 |
| 133 | Respiratory Distress Syndrome, Adult/ | 23558 |
| 134 | Sepsis-Associated Encephalopathy/ [ MeSH 2015 ] | 195 |
| 135 | Vasoplegia/ | 235 |
| 136 | (acute adj2 ill*).mp. | 10766 |
| 137 | (acute adj2 injur*).mp. | 93840 |

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|---|---|---|
| 138 | (acute adj2 lung* adj2 injur*).mp. | 16256 |
| 139 | (acute adj2 respira* adj2 fail*).mp. | 8224 |
| 140 | (acute adj2 respiratory distress syndrome*).mp. | 16714 |
| 141 | (adult adj2 respiratory distress syndrome*).mp. | 4347 |
| 142 | (bacteri* adj2 blood*).mp. | 7415 |
| 143 | (bacter* adj2 shock).mp. | 943 |
| 144 | (blood* adj2 poison*).mp. | 277 |
| 145 | (Candid* adj2 blood*).mp. | 919 |
| 146 | (capillar* adj2 leak*).mp. | 2155 |
| 147 | cytokine release? syndrome?.mp. | 3045 |
| 148 | (cytokine? adj2 storm*).mp. | 3931 |
| 149 | (endotox* adj2 shock).mp. | 4352 |
| 150 | (fung* adj2 blood*).mp. | 334 |
| 151 | (hemorrhag* adj2 septic*).mp. | 1145 |
| 152 | (lung* adj2 shock).mp. | 603 |
| 153 | (multi* adj2 organ* adj2 dysfunction).mp. | 5084 |
| 154 | (multi* adj2 organ* adj2 fail*).mp. | 19547 |
| 155 | (sep*3 adj2 associated adj2 deliri*).mp. | 17 |
| 156 | (sep*3 adj2 associated adj2 encephalopath*).mp. | 361 |
| 157 | (septic adj2 disease?).mp. | 645 |
| 158 | (septic adj2 shock).mp. | 35067 |
| 159 | (shock adj2 syndrom*).mp. | 6095 |
| 160 | (sever* adj2 infect*).mp. | 31660 |
| 161 | (toxi* adj2 shock).mp. | 5058 |
| 162 | bacteraemi*.mp. | 6837 |
| 163 | bacteremi*.mp. | 40879 |
| 164 | candidaemia?.mp. | 658 |
| 165 | candidemia?.mp. | 3045 |
| 166 | endotoxaemi*.mp. | 1101 |
| 167 | endotoxemi*.mp. | 9572 |
| 168 | fungaemia?.mp. | 384 |
| 169 | fungemia?.mp. | 4047 |
| 170 | hypercytokinemia?.mp. | 407 |
| 171 | hypercytokinaemia?.mp. | 34 |
| 172 | parasitemi*.mp. | 10135 |
| 173 | pyaemia*.mp. | 56 |

