



HAL
open science

Reporting of Organ Support Outcomes in Septic Shock Randomized Controlled Trials: A Methodologic ReviewSepsis Organ Support Study

Simon Bourcier, Patrick Hindlet, Bertrand Guidet, Agnès Dechartres

► **To cite this version:**

Simon Bourcier, Patrick Hindlet, Bertrand Guidet, Agnès Dechartres. Reporting of Organ Support Outcomes in Septic Shock Randomized Controlled Trials: A Methodologic ReviewSepsis Organ Support Study. *Critical Care Medicine*, 2019, 47 (7), pp.984–992. 10.1097/CCM.0000000000003746 . hal-03894233

HAL Id: hal-03894233

<https://hal.sorbonne-universite.fr/hal-03894233>

Submitted on 15 Mar 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Reporting of Organ Support Outcomes in Septic Shock Randomized Controlled Trials:
a methodological review**

The Sepsis Organ Support Study.

Simon Bourcier¹, MD, Patrick Hindlet^{2,3}, PharmD, PhD, Bertrand Guidet¹, MD, Agnès Dechartres⁴, MD, PhD

¹Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Service de Réanimation médicale, Hôpital Saint-Antoine, AP-HP, F75012 Paris, France

² Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Pharmacie, Hôpital Saint-Antoine, AP-HP, F75012 Paris, France

³Faculté de pharmacie, Univ Paris-Sud, F92296 Châtenay-Malabry, France

⁴Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Service de Biostatistique santé publique information médicale, Hôpital Pitié Salpêtrière, AP-HP, F75013 Paris, France

Corresponding author: Simon Bourcier, Service de Réanimation médicale, Hôpital Saint-Antoine, 184 rue du Faubourg Saint-Antoine, Cedex 12, 75571, Paris, France, Tel: +33 (0)1 49282943; Fax: +33 (0)1 49 28 2145. E-mail: simon.bourcier@aphp.fr

Key words: systematic review, randomized controlled trial, septic shock, outcome

Word count: 2925/3,000 words

Abstract word count: 298/300 words

ABSTRACT

Objective: Many recent randomized controlled trials (RCTs) in the field of septic shock failed to demonstrate a benefit on mortality. RCTs increasingly report organ support duration (OSD) and organ support-free days (OSFD) as primary or secondary outcomes. We conducted a methodological systematic review to assess how organ support outcomes were defined and reported in septic shock RCTs.

Data sources: MEDLINE via PubMed, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science.

Study selection: We included RCTs published between January 2004 and March 2018 that involved septic shock adults and assessed OSD and/or OSFD for hemodynamic support, respiratory support or renal replacement therapy (RRT).

Data extraction: For each RCT, we extracted the definitions of OSD and OSFD. We particularly evaluated how non-survivors were accounted for. Study authors were contacted to provide any missing information regarding these definitions.

Data synthesis: We included 28 RCTs. OSD and OSFD outcomes were reported in 17 and 15 RCTs, respectively, for hemodynamic support, 15 and 15 for respiratory support, and 5 and 9 for RRT. Non-survivors were included in the OSD calculation in 13/14 RCTs (93%) for hemodynamic support and 9/10 (90%) for respiratory support. The OSFD definition for hemodynamic support, respiratory support and RRT was reported in 6/15 (40%), 8/15 (53%) and 6/9 (67%) RCTs reporting an OSFD outcome, respectively. Of these, one half assigned “0” to non-survivors and the other half attributed one point per day alive free of organ support up to a predefined time point.

Conclusions: This study highlights the heterogeneity and infrequency of OSD/OSFD outcome reporting in septic shock trials. When reported, the definitions of these outcome measures and methods of calculation are also infrequently reported, in particular how non-survivors were accounted for, which may have an important impact on interpretation.

