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REVIEW

Beyond the Surviving Sepsis Campaign Guidelines: a systematic review of interventions affecting mortality in sepsis

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ABSTRACT

INTRODUCTION: Sepsis-related mortality is decreasing over time after the introduction of "Surviving Sepsis Campaign" Guidelines in 2004. The last Guidelines version collects 93 recommendations, but several interventions supported by randomized evidence of mortality reduction are not included.

EVIDENCE ACQUISITION: We performed a systematic review of all randomized controlled trials reporting a statistically significant mortality reduction in septic patients and compared the identified studies to the Surviving Sepsis Campaign Guidelines 2021 to highlight discrepancies.

EVIDENCE SYNTHESIS: We identified 83 randomized controlled trials (58 interventions) influencing mortality in sepsis. Only 9/58 of these interventions were included in the Guidelines: lactate measurement and lactate-guided hemodynamic management, procalcitonin-guided antibiotics discontinuation, balanced crystalloids as first choice fluids, albumin infusion, avoidance of starches, noradrenaline as first line vasopressor, vasopressin as an adjunctive vasopressor to noradrenaline, neuromuscular blocking agents in moderate-severe sepsis-associated acute respiratory distress syndrome, and corticosteroids use. Only 11/93 Guidelines recommendations were supported by randomized evidence with mortality difference. Five of the interventions with survival benefit in literature (vitamin C, terlipressin, polymyxin B, liberal transfusion strategy and immunoglobulins) were recommended to avoid in the Guidelines, while 44 interventions were not mentioned, including three interventions (esmolol, omega 3, and external warming) with at least two randomized controlled trials with a documented survival benefit.

CONCLUSIONS: Several discrepancies exist between the randomized controlled trials with mortality difference in septic patients and the latest Surviving Sepsis Campaign Guidelines. This systematic review can be of help for improving future guidelines and may guide research on specific promising topics.

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KEY WORDS: Sepsis; Survival; Guidelines as topic; Mortality; Critically illness.

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, according to the Sepsis-3 definition.[1] Septic shock is a condition characterized by circulatory, metabolic and cellular dysfunction which is associated with a relevant risk of mortality. Sepsis involves more than 19 million patients every year and almost 14 million survive to hospital discharge.[2] One third of discharged patients subsequently die from re-infection within 12 months.[3, 4]

Nevertheless, sepsis-related mortality is decreasing over time and is estimated to be around 17% in a recent meta-analysis,[5] whereas it was about 35% before 2005. The impressive reduction of mortality might be related to the development and diffusion of Guidelines in 2004, the first year of publication of the Surviving Sepsis Campaign (SSC).[6] Today, clinicians worldwide use the revision published in October 2021.[7] After the emergence and diffusion of coronavirus disease 2019 (COVID-19) specific Guidelines for the treatment of sepsis in COVID-19 patients were published in 2020 and updated in 2021.[8, 9] The last version of the SSC provides 93 final recommendations. The level of evidence and the strength of recommendations reflect both the quality of already published literature in a specific setting and the authors' opinion according to GRADE methodology.[10] The pathway from evidence to recommendations is often far from linear, and it may depend on factors such as the balance between desirable and undesirable effects, the quality of the evidence, the values and preferences of panelists and the costs of the interventions.

Notably, not all the recommendations included are based evidence from randomized controlled trials (RCTs) conducted in septic population, and they are often derived from studies performed in critically ill patients in general. Moreover, some interventions with randomized evidence in favor of a survival benefit were not included in the Guidelines, possibly because the evidence was insufficient to approve or reject them or because these studies were published after the latest guidelines.

We performed a systematic review of all RCTs reporting a statistically significant difference in mortality in septic population and compared them with current recommendations from SSC Guidelines. Aim of our study was to highlight potential discrepancies between current SSC Guidelines and available literature suggesting potential benefit or harm from a specific intervention in terms of survival. The ultimate purpose is to help next Guidelines drafting and stimulate further research on these topics.

