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SYSTEMATIC REVIEW

Control groups in recent septic shock trials: a systematic review

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Abstract

Purpose: The interpretation of septic shock trial data is profoundly affected by patients, control intervention, co-interventions and selected outcome measures. We evaluated the reporting of control groups in recent septic shock trials.

Methods: We searched for original articles presenting randomized clinical trials (RCTs) in adult septic shock patients from 2006 to 2016. We included RCTs focusing on septic shock patients with at least two parallel groups and at least 50 patients in the control group. We selected and evaluated data items regarding patients, control group characteristics, and mortality outcomes, and calculated a data completeness score to provide an overall view of quality of reporting.

Results: A total of 24 RCTs were included (mean $n = 287$ patients and 71 % of eligible patients were randomized). Of the 24 studies, 14 (58 %) presented baseline data on vasopressors and 58 % the proportion of patients with elevated lactate values. Five studies (21 %) provided data to estimate the proportion of septic shock patients fulfilling the Sepsis-3 definition. The mean data completeness score was 19 out of 36 (range 8–32). Of 18 predefined control group characteristics, a mean of 8 (range 2–17) were reported. Only 2 (8 %) trials provided adequate data to confirm that their control group treatment represented usual care.

Conclusions: Recent trials in septic shock provide inadequate data on the control group treatment and hemodynamic values. We propose a standardized trial dataset to be created and validated, comprising characteristics of patient population, interventions administered, hemodynamic values achieved, surrogate organ dysfunction, and mortality outcomes, to allow better analysis and interpretation of future trial results.

Keywords: Septic shock, Control group, Randomized, Trial, Reporting, Standardization

Background

Septic shock affects millions of people annually (approximately 300–700 per 100,000 adult population per year), and a recent meta-analysis of observational studies indicated that it leads to death in 46 % of cases [1] in spite of recent progress in diagnosis and treatment.

In addition to the recently revised definition of septic shock [1], future progress requires improved design of randomized controlled trials (RCTs). For correct interpretation of the results of RCTs in septic shock, it is crucial to report all recommendations and restrictions stipulated in the protocol and the main co-interventions performed in the control group. The most important issues to be considered are representativeness of the study population, control group treatment, possible misalignment due to titrated treatment in usual care [2], detailed description of the given treatment and

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Take-home message: Recent trials in septic shock provide inadequate data on the treatment given the control group and the hemodynamic values achieved. We propose a standardized trial dataset comprising characteristics of patient population, co-interventions administered, hemodynamic values achieved, surrogate organ dysfunction, and mortality outcomes.

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co-interventions, and their agreement with guidelines and with usual care. A deeper understanding of these factors may improve the clinical utility of trial results.

Accordingly, we aimed to evaluate information reported about the control groups in recent septic shock trials [3]. We specifically aimed to evaluate (1) the selection of the patient population, (2) the description of treatments and co-interventions of the control group, especially the hemodynamic treatment and hemodynamic values achieved, (3) the mortality outcome measures, (4) the representativeness of control groups compared to usual care, and (5) the overall completeness of the data reported.

Methods

The search strategy and selection of trials

We searched Pubmed, Scopus, and the Cochrane Central Register of Controlled Trials for original articles presenting RCTs in adult septic shock patients and published during the last 10 years (from February 10, 2006, to February 10, 2016). The search strategy is presented in the ESM. Due to the evolution of publication requirements and treatment concepts, we considered earlier trials as not representative. Two investigators (V.P. and P.H.) independently extracted the pre-selected data items from the original papers and supplementary material of these trials. We excluded the study if: (1) it was not a parallel-group randomized trial; (2) it did not include an adult septic shock population (less than 75 % of the patients or not stated); (3) there were fewer than 50 patients in the control group; (4) it was a sub-study or a post hoc analysis; or (5) it was not published in the English language. All discrepancies in inclusion and evaluation of the studies between the two assessors were registered and discussed.

We used predefined data items and the PICO approach: patients (P), intervention (I), control (C), and outcome (O), however without assessment of (I), the experimental intervention studied.