Introduction

Considered as providing the highest level of evidence to evaluate the efficacy of healthcare interventions,(1) randomized controlled trials (RCTs) in the field of septic shock frequently define mortality as the primary outcome. Short-term mortality is deemed as the most clinically relevant outcome in this setting and is considered unbiased. However, large RCTs evaluating new therapies almost all failed to demonstrate an improvement in mortality, which may be partly explained by the decrease in septic shock mortality observed during the last decades.(2–7) Many RCTs in the field of septic shock lack sufficient power to detect a treatment effect when using mortality as primary outcome because sample size calculations are frequently based on unrealistic mortality improvement or predicted control-arm mortality rates.(3) The mortality outcome is also criticized because of the different time points reported, so comparisons across trials are difficult; the lack of ability to provide insight into mechanisms of intervention; and the underreporting of end-of-life decisions, which may influence the results.(8, 9)

As a consequence, RCTs of septic shock increasingly consider other outcomes such as organ support duration (OSD) and organ support-free days (OSFD) as primary or secondary outcomes. Organ support durations should be interpreted carefully because patients with increased risk of death may have a short OSD because of the competing risk of death.(8, 10) To address this issue, the outcome OSFD, which combines mortality and organ support over a specific time period, emerged in the 1990s and was found statistically valid for a smaller sample size.(11–14) OSFD was first used with ventilation-free days and then extrapolated to vasopressor and renal replacement therapy. It was initially defined as the number of days alive and free of mechanical ventilation.(12) However, various methods were reported to define ventilator-free days in acute lung-injury RCTs.(15)

In this study, we aimed to evaluate in septic shock RCTs, 1) the frequency of OSD and OSFD outcomes reported; 2) the frequency of OSD and OSFD definitions reported; and 3) the variability in methods by which non-survivors are accounted for in OSD and OSFD calculations.

Methods

Design

We performed a methodological systematic review reported according to the PRISMA statement.(16)

Search strategy

We searched MEDLINE via PubMed, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE using a strategy relying on algorithms adapted to each database including specific key words (MeSH terms for MEDLINE and Emtree terms for EMBASE) and free text words. The search equations were developed in collaboration with two librarian experts (see Supplemental Digital Content 1 for search equations). We restricted our search to beginning in 2004 because it was the year of publication of the first Surviving Sepsis Campaign guidelines publication.(19)

The search was initially conducted on April 2016. We manually updated this search in March 2018 for the period from April 2016 to March 2018.

We also screened all reference lists and citing articles for additional studies.

Article eligibility criteria

We included articles written in English reporting results of a RCT in an intensive care unit setting that involved adults with septic shock and assessed OSD and/or OSFD for at least one of the following organ supports:

- Hemodynamic support defined as vasopressor requirement (generally norepinephrine as recommended in the Surviving Sepsis Campaign guidelines)
- Respiratory support defined as invasive mechanical ventilation support
- Renal support defined as continuous or intermittent renal replacement therapy

We retained septic shock criteria according to the published consensus definition(18, 19) corresponding to suspected or confirmed infection complicated by at least 1 organ dysfunction and vasopressor requirement after adequate fluid expansion. We did not consider the updated definition proposed by Singer and colleagues because it was published too recently.(20) These choices were made to have a more homogeneous sample of RCTs in accordance with the consensus definition available during our period of recruitment.

We excluded pediatric trials as well as post-hoc analyses and ancillary studies of RCTs.

Selection process

After removing duplicates, 2 investigators (SB and PH) independently screened titles and abstracts and then full texts to identify eligible articles. Disagreements were resolved by discussion with the help of a third investigator (BG) whenever necessary to reach consensus.

Data collection

The following characteristics were collected in a standardized data extraction form:

- General characteristics: date of publication, journal, period of recruitment, study duration, countries, whether the trial was single-center or multicenter, and sample size
- Population characteristics: septic shock definition, inclusion criteria

- Interventions evaluated in the experimental and control groups
- Primary and secondary outcomes
- Quality of reporting by using the items of the CONSORT statement(21), which we graded as completely, incompletely or not reported.
- Risk of bias by the Risk of Bias tool developed by the Cochrane Collaboration(22).

We evaluated selection, performance, detection, attrition and reporting bias.