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| 174 | pyemia*.mp. | 68 |
| 175 | pyohemia*.mp. | 12 |
| 176 | sepses.mp. | 31 |
| 177 | sepsis*.mp. | 128461 |
| 178 | septic*.mp. | 86877 |
| 179 | septicaemi*.mp. | 6469 |
| 180 | septicemi*.mp. | 15350 |
| 181 | sirs.mp. | 5593 |
| 182 | systemic inflammatory response syndrome.mp. | 9816 |
| 183 | uroseps#s.mp. | 1228 |
| 184 | uro-seps#s.mp. | 6 |
| 185 | urosept*.mp. | 50 |
| 186 | uro-sept*.mp. | 0 |
| 187 | vasoplegi*.mp. | 561 |
| 188 | viremi??.mp. | 19503 |
| 189 | or/118-188 [ Sepsis and Related Terms ] | 472684 |
| 190 | exp Heart Failure/ or exp Cardio-Renal Syndrome/ or exp Dyspnea, Paroxysmal/ or exp Edema, Cardiac/ or exp Heart Failure, Diastolic/ or exp Heart Failure, Systolic/ or (cardiac failure or congestive heart failure or heart decompensation or heart failure or left sided heart failure or left-sided heart failure or myocardial failure or right sided heart failure or right-sided heart failure).mp. | 225113 |
| 191 | exp Ventricular Dysfunction/ or exp Ventricular Dysfunction, Left/ or exp Ventricular Dysfunction, Right/ or ventricular dysfunction?.mp. | 51402 |
| 192 | exp Liver Cirrhosis/ or exp Liver Cirrhosis, Alcoholic/ or exp Liver Cirrhosis, Biliary/ or exp Liver Cirrhosis, Experimental/ or (cirrho* or liver fibrosis).mp. | 139718 |
| 193 | exp Kidney Failure, Chronic/ or exp Frasier Syndrome/ or (chronic kidney failure or chronic renal failure or esrd or end stage kidney disease or end stage renal disease or eskd).mp. | 122381 |
| 194 | 190 or 191 or 192 or 193 | 513064 |
| 195 | 194 [ Selected Diseases ] | 513064 |
| 196 | 117 and 189 and 195 [ Fluids + Sepsis + Selected Diseases ] | 3440 |
| 197 | Clinical Trial, Phase III/ | 20884 |
| 198 | exp Clinical Trial/ | 949066 |
| 199 | Clinical Trials, Phase III as Topic/ | 10905 |
| 200 | Comparative Study/ | 1911363 |
| 201 | Controlled Clinical Trial/ | 94969 |
| 202 | Controlled Clinical Trials as Topic/ | 5637 |
| 203 | Cross-Sectional Studies/ | 438332 |
| 204 | Double-Blind Method/ | 172836 |

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| 205 | Equivalence Trial/ | 1039 |
| 206 | Equivalence Trials as Topic/ | 589 |
| 207 | exp Case-Control Studies/ | 1346545 |
| 208 | exp Cohort Studies/ | 2385601 |
| 209 | exp Randomized Controlled Trial/ | 576830 |
| 210 | exp Randomized Controlled Trials as Topic/ | 161270 |
| 211 | Longitudinal Studies/ | 160155 |
| 212 | Meta-Analysis as Topic/ | 21680 |
| 213 | Meta-Analysis/ | 165842 |
| 214 | Multicenter Studies as Topic/ | 21624 |
| 215 | Multicenter Study/ | 324974 |
| 216 | Observational Study/ | 131500 |
| 217 | Observational Studies as Topic/ | 8109 |
| 218 | Placebos/ | 35921 |
| 219 | Pragmatic Clinical Trial/ | 2137 |
| 220 | Pragmatic Clinical Trials as Topic/ | 806 |
| 221 | Prospective Studies/ | 636831 |
| 222 | Retrospective Studies/ | 1051976 |
| 223 | Systematic Review/ [ New MeSH 2019 ] | 199603 |
| 224 | Systematic Reviews as Topic/ [ New MeSH 2019 ] | 8984 |
| 225 | Validation Studies/ | 109085 |
| 226 | ("phase 1" or "phase1" or "phase I").mp. | 68092 |
| 227 | ("phase 2" or "phase2" or "phase II").mp. | 92901 |
| 228 | ("phase 3" or "phase3" or "phase III").mp. | 62507 |
| 229 | ((multicenter* or multicentre* or multicentric) adj2 (trial? or study or studies)).mp. | 366072 |
| 230 | ((noninferiority or non-inferiority) adj4 (trial? or study or studies)).mp. | 5685 |
| 231 | ((single or double or triple or treble) adj3 (blind* or mask*)).mp. | 245537 |
| 232 | (case control* adj2 (study or studies)).mp. | 349305 |
| 233 | (comparative adj2 (trial? or study or studies)).mp. | 1971101 |
| 234 | (conceal* adj2 allocat*).mp. | 3002 |
| 235 | (controlled adj1 clinical adj2 (trial? or study or studies)).mp. | 130583 |
| 236 | (cross-sectional* adj2 (study or studies)).mp. | 463061 |
| 237 | (equivalen* adj4 (trial? or study or studies)).mp. | 5961 |
| 238 | (evaluation adj1 (study or studies)).mp. | 389411 |
| 239 | (longitudinal* adj2 (study or studies)).mp. | 199829 |
| 240 | (meta-anal* or metanal* or metaanal*).mp. | 237511 |