Evidence acquisition

Six investigators identified all the RCTs ever published in peer-reviewed literature, with no time limits, searching on MEDLINE/PubMed, Scopus and Embase up to August 2022. Full details about search strategy are available in Supplementary Digital Material 1 (Supplementary Text File 1). Inclusion criteria were: 1) article published in a peer-reviewed journal; 2) randomized controlled trial; 3) involving critically ill or perioperative patients; 4) related to nonsurgical intervention (drug/strategy/technique); 5) statistically significant impact on unadjusted mortality (increase or reduction); 6) focusing on sepsis and/or septic shock populations. Exclusion criteria were: 1) not randomized or quasi-randomized trial; 2) trend to but not statistically significant difference in mortality; 3) adjusted mortality differences; 4) studies with overlapping populations; 5) studies involving COVID-19 patients. We did not include grey literature.

Patients were considered critically ill when presenting an acute failure of one or more organs according to sequential organ failure assessment (SOFA) score[11, 12] requiring urgent treatment or intensive care unit admission. Only RCTs involving 100% patients with sepsis at study enrolment reached the systematic review requirements. These studies were categorized according to the intervention investigated and the impact on mortality (reduction or increase). Data collection included: number of centers involved, single nation or multinational study, presence/absence of study blinding, presence/absence of intention to treat protocol, mortality as primary outcome, mortality difference only in a specific subgroup of patients and longest follow up with statistically significant mortality difference.

Descriptive statistics and fragility index calculation were completed for all studies with STATA 15 (StataCorp, College Station, TX, USA). Results are presented as number (percentage) and median [Interquartile Range]. We considered open-label studies, single-center studies, studies not analyzing data by intention-to-treat, and studies with fragility index zero as potential high-risk-of-bias studies.

Finally, all the interventions affecting mortality in septic population were compared to the 93 recommendations included in the current version of the SSC Guidelines.[7] In particular we highlighted: A) the interventions already suggested in the Guidelines with at least one existing RCT with a statistically significant difference in mortality; B) the interventions already included in the Guidelines as

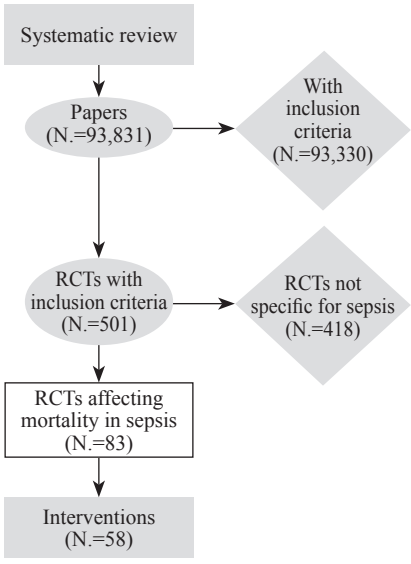

Figure 1.—Flow chart of systematic review process for selection of all the 83 randomized controlled trials (RCTs) with statistically significant impact on mortality in septic population ever performed.

"recommended to avoid" with at least one existing RCT with a statistically significant reduction of mortality; C) the interventions not mentioned in the Guidelines even if they have more than one published RCTs with a statistically significant difference in mortality.

Evidence synthesis

From the search strategy 93,831 papers were identified and 93,330 excluded because they did not fulfill the inclusion/exclusion criteria (Figure 1). In total, 501 RCTs with statistically significant differences in mortality were therefore identified. Among these, 83 studies dealing with 58 different interventions were conducted in septic population. For simplicity purpose, we unified all steroids studies as a single intervention. A short summary of all the 83 RCTs documenting mortality difference in sepsis is reported in Supplementary Digital Material 2 (Supplementary Table I).

Study design

Multicentric studies were 50/83 (60%) and 14/83 (17%) were multinational. Study blinding was adopted in 52/83 (62%) RCTs, while intention-to-treat analysis in 49/83 (59%) RCTs.

Mortality

Mortality was the primary outcome of 56/83 (68%) of these RCTs. In 59/83 (71%) RCTs the statistically significant difference in mortality was in the whole population, whereas in 24/83 (29%) the difference was observed only in a specific subgroup of patients. Interventions reduced or increased mortality in 73/83 (88%) and in 10/83 (12%) RCTs respectively. Mortality differences were observed at a follow-up >28 days in 58/83 (70%) RCTs.