Quality of reporting and risk of bias were systematically evaluated independently by the two investigators (SB and PH) with the help of a third investigator (AD) whenever necessary to reach consensus.

Organ support duration or organ support-free days

For each OSD endpoint, we evaluated the organ concerned, whether the definition was reported and whether the OSD evaluation concerned only alive patients or also included non-survivors and if so, whether non-survivors were censored in the analysis or not.

For each OSFD endpoint, we evaluated the organ concerned, whether a definition and the method used to calculate OSFD were reported and how non-survivors were accounted for. Specifically, we evaluated whether non-survivors were attributed one point per day alive free of organ support up to the predefined time point or whether they were systematically attributed a “0” value.

We also collected from each trial the value of OSD and OSFD in the control group for hemodynamic support, respiratory support and renal replacement therapy.

This evaluation was performed in duplicate (SB and PH) with disagreements solved by discussion. In case of missing or unclear data, we systematically contacted the principal investigator of the trial by email to request further information.

On the basis of a reviewer's comments, we *a posteriori* reviewed all included studies to explore whether end-of-life decisions and withdrawal of organ support therapy were reported and how they may affect the results of OSD and OSFD.

Statistical analyses

Agreement between the two investigators for article screening was assessed by the Cohen Kappa coefficient; a Kappa coefficient 0.60 to 0.74 was considered good and ≥ 0.75 very good (23).

The analysis was mainly descriptive, involving frequencies (%) for categorical data and median (Q1-Q3) for quantitative data. We graphically represented OSD and OSFD in the control group for each RCT by type of organ support by using forest plots. We performed this for only control groups because we assumed that the results would be comparable across studies. We did not consider experimental groups because the type of interventions evaluated differed greatly across trials and may have biased the results.

All analyses were conducted using R v3.3.0 (R foundation for Statistical Computing, Vienna, Austria).

Results

Selection of articles and inter-reviewer agreement

The literature search identified 2782 records, and 183 articles were screened on the basis of the full text. Among 109 septic shock RCTs meeting the inclusion criteria, 28 (26%) reported OSD or OSFD as outcomes, which represents our final sample (Figure 1) (24–51).

Agreement for full-text eligibility between the two investigators was good (Kappa=0.70 (95% CI 0.54-0.84)).

Characteristics of the 28 included RCTs

As described in Supplemental Table 1 (Supplement Digital Content 2), 16 trials (57%) were multicenter; 5 were multinational studies. Nineteen trials investigated a drug intervention, 8 explored a bundle of care or a therapeutic strategy and 1 tested a device for catecholamine weaning.

The septic shock definition and inclusion criteria reported were mainly based on 1992 guideline criteria including the presence of suspected or confirmed infection with at least one organ failure and vasopressor requirement after volume expansion. In addition, 3 trials included mechanical ventilation in the eligibility criteria; 1 trial, the presence of acute kidney injury \geq INJURY stage of the RIFLE classification; 1, requirement for renal replacement therapy; and 1 was restricted to cirrhotic patients.

Mortality was defined as the primary outcome in 16 trials, although using 4 different time points (day 28 in 8 trials, day 60 in 1, day 90 in 6 and hospital mortality in 1). Six trials reported OSD or OSFD as the primary outcome. Four trials defined other primary outcomes

(total fluid expansion, difference in vasopressin concentration, decrease in vasopressor dose and kidney failure-free days during the 28-day period) and 2 did not define any primary outcome. All the 28 RCTs were negative for the primary-outcome superiority hypothesis except the APROCCHSS trial (90-day all-cause mortality)(43), the Oppert et al. study (time to vasopressor support cessation)(45), the Boussekey et al. study (decrease in vasopressor dose)(47) and the Zabet et al. trial (vasopressor dose and duration)(51).

Quality of reporting and risk of bias

Quality of reporting for the 25 CONSORT statement items is described in Supplement Digital Content 3. The CONSORT items were generally well reported except the item concerning the availability of the protocol, which was reported for 12 RCTs (43%), and the reporting of the study design in the title, which was reported for 13 RCTs (46%).