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|---|---|---|
| 241 | (observational adj2 (trial? or study or studies)).mp. | 218289 |
| 242 | (overview? adj4 (review or reviews)).mp. | 20267 |
| 243 | (pragmatic adj2 (trial? or study or studies)).mp. | 5417 |
| 244 | (prospective* adj2 (study or studies)).mp. | 730026 |
| 245 | (retrospective* adj2 (study or studies)).mp. | 1087989 |
| 246 | (superiority adj4 (trial? or study or studies)).mp. | 3892 |
| 247 | (systematic adj4 (review or reviews or overview or overviews)).mp. | 242401 |
| 248 | (validation adj1 (study or studies)).mp. | 123222 |
| 249 | cohort*.mp. | 784345 |
| 250 | placebo*.mp. | 233244 |
| 251 | quasirandom*.mp. | 130 |
| 252 | random*.mp. | 1396764 |
| 253 | semiquantitative.mp. | 19431 |
| 254 | quantitativ*.mp. | 712863 |
| 255 | or/197-254 [ Quantitative Studies ] | 7125796 |
| 256 | 196 and 255 [ Fluids + Sepsis + Selected Diseases + Studies ] | 1320 |
| 257 | 256 not (exp animals/ not (exp animals/ and exp humans/)) | 1260 |
| 258 | limit 256 to humans | 1260 |
| 259 | 257 or 258 | 1260 |
| 260 | limit 259 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") | 219 |
| 261 | 259 not 260 | 1041 |
| 262 | limit 259 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") | 934 |
| 263 | 261 or 262 | 1173 |
| 264 | remove duplicates from 263 [ removal of internal database duplicates ] | 1168 |

# Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Title** | | | |
| Identification | #1a | Identify the report as a protocol of a systematic review | 1 |
| Update | #1b | If the protocol is for an update of a previous systematic review, identify as such | N/A |
| **Registration** | | | |
| | #2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 4 |
| **Authors** | | | |
| Contact | #3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contribution | #3b | Describe contributions of protocol authors and identify the | 14 |

| | | | |
|---|---|---|---|
| | | guarantor of the review | |
| **Amendments** | | | |
| | #4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | 7 |
| **Support** | | | |
| Sources | #5a | Indicate sources of financial or other support for the review | 14 |
| Sponsor | #5b | Provide name for the review funder and / or sponsor | N/A |
| Role of sponsor or funder | #5c | Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol | N/A |
| **Introduction** | | | |
| Rationale | #6 | Describe the rationale for the review in the context of what is already known | 6 |
| Objectives | #7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 7 |
| **Methods** | | | |
| Eligibility criteria | #8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 7 |
| Information sources | #9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 9 |
| Search strategy | #10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 9 |
| Study records - data management | #11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 10 |
| Study records - | #11b | State the process that will be used for selecting studies (such | 10 |

| | | | |
|---|---|---|---|
| selection process | | as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | |
| Study records - data collection process | #11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 10 |
| Data items | #12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 10 |
| Outcomes and prioritization | #13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 8 |
| Risk of bias in individual studies | #14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 11 |
| Data synthesis | #15a | Describe criteria under which study data will be quantitatively synthesised | 10 |
| Data synthesis | #15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ) | 11 |
| Data synthesis | #15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 11 |
| Data synthesis | #15d | If quantitative synthesis is not appropriate, describe the type of summary planned | N/A |
| Meta-bias(es) | #16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 11 |
| Confidence in cumulative evidence | #17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 12 |