Journals

The 83 RCTs were published in 35 different journals, the three most represented being Critical Care Medicine (N.=18), Journal of American Medical Association (N.=10) and New England Journal of Medicine (N.=10). The complete list of Journal is available in Supplementary Digital Material 3 (Supplementary Table II).

Study quality

Median number of randomized patients of the 83 RCTs was 127 [63-303] and median fragility index was 2 [0-4]. Fragility index was zero in 29/83 RCTs. The fragility index of the single studies is reported in Supplementary Table I. Among 83 RCTs were: 33 RCTs were single-center, 31 RCTs were unblind, 34 RCTs adopted non-intention-to-treat protocol and in 29 RCTs the fragility index was zero.

TABLE I.—*Interventions with agreement between surviving sepsis campaign recommendations and systematic review results.*

Intervention	Surviving Sepsis Campaign Recommendation #	N. of RCTs
Lactate measurement and lactate-guided hemodynamic management	3 and 7	1
Procalcitonin-guided ABT discontinuation	31	2
Balanced crystalloids as first choice fluids	32 and 33	1
Albumin infusion	34	1
Avoidance of starches	35	1
Noradrenaline as first choice vasopressor	37	1
Vasopressin as adjunctive vasopressor to noradrenaline	38	1
NMBA in moderate-severe sepsis-associated ARDS	56	1
Use of corticosteroids	58	6 (plus 2 against corticosteroids)

ABT: antibiotics; ARDS: acute respiratory distress syndrome; NMBA: neuromuscular blocking agents; RCTs: randomized controlled trials.