Risk of bias evaluation (see Supplement Digital Content 4) revealed a high risk of bias for the blinding of participants and personnel (18 RCTs, 64%). Risk of bias was generally low for random sequence generation (22 RCTs, 79%), allocation concealment (19 RCTs, 68%), blinding of outcome assessment (21 RCTs, 75%), incomplete outcome data (19 RCTs, 68%) and selective reporting (20 RCTs, 71%).

OSD and OSFD

The cumulative number of RCTs assessing OSD or OSFD by year of publication during the studied period is in Figure 2, showing no particular time trend in the reporting of OSD and OSFD. Five studies reported OSD or OSFD for one organ support, 9 studies for 2 organ supports and 14 for 3 organ supports.

Table 1 summarizes the qualitative analysis of OSD and OSFD in the 28 included trials (see Supplemental Table 2, Supplemental Digital Content 5, which presents OSD and OSFD information for each RCT). For 23 RCTs, we contacted the investigators, who provided missing information for 16. Regarding OSD, 5/17 (29%), 4/15 (27%) and 1/5 (20%) trials for hemodynamic, respiratory support and renal replacement therapy, respectively, reported whether OSD concerned non-survivors and alive patients together or separately. According to the information provided by authors after e-mail contact, OSD calculation included non-survivor measurement in 13/14 (93%) trials for hemodynamic support, 9/10 (90%) for respiratory support and 1/3 (33%) for renal replacement therapy. Overall, 7/13 (54%) studies for hemodynamic OSD and 4/9 (44%) for respiratory OSD censored non-survivors by Kaplan Meier curves or competing risk analysis. In one study, authors censored at 60 days the duration of hemodynamic, respiratory and renal OSD measurement(39) and in 2 studies, the authors censored at 28 days the duration of hemodynamic support measurement(46) and duration of respiratory support(48).

The definition of OSFD was reported in 6/15 (40%), 8/15 (53%) and 6/9 (67%) trials reporting an OSFD outcome for hemodynamic support, respiratory support and renal replacement therapy, respectively. Concerning non-survivors, 7/13 (54%), 7/14 (50%) and 4/9 (44%) trials systematically assigned “0” to non-survivors, whereas the other studies attributed one point per day alive free of organ support. The timing of measurements varied across trials, with 4 different time points used for hemodynamic OSFD (days 7, 28, 30 and 90), 3 for respiratory (days 28, 30 and 90) and 2 for renal OSFD (days 28 and 90).

The values for OSD and OSFD in the control groups showed marked heterogeneity across trials without the same definition of OSD/OSFD (see Supplemental Figure 1, Supplemental Digital Content 6) but also among RCTs sharing the same definition, which might be

explained by other factors such as baseline characteristics or post-randomization co-interventions.

End of life decision and withdrawal of organ support therapy

Five studies reported these elements, with important differences across studies ranging from do not resuscitate orders in case of cardiac arrest to decision to withhold or withdraw active treatment (See Table 1, Supplemental Digital Content 2). Because of this heterogeneous information, we were unable to analyze how this may affect the quantitative results of OSD and OSFD.

Discussion

In this methodological review of 28 RCTs of septic shock published from 2005 to 2018, we found that the quality of reporting of OSD and OSFD outcomes was suboptimal. How OSD and OSFD were calculated was frequently not defined in the articles. After obtaining information from authors, we found high heterogeneity in methods used across studies. OSD frequently included non-survivors, which could result in an apparent lower OSD because of the competing risk of death. The OSFD definition varied among studies by the time point of measurement and the weight attributed to death, but this last point was also rarely reported in articles.

Our results are consistent with a methodological review of acute respiratory distress syndrome studies showing that definitions of ventilation duration and ventilator-free days were reported in only 25% and 64% of trials, respectively. The definition of ventilator-free days was also heterogeneous across trials(52).