Patient (P) populations

We extracted numbers of screened, eligible, all randomized, and control group patients. In all trials, patients with all inclusion criteria and no pre-defined exclusion criteria were considered eligible [4–6], regardless of reasons for missing informed consent or any logistic issues. We calculated the following ratios: randomized per screened, randomized per eligible, and septic shock per randomized patients. We judged the representativeness of the control populations based on the proportion of included patients per eligible patients. We regarded less than 50 % randomization per eligible patients as unclear representativeness of the study inclusion and exclusion criteria. We evaluated the proportion of patients who at baseline (1) had vasopressor infusion to target a mean arterial pressure (MAP) of 65 mmHg, (2) had lactate of at least 2 mmol/L, and (3) fulfilled both abovementioned criteria, as well as (4) whether the trial population was representative of a septic shock population according to the Sepsis-3 definition (with >50 % of patients fulfilling the Sepsis-3 definition of septic shock).

Control (C) group characteristics, interventions, and co-interventions

First, we evaluated (1) whether the trial comprised a group of usual care and/or protocolized care, (2) whether co-interventions were restricted or recommended, and (3) whether the control group was designed to represent usual care. Second, we evaluated inclusion of baseline characteristics, intervention characteristics, focus of infection, pathogens, basic co-morbidities, co-interventions (mechanical ventilation, renal replacement therapy, red blood cell transfusions, inotrope use), daily Sequential Organ Failure Assessment (SOFA), and hemodynamic data for the first 24 h after randomization [eight items: MAP, central venous pressure, urine output, lactate, norepinephrine (vasopressor) dose and duration, administered fluids, and fluid balance]. Additionally, if data for the entire 24 h were not reported, we used data for the first 6 h, and if not available, we recorded data at baseline. We calculated the number of reported items for hemodynamic data, and described fluid and vasopressor therapy. Finally, we assessed whether the achieved and presented hemodynamic values in the study control group were adherent to guidelines. If at least 50 % (4 of 8) of predefined hemodynamic items were reported and no major deviation from usual care could be detected, the study control group was judged as adherent to guidelines.

Outcomes (O)

We included only the most common mortality outcomes (hospital, 28-/30-day, and 90-day mortality) in our evaluation of both the control and the intervention groups.

Completeness of the reported data

The data completeness score was calculated based on 33 data items (Table 1) with a maximum of 36 points: 12 for patient population (P1–P12; one point each), 18 for control group (C1–C18; based on 18 items, one point each), and 6 for mortality outcomes (O1–O3; 1 point for reporting hospital, 2 points for 28-day/30-day, and 3 points for 90-day mortality or longer). Finally, we compared the data completeness scores for the two periods earlier (from 2006 to 2011) and later (from 2012 to 2015), and separately between studies focusing on hemodynamic treatment and the others. We used the Mann–Whitney test and considered $p < 0.05$ as indicating statistical significance.

Table 1 Data items and completeness score for randomized controlled trials in adult septic shock (max 36 points per 33 items)

Items		Data completeness score
Patients (P1–P12)		Max 12
P1	Number of screened patients	1
P2	Number of eligible patients	1
P3	Number of randomized patients	1
P4	Proportion (%) of randomized to screened	1
P5	Proportion (%) of randomized to eligible	1
P6	Number of septic shock patients in the control group	1
P7	Total number of patients in the control group	1
P8	Proportion (%) of septic shock patients in the control group	1
P9	Proportion (%) of control group patients with norepinephrine (NE) to target mean arterial pressure (MAP) of 65 mmHg	1
P10	Proportion (%) of control group patients with blood lactate >2 mmol/L	1
P11	Proportion(%) of control group patients with both NE and lactate >2 mmol/L	1
P12	Studies presenting proportion of patients fulfilling the Sepsis-3 septic shock criteria	1
Control group data (C1–C18)		Max 18
Baseline data (C1–C5)		
C1	Baseline characteristics—adequate	1
C2	Intervention characteristics—adequate	1
C3	Focus of infection	1
C4	Pathogens	1
C5	Comorbidities	1
Co-interventions presented (C6–C10)		
C6	Mechanical ventilation	1
C7	Renal replacement therapy	1
C8	Red blood cell transfusions	1
C9	Inotropes	1
C10	Daily Sequential Organ Failure Assessment (SOFA)	1
Hemodynamic data for the first 24 h after randomization (C11–C18)		
C11	Mean arterial pressure (MAP)	1
C12	Central venous pressure (CVP)	1
C13	Urine output	1
C14	Lactate	1
C15	Norepinephrine (vasopressor) dose	1
C16	Norepinephrine (vasopressor) duration	1
C17	Total amount of administered fluids	1
C18	Fluid balance	1
Outcome data on mortality (O1–O3)		Max 6
O1	Hospital	1
O2	28-/30-day	2
O3	90-day	3
Total		Max 36