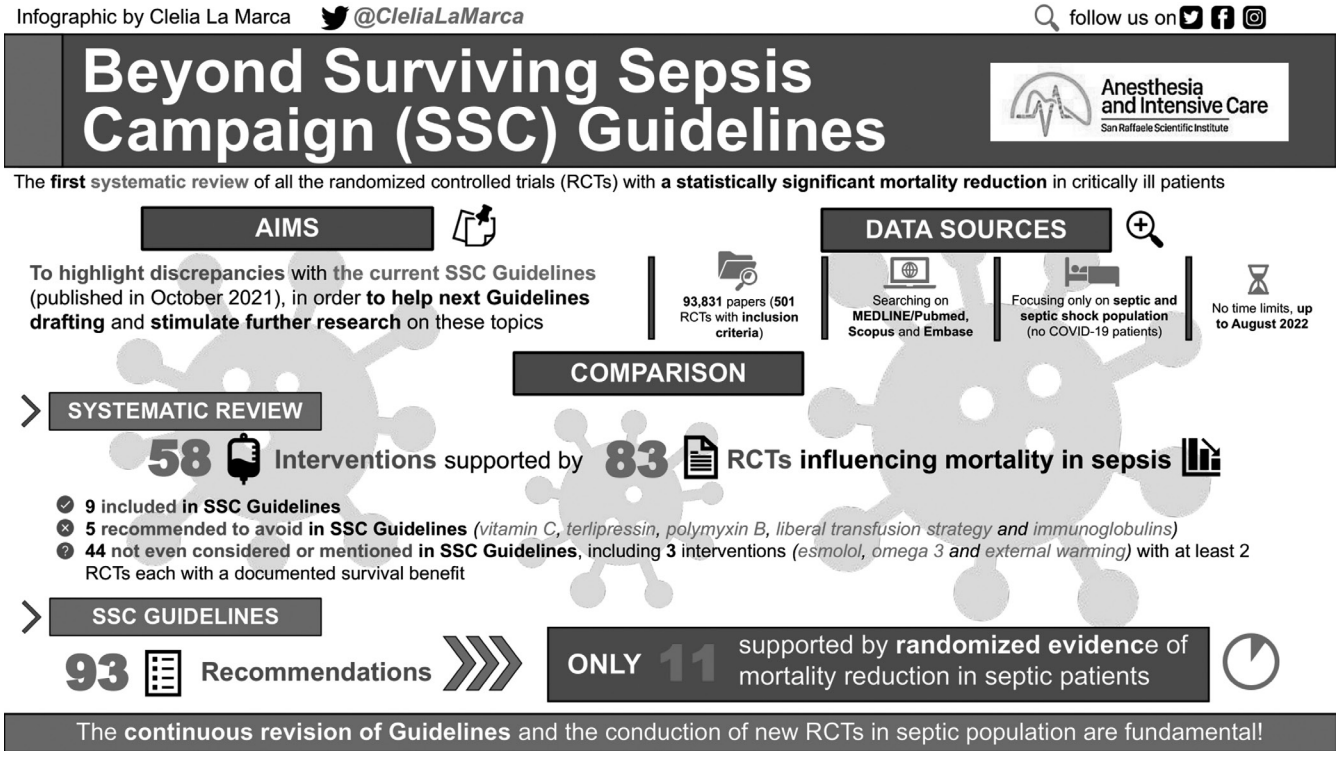

Figure 2.—Visual abstract presenting main article structure, objective and results.

When comparing the 58 identified interventions with the 93 SSC recommendations, we found that only 11/93 recommendations of the SSC are supported by published randomized evidence of mortality reduction in a sepsis/septic shock setting (Table I). One of these interventions (corticosteroids) has 6 RCTs documenting a mortality reduction and two RCTs documenting a survival reduction.

Main results are presented in Figure 2.

We identified 58 interventions with randomized published evidence of mortality reduction/increase in septic patients. Interestingly, only nine out of 58 are recommended in the SSC Guidelines, five out of 58 are recommended to avoid and 44 out of 58 are not even considered or mentioned, including three which have two or more RCTs with a documented mortality difference in septic patients.

We highlighted that only 11 of the 93 recommendations of the SSC Guidelines are supported by randomized evidence of mortality reduction in septic patients.

The 11 recommendations supported by randomized evidence of mortality reduction in septic patients include: measuring lactate in adults suspected of having sepsis and to guide resuscitation to decrease serum levels (two recommendations);[13] discontinuing antibiotic therapy based on clinical evaluation and procalcitonin levels;[14, 15] using balanced crystalloids as first line fluid for resuscitation (two recommendations);[16] adding albumin for patients receiving large volumes of crystalloids;[17, 18] avoiding starches for fluid resuscitation in sepsis;[19] using noradrenaline as the vasopressor of choice in septic shock;[20, 21] adding vasopressin in case of inadequate mean arterial pressure despite noradrenaline infusion;[22] using neuromuscular blocking agents in case of moderate-severe sepsis-induced acute respiratory distress syndrome;[23] and using intravenous corticosteroids in case of ongoing requirement for vasopressors.[24-26]

In five situations the expert authors of the Guidelines "recommended against" interventions which had randomized evidence of survival benefit in septic patients, probably because of low quality of the "positive" trials, of large RCTs showing no difference (vitamin C),[27-29] high costs of the intervention (polymyxin B),[30, 31] high incidence of side effects (terlipressin),[32-34] health equality considerations (transfusions)[35] or non-updated evidence (immunoglobulins).[36]

Notably, we found 44 interventions with randomized evidence of statistically significant survival differences

which are not even mentioned in the Guidelines (Supplementary Table I). Three of them have more than one RCTs documenting a statistically significant reduction in mortality: esmolol with three RCTs documenting a mortality reduction; omega-3 with three RCTs documenting a mortality reduction; and external warming with two RCTs documenting a mortality reduction.

Importantly, three of these interventions had two or more RCTs showing a statistically significant reduction in mortality.

Esmolol, which has never been considered in SSC Guidelines, reduces beta-adrenergic response which leads to stress cardiomyopathy and tachyarrhythmias. Three RCTs have demonstrated a survival benefit in septic shock[37-39] despite their small sample size: 77, 48, and 90 patients, respectively. Meta-analyses confirmed the reduced 28-days mortality in septic shock when using esmolol[40-42] and this treatment should at least be reconsidered.

