BMJ Open

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

Aadil Bharwani,[1] María Lucía Pérez,[1] Marina Englesakis,[2] Tine Sylvest Meyhoff,[3] Anders Perner,[3] Praleene Sivapalan,[3] Mary Elizabeth Wilcox[4]

To cite: Bharwani A, Pérez ML, Englesakis M, *et al*. 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. *BMJ Open* 2023;**13**:e069601. doi:10.1136/bmjopen-2022-069601

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-069601).

Received 26 October 2022
Accepted 03 May 2023

[1]Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[2]Library and Information Services, University Health Network, Toronto, Ontario, Canada
[3]Department of Intensive Care, University of Copenhagen, Kobenhavn, Denmark
[4]Department of Critical Care Medicine, University of Alberta, Edmonton, Alberta, Canada

Correspondence to
Dr Mary Elizabeth Wilcox; Mwilcox@ualberta.ca

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.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

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.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Rivers E, Nguyen B, Havstad S, *et al*. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–77.
2 Rhodes A, Evans LE, Alhazzani W, *et al*. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017;43:304–77.
3 Rowan KM, Angus DC, Bailey M, *et al*. Early, goal-directed therapy for septic shock—a patient-level meta-analysis. *N Engl J Med* 2017;376:2223–34.
4 Rhodes A, Phillips G, Beale R, *et al*. The surviving sepsis campaign bundles and outcome: Results from the International Multicentre prevalence study on sepsis (the impress study). *Intensive Care Med* 2015;41:1620–8.
5 Abou Dagher G, Harmouche E, Jabbour E, *et al*. Sepsis in Hemodialysis patients. *BMC Emerg Med* 2015;15:30.
6 Duttuluri M, Rose K, Shapiro J, *et al*. Fluid resuscitation dilemma in patients with congestive heart failure presenting with severe sepsis/septic shock. In: D45. critical care: Circulatory Hemodymanics, shock, cardiovascular disease, and fluid management. *American Thoracic Society* 2016:A7048.
7 Leisman DE, Goldman C, Doerfler ME, *et al*. Patterns and outcomes associated with timeliness of initial Crystalloid resuscitation in a prospective sepsis and septic shock cohort. *Crit Care Med* 2017;45:1596–606.
8 Khan RA, Khan NA, Bauer SR, *et al*. Association between volume of fluid resuscitation and intubation in high-risk patients with sepsis, heart failure, end-stage renal disease, and cirrhosis. *Chest* 2020;157:S0012-3692(19)34013-9:286–92.:.
9 Abou Dagher G, Harmouche E, Jabbour E, *et al*. Sepsis in Hemodialysis patients. *BMC Emerg Med* 2015;15:30.:.
10 Pence M, Tran QK, Shesser R, *et al*. Outcomes of CMS-mandated fluid administration among fluid-overloaded patients with sepsis: A systematic review and meta-analysis. *Am J Emerg Med* 2022;55:S0735-6757(22)00159-0:157–66.:.
11 PRISMA-P Group, Moher D, Shamseer L, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1–9.
12 Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
13 Higgins JPT, Thomas J, Chandler J, *et al*. Cochrane Handbook for systematic reviews of interventions. In: *Cochrane handbook for systematic reviews of interventions*. John Wiley & Sons, 23 September 2019.
14 Vincent J-L, Sakr Y, Sprung CL, *et al*. Sepsis in European intensive care units: Results of the SOAP study. *Critical Care Medicine* 2006;34:344–53.

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