For scoring of the data items, see Table 2 (P1–12), Table 3 (C1–C18), and Table 4 (O1–O3 and the summary score)

Results

Selection of trials

The trial selection is presented in Fig. 1. The database searches revealed a total of 542 references, of which 498 were excluded based on the abstract reviews. After review of the full text of the remaining 44, an additional 20 trials were excluded, 4 of them at the final stage because less than 75 % of patients had septic shock [7–10]. For 14 of the 542 trials (2.6 %) there was initial disagreement regarding the reason for exclusion; this was resolved after discussion in all cases. Thus, in the final analysis we included 24 original articles presenting primary data from 24 RCTs. These

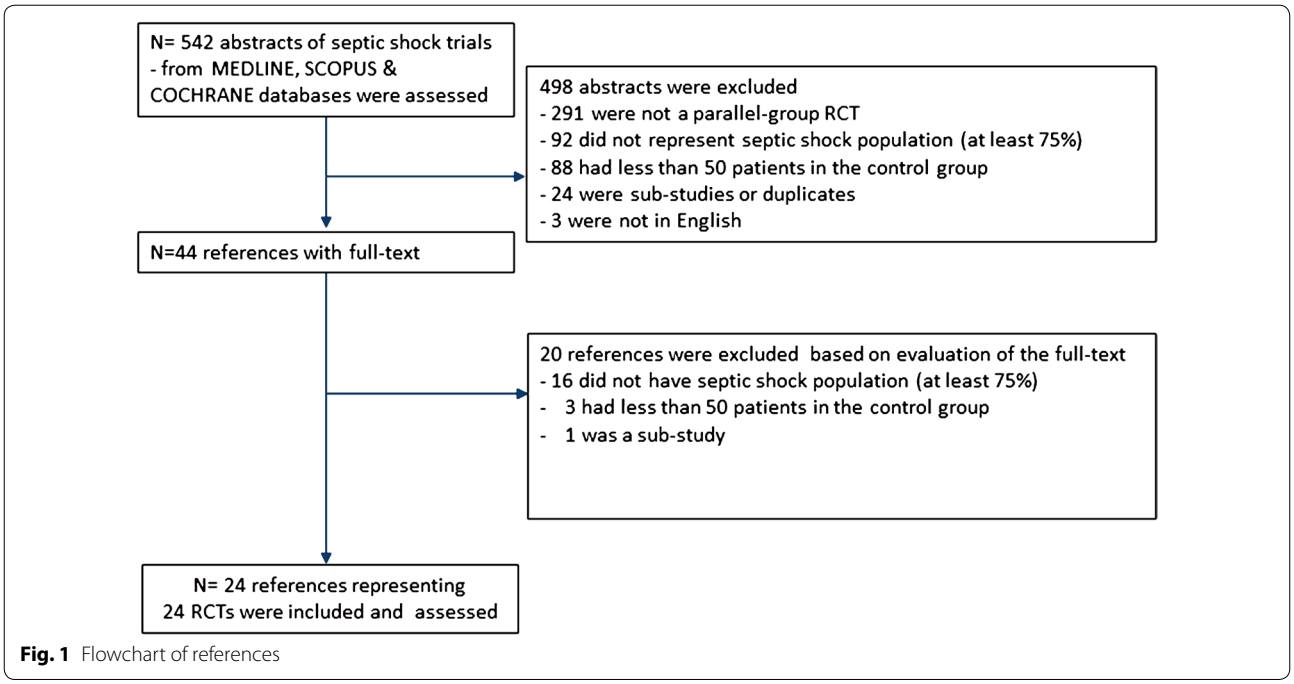

Fig. 1 Flowchart of references

trials enrolled patients between 1991 and 2014 (Table 2). Twelve trials were published between 2006 and 2011 [11–22] and 12 between 2012 and 2015 [4–6, 23–31].

Patient populations

Details on the patient populations are presented in Table 2. The 24 RCTs included had an average of 287 patients (and 71 % of eligible patients). Six studies (25 %) did not follow the CONSORT guidelines to provide number of screened patients and reasons for exclusions [11, 13, 14, 17, 18, 30]. In four (17 %) trials less than 50 % of the eligible patients were randomized [4, 6, 12, 16], with the reported ratio varying between 32 and 100 % among all RCTs. Due to exclusion of studies with less than 75 % of septic shock patients, the proportion of septic shock patients per included patients was high—98 % on average (range 75–100 %).