Such observations raise important concerns. The interpretation of results is difficult because the definition used may influence the results. Also, comparison of results between studies and their combination in a meta-analysis is challenging(53). Heterogeneity in the definitions and poor reporting cannot facilitate the planning of future trials, with possible misleading sample size calculation depending on the hypotheses and methods used.

OSD should not be estimated independent of mortality. Death is a competing event when evaluating organ support weaning and consequently organ support duration. Accounting for death in OSD may result in misleading evaluations of treatment effect. For example, if an intervention is associated with increased risk of early death, there will be an apparent benefit with lower OSD because of these early deaths. OSFD validity may also be discussed. From a statistical point of view, if OSFD as a composite endpoint allows for reducing the sample size

requirement, several conditions limit its validity. Indeed, because organ support duration and mortality are assigned an equal weight, endpoint components should have similar frequency and similar importance to the patient and also similar treatment effect.(14, 54, 55) Attributing a score of “0” to non-survivors will give more weight to death and may be more clinically relevant. However, we lack empirical evidence of the consequences of these choices on treatment effects. Such evidence would be helpful to define the most relevant method to estimate OSFD.

Implications for investigators and clinicians

Any intervention tested in a septic shock RCT may evaluate mortality or other patient-important outcomes such as quality of life, but organ support outcomes are also required to understand the clinical significance of the intervention.(9, 56) Such outcomes may also be particularly useful in the context of benchmarking or cost-analysis study. As a consequence, and given the heterogeneity of OSD/OSFD we highlight, there is a need for a specific consensus on standardized outcomes definitions and guidance for protocols in septic shock RCTs. Establishing a core set of outcomes as promoted by the Core Outcome Measures Effectiveness Trials (COMET) initiative (<http://www.comet-initiative.org>) and systematic reporting of the OSD/OSFD definitions used in septic shock trials could improve the interpretation of results and enable comparisons between trials and their combination in meta-analysis. In parallel, the US National Heart, Lung and Blood Institute also called for a standardization of endpoints definitions in acute lung injury trials.(54) Although future studies including simulation studies are needed to elaborate evidence-based recommendations, we could reasonably recommend not using OSD as an outcome because of the concerns raised. Including non-survivors in the OSD calculation is inappropriate because of the competing risk

of death, whereas reporting OSD only in survivors gives a partial picture. OFSD outcomes seem more appropriate because they account for both organ support duration and death. We recommend attributing “0” to non-survivors to give more weight to this major event, which is consistent with other authors.(15) We also recommend that RCT researchers transparently report the definition used, in particular how non-survivors were taken into account.

Although we focused on septic shock trials, the problems we identified may concern other domains of critical care medicine, for which this discussion may be of interest.

Limitations

We limited our search to trials published between 2004 and 2018. However, the inclusion of the oldest studies may have introduced heterogeneity in organ-support standard of care, not representative of current practice. We did not investigate another potential bias related to OSD and OSFD, which is the use of various definitions of support weaning such as tracheal tube removal.(15) Protocols to conduct organ support withdrawal and time from when organ support withdrawal is considered effective are rarely reported in septic shock RCTs. Finally, because we found different time points for OSFD (days 7, 28, 30 and 90), some studies likely censured OSD after time points not reported in the methodology. Only 3 studies reported censoring OSD at day 28 or 60, which could also be another limitation of OSD validity that we did not explore.

Conclusion

This methodological review highlights the heterogeneity and incomplete reporting of OSD and OSFD definitions in septic shock RCTs, which raises concerns about the validity and interpretation of results. These outcomes, among others, such as mortality and quality of life,

are still needed in the field of septic shock RCTs to increase our knowledge of the efficacy of interventions and therefore minimize the burden of septic shock. Simulation studies to explore the best definition for OSFD and a consensus on a core outcome set to be reported could help improve the planning and interpretation of septic shock RCTs.

Acknowledgments

We thank Catherine Weill and David Benoist, BIU Santé, Paris, France, for helpful assistance in the database search strategy.

We thank Laura Smales, BioMedEditing for English revision of the manuscript.