Nutritional supplementation with omega-3 fatty acids has been proposed to modulate the immune response in critical illness by improving the ratio of arachidonic to eicosapentaenoic acid and thus inhibiting pro-inflammatory while promoting anti-inflammatory mediators. While in a previous version a recommendation to avoid omega-3 was made (strong recommendation, low quality of evidence),[6] current Guidelines do not mention this topic. In literature we found three RCTs with survival benefit associated with omega 3 supplementation. The first is a multicentric study in 165 patients randomized to omega 3 versus placebo, with a reduction in 28-day mortality in the treatment group.[43] The second study, published in 2017, found the same result in 48 patients.[44] A previous RCT published in 2014 enrolled 60 patients and found reduced in-hospital mortality only in the subgroup with less severe sepsis.[45] Moreover, recent meta-analyses confirmed this results in septic and critically ill population, also with a possible effect on sepsis-prevention.[46-48]

Warming of afebrile patients with infection or allowing a higher temperature might improve immune function. In 2022, 56 afebrile septic patients were randomized to be warmed above 37.5 °C for 48 hours *versus* standard care. There was a reduction in 28-days mortality in the treatment group (P=0.041).[49] A RCT conducted in 2014 randomized 65 patients to a low temperature group (36-37.5 °C) and high temperature group (37.5-38.3 °C, the same range as the abovementioned RCT). Twenty-eight-day mortality was increased in low temperature group (P=0.001).[50] Cooling septic patients could be harmful as also suggested by a meta-analysis of high quality RCTs performed in critically ill patients[51] and this topic deserves further studies.

To our knowledge, this is the first systematic review focused on intervention influencing mortality in sepsis. Our group previously performed systematic reviews including all the interventions reducing and increasing mortality in critically ill and perioperative patients which have been published in 2019[52, 53] and which included heterogenous settings.

We identified all the drugs, techniques or strategies associated with reduced and increased mortality in septic patients and compared them to the SSC recommendations. We identified discrepancies and gaps between SSC Guidelines and the evidence arising from RCTs. These differences might be attributed to the fact that some recommendations are based upon studies not specifically involving septic patients but, in general, critically ill population, while other recommendations arise from a beneficial or detrimental effect in outcomes other than mortality.

Several RCTs are in contrast with SSC recommendations, and this is one of the difficulties of writing guidelines which should apply to heterogenous intensive care units in different continents. It is also a reminder that scientific evidence is a process in continuous evolution.

This is the first systematic review identifying all the RCTs with impact on mortality of septic patients. The aim of the study was to highlight differences between Surviving Sepsis Campaign Guidelines and evidence arising from RCTs with mortality impact involving septic patients, suggesting potential new promising topics to be investigated and possibly to be considered in new guidelines.

Our search strategy was based on a very comprehensive search string and study selection. We focused on RCTs involving patients with sepsis or septic shock as an exclusive setting. We excluded quasi-randomized trials and studies reporting adjusted mortality.

Limitations of the study

This study has limitations. We selected only RCTs with statistically significant differences in mortality, but this can also be considered as a further strength of the study. We did not include RCTs with neutral results. However, we believe that focusing on RCTs showing mortality difference allowed us to consider only the most clinically relevant interventions, or those with the most striking difference with guidelines. We did not consider the wide range of grey literature, but this can also be considered a further strength of the study, as grey literature has been frequently shown to present biased results.[54, 55] The aim

of our manuscript was not to perform a meta-analysis for each one of the investigated topics, and it should be acknowledged, as a strength of the study, that several meta-analyses on the majority of these interventions already exist and confirm the findings of the RCTs. It should also be noted that some SSC recommendations, included in the abovementioned 93, cannot be investigated through RCTs (*e.g.*, new recommendations regarding palliative care). Finally, as we did not perform a meta-analysis of all RCTs investigating a single intervention, we chose not to perform the quality assessment of the single RCTs, nor the analysis of publication bias. Nevertheless, we identified and described in detail several factors associated with potential high risk of bias, including single-center design, lack of blinding, lack of intention-to-treat analysis, and low fragility index.

The present study could be implemented with detailed analysis and inclusion of those intervention supported by a single RCT with statistically significant mortality difference in septic patients which were not mentioned or included in the guidelines. Due to time and space concerns, we've simply identified them and included them in a table, but we did not discuss them in detail. Since guidelines are the milestone of clinical practice, our methodology including a systematic review and comparison with guidelines, could be extended to guidelines other than sepsis.