We thank all authors of included articles who gave details on outcome definitions and organ support data:

Jean-Pierre Quenot, Intensive Care Unit, University Hospital of Dijon, Dijon, France.

Christine Biquet, INSERM CIC 1432, University Hospital, Dijon, France.

Yaseen Arabi, Intensive Care Department, King Abdulaziz Medical City and King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

Anthony Gordon, ICU, Charing Cross Hospital, Imperial College London, London, UK.

Frédéric Adnet, SAMU 93, Hôpital Avicenne, Bobigny, France.

Jean-Christophe Richard, Service de Réanimation Médicale, Hôpital De La Croix Rousse, Hospices Civils de Lyon, Lyon, France.

Jim Russel, Critical Care Medicine, St. Paul's Hospital, Vancouver, BC, Canada.

Tamas Szakmany, Department of Anesthesia, Intensive Care and Pain Medicine, Medical School, Cardiff University, Cardiff, Wales, UK.

Derek Angus, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh.

Olivier Johannes-Boyau, Anesthésie-Réanimation, CHU de Bordeaux, France.

Belinda Howe, Australian and New-Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia.

Lisa Higgins, Australian and New-Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia.

Diane Stephens, Department of Intensive Care, Royal Darwin Hospital, Darwin, NT, Australia.

Nicolas Boussekey, Intensive Care and Infectious Disease Unit, Tourcoing Hospital, Tourcoing, France.

René Robert, Medical Intensive Care, La Milèterie University Hospital, University Poitiers, Poitiers, France.

Djillali Annane, Service de Médecine Intensive et Réanimation, Hôpital Raymond Poincaré, Garches, France.

Funding

None

References

1. Concato J, Shah N, Horwitz RI: Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000; 342:1887–1892
2. Ospina-Tascón GA, Büchele GL, Vincent J-L: Multicenter, randomized, controlled trials

evaluating mortality in intensive care: doomed to fail? *Crit Care Med* 2008; 36:1311–1322

3. Harhay MO, Wagner J, Ratcliffe SJ, et al: Outcomes and statistical power in adult critical care randomized trials. *Am J Respir Crit Care Med* 2014; 189:1469–1478
4. Angus DC, van der Poll T: Severe sepsis and septic shock. *N Engl J Med* 2013; 369:840–851
5. Kumar G, Kumar N, Taneja A, et al: Nationwide trends of severe sepsis in the 21st century (2000-2007). *Chest* 2011; 140:1223–1231
6. Angus DC, Linde-Zwirble W, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
7. Galbois A, Aegerter P, Martel-Samb P, et al: Improved prognosis of septic shock in patients with cirrhosis: a multicenter study*. *Crit Care Med* 2014; 42:1666–1675
8. Rubenfeld GD, Angus DC, Pinsky MR, et al: Outcomes research in critical care: results of the American Thoracic Society Critical Care Assembly Workshop on Outcomes Research. The Members of the Outcomes Research Workshop. *Am J Respir Crit Care Med* 1999; 160:358–367
9. Angus DC, Mira J-P, Vincent J-L: Improving clinical trials in the critically ill. *Crit Care Med* 2010; 38:527–532
10. Eggleston BL, Scharfstein DO, Freeman EE, et al: Causal inference for non-mortality outcomes in the presence of death. *Biostat Oxf Engl* 2007; 8:526–545
11. Sevransky JE, Checkley W, Martin GS: Critical care trial design and interpretation: a primer. *Crit Care Med* 2010; 38:1882–1889
12. Bernard GR, Wheeler AP, Arons MM, et al: A trial of antioxidants N-acetylcysteine and procysteine in ARDS. The Antioxidant in ARDS Study Group. *Chest* 1997; 112:164–172
13. Cohen J, Guyatt G, Bernard GR, et al: New strategies for clinical trials in patients with sepsis and septic shock. *Crit Care Med* 2001; 29:880–886
14. Schoenfeld DA, Bernard GR, ARDS Network: Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med* 2002; 30:1772–1777
15. Contentin L, Ehrmann S, Giraudeau B: Heterogeneity in the definition of mechanical ventilation duration and ventilator-free days. *Am J Respir Crit Care Med* 2014; 189:998–1002
16. Moher D, Shamseer L, Clarke M, et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4:1
17. Dellinger RP, Carlet JM, Masur H, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873
18. Bone RC, Balk RA, Cerra FB, et al: Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101:1644–1655

19. Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31:1250–1256
20. Singer M, Deutschman CS, Seymour CW, et al.: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315:801–810
21. Schulz KF, Altman DG, Moher D, et al.: CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340:c332
22. JPT Higgins, Altman D, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. 2011. Available from: <http://handbook.cochrane.org>
23. Cohen J: A coefficient of agreement for nominal scales. *Educ Psychol Meas* 1960; 20:37–46
24. COIITSS Study Investigators, Annane D, Cariou A, et al: Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA* 2010; 303:341–348
25. Arabi YM, Aljumah A, Dabbagh O, et al: Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. *Can Med Assoc J* 2010; 182:1971–1977
26. Asfar P, Meziani F, Hamel J-F, et al: High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 2014; 370:1583–1593
27. Chen C, Kollef MH: Targeted Fluid Minimization Following Initial Resuscitation in Septic Shock: A Pilot Study. *Chest* 2015; 148:1462–1469
28. Gordon AC, Mason AJ, Perkins GD, et al: The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. *Crit Care Med* 2014; 42:1325–1333
29. Joannes-Boyau O, Honoré PM, Perez P, et al: High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. *Intensive Care Med* 2013; 39:1535–1546
30. Huh JW, Choi H-S, Lim C-M, et al: Low-dose hydrocortisone treatment for patients with septic shock: a pilot study comparing 3 days with 7 days. *Respirology* 2011; 16:1088–1095
31. Merouani M, Guignard B, Vincent F, et al: Norepinephrine weaning in septic shock patients by closed loop control based on fuzzy logic. *Crit Care* 2008; 12:R155
32. Mouncey PR, Osborn TM, Power GS, et al: Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015; 372:1301–1311
33. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, et al: Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014; 371:1496–1506
34. Quenot J-P, Binquet C, Vinsonneau C, et al: Very high volume hemofiltration with the Cascade system in septic shock patients. *Intensive Care Med* 2015; 41:2111–2120
35. Richard J-C, Bayle F, Bourdin G, et al: Preload dependence indices to titrate volume expansion during septic shock: a randomized controlled trial. *Crit Care* 2015; 19:5

36. Russell JA, Walley KR, Singer J, et al: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–887
37. Stephens DP, Thomas JH, Higgins A, et al: Randomized, double-blind, placebo-controlled trial of granulocyte colony-stimulating factor in patients with septic shock. *Crit Care Med* 2008; 36:448–454
38. Toth I, Mikor A, Leiner T, et al: Effects of IgM-enriched immunoglobulin therapy in septic-shock-induced multiple organ failure: pilot study. *J Anesth* 2013; 27:618–622
39. ProCESS Investigators, Yealy DM, Kellum JA, et al: A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; 370:1683–1693
40. Holst LB, Haase N, Wetterslev J, et al: Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med* 2014; 371:1381–1391
41. Gordon AC, Mason AJ, Thirunavukkarasu N, et al: Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. *JAMA* 2016; 316:509–518
42. Venkatesh B, Finfer S, Cohen J, et al: Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *N Engl J Med* 2018; 378:797–808
43. Annane D, Renault A, Brun-Buisson C, et al.: Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *N Engl J Med* 2018; 378:809–818
44. Asfar P, Schortgen F, Boisramé-Helms J, et al: Hyperoxia and hypertonic saline in patients with septic shock (HYPER2S): a two-by-two factorial, multicentre, randomised, clinical trial. *Lancet Respir Med* 2017; 5:180–190
45. Oppert M, Schindler R, Husung C, et al: Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock*. *Crit Care Med* 2005; 33:2457–2464
46. Annane D, Vignon P, Renault A, et al: Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *The Lancet* 2007; 370:676–684
47. Boussekey N, Chiche A, Faure K, et al: A pilot randomized study comparing high and low volume hemofiltration on vasopressor use in septic shock. *Intensive Care Med* 2008; 34:1646–1653
48. Trof RJ, Beishuizen A, Cornet AD, et al: Volume-limited versus pressure-limited hemodynamic management in septic and nonseptic shock*. *Crit Care Med* 2012; 40:1177–1185
49. Payen DM, Guilhot J, Launey Y, et al: Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial. *Intensive Care Med* 2015; 41:975–984
50. Meng J, Hu M, Lai Z, et al: Levosimendan Versus Dobutamine in Myocardial Injury Patients with Septic Shock: A Randomized Controlled Trial. *Med Sci Monit* 2016; 22:1486–1496
51. Zabet MH, Mohammadi M, Ramezani M, et al: Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock. *J Res Pharm Pract* 2016; 5:94
52. Blackwood B, Clarke M, McAuley DF, et al: How Outcomes Are Defined in Clinical Trials of