Conclusions

Our systematic review of trials focusing on sepsis and septic shock identified 44 interventions with mortality differences according to published RCTs which are not included, considered or even mentioned in the SCC Guidelines. The identification of such discrepancies can be of help for improving future guidelines and to suggest researchers worldwide on which topics to focus their research over the next few years. The continuous revision of Guidelines and the conduction of new RCTs in septic population should be encouraged.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY DIGITAL MATERIAL 1

Full MEDLINE/PubMed search strategy

((((dead[tiab] or death[tiab] or die[tiab] or died[tiab] or mortality[tiab] or fatalit*[tiab] or exitus[tiab] or surviv*[tiab]) AND("anesthesia"[tiab] OR "cardiac arrest"[tiab] or "critical care"[tiab] or sepsis[tiab] or "critical illness"[tiab] or "critically ill" [tiab] or "ARDS"[TIAB] or "acute respiratory distress syndrome"[tiab] OR "ecmo"[tiab] OR "intensive care"[tiab] or emergen*[tiab]) AND (“randomized controlled trial”[tiab] OR “controlled clinical trial”[tiab] OR “randomized controlled trials”[tiab] OR blind*[tiab] OR “clinical trial”[tiab] OR “clinical trials”[tiab] OR placebo*[tiab] OR random*[tiab]) NOT (animal[mh] NOT human[mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt] OR pediatrics[mh]))) OR ((dead[tiab] or death[tiab] or die[tiab] or died[tiab] or mortality[tiab] or fatalit*[tiab] or exitus[tiab] or surviv*[tiab]) AND ("anesthesia"[tiab] OR "cardiac arrest"[tiab] or "critical care"[tiab] or sepsis[tiab] or "critical illness"[tiab] or "critically ill" [tiab] or "ARDS"[TIAB] or "acute respiratory distress syndrome"[tiab] OR "ecmo"[tiab] OR "intensive care"[tiab] or emergen[tiab]) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[tw] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh])))) OR ((surgery[tiab] OR surgic*[tiab] OR operation*[tiab]) AND ((death* OR survival OR mortality)) AND (prevent* OR reducti* OR reduci*) AND (significat* OR significan*) AND (randomised controlled trial[pt] OR controlled clinical trial[pt] OR randomised controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[tw] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt])))

SUPPLEMENTARY DIGITAL MATERIAL 2

Supplementary Table I.—Brief description of the 83 RCTs performed in septic patients and documenting a statistically significant difference in mortality. Grey lines represent 10 RCTs with increased mortality.

Topic	Intervention	Control	Subgroup	Time point	First Author	Publication Date	Fragility Index
Antibiotics	Fluconazole	Placebo	No	30 d	Jacobs[1]	2003	3
	Clarithromycin	Placebo	No	90 d	Tsaganos[2]	2016	4
Procalcitonin	Procalcitonin guided ABT stop	Standard treatment	No	1 y	De Jong[3]	2016	10
		Standard treatment	No	28 d	Kyriazopoulou[4]	2021	4
Coagulation	Antithrombin III	Placebo	Septic shock	30 d	Baudo[5]	1998	NA
	Platelet activating factor	Placebo	Low dose treatment	28 d	Schuster[6]	2003	2
		Placebo	No	28 d	Dhainaut[7]	1994	4
	Protein C zymogen	Placebo	No	90 d	Pappalardo[8]	2016	2
	Recombinant activated protein C	Placebo	No	28 d	Bernard[9]	2001	20
Hemodynamic drugs	Esmolol	Standard treatment	No	28 d	Morelli[10]	2013	14
		Standard treatment	No	28 d	Xinqiang[11]	2015	3
		Standard treatment	No	28 d	Wang[12]	2015	3
	Magnesium	Placebo	No	28 d	Noormandi[13]	2019	7
	Angiotensin II	Placebo	No	28 d	Tumlin[14]	2018	NA
	Early noradrenaline	Standard Volume Replacement	No	Hosp	Elbouhy[15]	2019	4
	Terlipressin	Noradrenaline	No	48 h	Choudhury[16]	2016	3
		Noradrenaline	No	7 d	Xiao[17]	2016	2
	Vasopressin	Noradrenaline	Less severe septic shock	90 d	Russell[18]	2008	0
	Midodrine	Noradrenaline	No	Hosp	El Adly[19]	2022	na
Fluids Replacement	Albumin	Crystalloids	Septic shock	90 d	Caironi[20]	2014	0
		Saline	No	7 d	Philips[21]	2021	0
	Balanced solutions	Saline	Admitted for medical reason	30 d	Brown[22]	2019	5

	Hydroxyethyl starch	Ringer acetate	No	90 d	Perner[23]	2012	1
Hemodynamic Management	Early goal directed therapy	Standard treatment	No	60 d	Rivers[24]	2001	0
		Standard treatment	No	Hosp	Lin[25]	2006	6
	Lactate-guided management	$ScvO_2$-guided management	No	60 d	Zhou[26]	2017	2
	Perfusion-guided management	Lactate-guided management	SOFA <10	28 d	Hernandez[27]	2019	0
	"Early resuscitation" management	Standard treatment	No	28 d	Andrews[28]	2017	8
	DO_2 monitoring	$PtcO_2$ monitoring	No	Hosp	Yu[29]	2007	3
Immune-modulation	C1 esterase Inhibitor	Placebo	No	28 d	Igonin[30]	2012	4
	Deltibant (bradykinin antagonist)	Placebo	Sepsis from G - bacteria	28 d	Fein[31]	1997	na
	Ibuprofen	Placebo	Sepsis with hypothermia	30 d	Arons[32]	1999	3
	High dose immunoglobulin	Placebo	Sepsis score >20	ICU	Dominioni[33]	1991	2
	Interleukin-1 receptor inhibitor	Placebo	DIC/hepatic dysfunction	28 d	Shakoory[34]	2016	0
	Anti-endotoxin antibodies	Placebo	Endotoxemia	28 d	Wortel[35]	1992	6
		Placebo	Sepsis from G- bacteria without septic shock	30 d	Greenman[36]	1991	0
	Anti-TNF antibodies	Placebo	High level IL-6	28 d	Panaceck[37]	2004	0
		Placebo	Septic shock	72 h	Abraham[38]	1995	0
	Nitric oxide synthase inhibitor	Placebo	No	28 d	Lopez[39]	2004	13
	Ulinastatin (tripsine inhibitor)	Placebo	No	28 d	Karnad[40]	2014	0
	Antiserum of J5 *E. coli* mutans	Preimmune serum	No	Missing	Ziegler[41]	1982	4
	Anti-LPS plasma	Placebo	No	Hosp	Lachman[42]	1984	2
	Micobacterium w	Placebo	No	28 d	Sehgal[43]	2021	2
Alternative Medicine	Traditional Chinese medicine	Standard treatment	No	28 d	Xing[44]	2019	3
	Acupuncture	Standard treatment	No	28 d	Xiao[45]	2015	NA
	Septimeb	Standard treatment	No	28 d	Eslami[46]	2012	0
	XueBiJing	Placebo	No	28 d	Song[47]	2019	9

	Safflower yellow	Placebo	No	28 d	Li[48]	2016	4
Nutrition and Vitamins	Arginine	Standard enteral nutrition	No	ICU	Galban[49]	2000	0
		Standard parenteral nutrition	Severe sepsis	ICU	Bertolini[50]	2003	0
	Branched chain amino acids	Standard treatment	No	ICU	Garcia[51]	1997	0
	Carnitine	Placebo	No	28 d	Puskarich[52]	2014	0
	Coenzyme Q10	Placebo	No	Hosp	Soltani[53]	2020	3
	Omega-3	Standard treatment	Less severe sepsis	Hosp	Hall[54]	2014	0
		Standard treatment	No	28 d	Chen[55]	2017	1
		Standard treatment	No	28 d	Pontes-Arruda[56]	2006	0
	Selenium	Placebo	No	28 d	Angstwurm[57]	2007	0
		Placebo	No procalcitonin guidance	28 d	Bloos[58]	2016	7
	Vitamin B1	Placebo	Thiamine deficiency	30 d	Donnino[59]	2016	0
	Vitamin C	Placebo	No	28 d	Zabet[60]	2016	2
		Placebo	No	28 d	Fowler[61]	2019	2
		Placebo	Positive pressure ventilation	28 d	Wacker[62]	2022	8
Steroids	Dexamethasone	Placebo	No	7 d	Cicarelli[63]	2007	2
	Dexamethasone/Methylprednisolone	Placebo	No	28 d	Schumer[64]	1976	13
		Placebo	133-150 h	150 h	Sprung[65]	1984	0
	Hydrocortisone	Placebo	No	60 d	Confalonieri[66]	2004	3
		Placebo	SRS2 subtype	28 d	Antcliffe[67]	2018	0
	Hydrocortisone + Fludrocortisone	Placebo	Adrenal failure	Hosp	Annane[68]	2002	0
		Placebo	No	180 d	Annane[69]	2018	4
	Methylprednisolone	Placebo	Creatinine >2 mg/dL	14 d	Bone[70]	1987	16
Blood Purification Techniques	Cytosorb	Standard treatment	No	60 d	Schädler[71]	2017	0
	Polymyxin B	Standard treatment	No	28 d	Nemoto[72]	2001	8
		Standard	No	ICU	Nakamura[73]	2003	7