Mechanically Ventilated Adults and Children. *Am J Respir Crit Care Med* 2014; 189:886–893

53. Yordanov Y, Dechartres A, Atal I, et al: Avoidable waste of research related to outcome planning and reporting in clinical trials. *BMC Med* 2018; 16:87

54. Spragg RG, Bernard GR, Checkley W, et al: Beyond mortality: future clinical research in acute lung injury. *Am J Respir Crit Care Med* 2010; 181:1121–1127

55. Ferreira-González I, Permanyer-Miralda G, Busse JW, et al: Methodologic discussions for using and interpreting composite endpoints are limited, but still identify major concerns. *J Clin Epidemiol* 2007; 60:651–657

56. Gaudry S, Messika J, Ricard J-D, et al: Patient-important outcomes in randomized controlled trials in critically ill patients: a systematic review. *Ann Intensive Care* 2017; 7:28

Tables and Figures

Table 1. Definitions of organ support outcomes observed in randomized controlled trials (RCTs)

Figure 1. Flowchart of study selection

Figure 2. Cumulative number of RCTs assessing organ support duration (OSD) or organ support-free days (OSFD) by year of publication during the studied period.

Supplemental Digital Contents

Supplemental Digital Content 1. Search equations

Supplemental Digital Content 2. Supplemental Table 1. Characteristics of included studies

Supplemental Digital Content 3. Quality assessment of CONSORT statement criteria reporting in the 28 septic shock randomized controlled trials (RCTs)

Supplemental Digital Content 4. Risk of bias of the 28 septic shock RCTs.

Supplemental Digital Content 5. Supplemental Table 2. Data extraction table

Supplemental Digital Content 6. Supplemental Figure 1. Forest plot comparing organ support duration (OSD) or organ support-free days (OSFD) measurements corresponding to similar definitions. RCTs are identified by the first author and year of publication, and OSD and OSFD findings are described by the number of patients in the control group, mean and 95% confidence interval (CI) values and illustrated by a graphical representation. Vasopressor, ventilation and renal replacement therapy support duration (days) are represented by the exclusion or inclusion of non-survivor patient measurements. OSFD (days) are summarized

for days free of vasopressor, ventilation and renal replacement therapy at the 28-day time point according to the value attributed to non-survivor patient OSFD.

List of abbreviations

OSD: organ support duration

OSFD: organ support-free day

RCT: randomized controlled trial

RRT: renal replacement therapy

Authors' contributions

SB was involved in the study conception, selection of RCTs, data extraction, data analysis, interpretation of results and drafting of the manuscript. PH was involved in the study conception, selection of RCTs, data extraction, data analysis, interpretation of results and drafting of the manuscript. BG was involved in the study conception, selection of RCTs, interpretation of results and drafting of the manuscript. AD was involved in the study conception, data extraction, data analysis, interpretation of results and drafting of the manuscript.