		treatment					
		Standard treatment	No	Hosp	Cruz[74]	2009	1
Miscellanea	Liberal transfusion strategy	Standard treatment	No	90 d	Bergamin[75]	2017	0
	Dexmedetomidine	Lorazepam	No	28 d	Pandharipande[76]	2010	0
	Atorvastatin	Placebo	Statin therapy	28 d	Kruger[77]	2013	0
	Machine learning based prediction algorithm	Standard treatment	No	Hosp	Shimabukuro[78]	2017	0
	Phosphatase alkaline	Placebo	High dose Treatment	28 d	Pickkers[79]	2018	2
	External Cooling	Standard treatment	No	14 d	Schortgen[80]	2012	4
		Temperature 37.5-38.3 °C	No	28 d	Yang[81]	2013	4
	External Warming	Standard treatment	No	28 d	Drewry[82]	2022	0
	Neuromuscular Blocking Agents	Placebo	No	21 d	Lyu[83]	2014	0

ABT: antibiotics; D: days; DIC: disseminated intravascular coagulopathy; DO_2: oxygen delivery; G-: gram negative; Hosp: in-hospital; ICU: intensive care unit; IL-1: interleukin 1; IL-6: interleukin 6; LPS: lipopolysaccharide; NA: not applicable; SOFA: sequential organ failure assessment; SRS2: sepsis response subtype 2; $ScvO_2$: central venous oxygen saturation; $PtcO_2$: tissue partial pressure oxygen; TNF: tumor necrosis factor; Y: year.

For five RCTs there were insufficient data for fragility index calculation.

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SUPPLEMENTARY DIGITAL MATERIAL 3

Supplementary Table II.—Journal of publication of the 84 RCTs with mortality difference in sepsis and relative number of RCTs.

Journal	**N. of RCTs**
Critical Care Medicine	18
JAMA	10
NEJM	10
American Journal of Respiratory and Critical Care Medicine	6
Intensive Care Medicine	4
Critical Care	2
Journal of Parenteral and Enteral Nutrition	2
Lancet	2
Shock	2
Chinese Critical Care Medicine	2
Annals of Surgery	1
Antimicrobial Agents and Chemotherapy	1
Archive of Medical Research	1
Archives of surgery	1
Blood Purification	1
BMJ Open Respiratory Research	1
Bratislava Medical Journal	1
Chest	1
Chinese Medical Journal	1
Chinese Journal of Integrative Medicine	1
Clinical Drug Investigation	1
Complementary Therapies in Medicine	1
Daru Journal of Pharmaceutical Sciences	1
European Journal of Clinical Pharmacology	1
Evidenced Based Complementary and Alternative Medicine	1
Experimental and Therapeutic Medicine	1
Hepatology International	1
Irish Journal of Medical Science	1
Journal of Hospital Infection	1
Journal of Pharmacol Practice and Reaserch	1
Journal of Surgical Research	1
Journal of Infectious Diseases	1
Liver International	1
PLoS One	1
Sao Paolo Medical Journal	1