Fourteen (58 %) trials presented baseline data on vasopressors. In three trials less than 25 % (range 3–22 %) of the patients received vasopressor treatment at randomization [4–6]. The proportion of patients with elevated lactate values was mentioned in 14 of 24 (58 %) trials. Five studies (21 %) provided adequate data to estimate the proportion of septic shock patients fulfilling the new Sepsis-3 definition (>50 % in all of them) [25–28, 31]. The average number of reported data items was 9 (range 4–12) of 12.

Control group characteristics, interventions, and co-interventions

The completeness of baseline characteristics, co-morbidities, and co-interventions is presented in Table 3. Of the 18 predefined control group data items, a mean of 8 (range 2–17) were reported. Focus of infection (in 96 %), microbiological findings in some detail (71 %), and co-morbidities (63 %) were reported in most trials. Of 24 trials, 18 (75 %) reported the proportion of control group patients with mechanical ventilation at baseline (ranging from 5 to 97 %) (Table 3, item MV) and 9 (38 %) reported the proportion having renal replacement therapy at baseline (ranging from 0 to 35 %) (Table 3, item RRT). Administration of RBCs, day-1 SOFA score, norepinephrine dose and duration, and hemodynamic values achieved during the first 24 h (MAP, CVP, UO, lactate, fluid balance) were reported in up to one-third of the trials (range regarding each item 8–33 %). The total amount of fluids administered in the first 24 h was reported in 9 of 24 (38 %) trials. The reported hemodynamic values for the first 24 h are presented as ESM Table 1. If not available, substitute data points are marked.

In all but one trial [21], the control group was designed to include or represent usual care. Six trials included restrictions and four had recommendations for the control group treatment. We judged that half of the trials had a usual care group, and 13/24 had a group with protocolized care as their control group (one trial included both groups [4]).

None of the control group protocols or treatment goals clearly contradicted current guidelines. The representativeness of the control populations was judged as unclear in 22 of 24 RCTs, mainly due to missing hemodynamic data, and in one trial due to deviation from the protocol

Table 2 Reported data items related to selection of patient population in 24 randomized controlled trials in adult septic shock patients

RCT	Year	Enrolment	Ref. no.	P1	P2	P3	P4 (%)	P5 (%)	P6	P7	P8 (%)	P9 (%)	P10 (%)	P11 (%)	P12	Items/12
Lin	2006	2003–2004	11		241	224		93	224	224	100					6
Annane	2007	1999–2004	12	1591	839	330	21	39	330	330	100		~75			8
Werdan	2007	1991–1995	13		624	624		100	228	303	75					6
Sprung	2008	2002–2005	14		500				248	248	100					4
Stephens	2008	2003–2007	15	213	205	166	78	81	83	83	100	>75	<50			10
Russell	2008	2001–2006	16	6229	2471	802	13	32	396	396	100	87				9
Dhainaut	2009	2004–2007	17			199			99	99	100	92				5
Palizas	2009	1998–2000	18			130			64	64	100					4
Jones	2010	2007–2009	19	452	388	300	66	77	123	150	82		>37			8
Patel	2010	2003–2008	20	3454		252	7		118	118	100					6
Annane	2010	2006–2009	21	946	858	509	54	59	138	138	100					8
Huh	2011	2004–2006	22	234	156	130	56	83	65	65	100					8
PROWESS-SHOCK	2012	2008–2011	23	27,816	2017	1697	6	84	834	834	100	100				9
6S	2012	2009–2011	24	1211	855	804	66	94	337	400	84		50			9
Schortgen	2012	2008–2009	25	579	280	200	35	71	99	99	100	100	>50	>50	1	12
Annane	2013	2008–2011	26	783	458	411	52	90	203	203	100	95	~75	~75	1	12
Joannes-Boyau	2013	2005–2010	27	187	167	140	75	84	71	71	100	100	>75	>75	1	12
TRISS	2014	2011–2013	28	1224	1039	1005	82	97	496	496	100	100	>50	>50	1	12
PROCESS	2014	2008–2013	4	12,707	3843	1351	11	35	456	456	100	15	79			10
ARISE	2014	2008–2014	5	3559	2970	1600	45	54	804	804	100	22	>50			10
PROMISE	2014	2011–2014	6	6192	3777	1260	20	33	630	630	100	22	64			9
SEPSISSPAM	2014	2010–2011	29	4098	1493	798	19	53	388	388	100	96	>50			10
Lu	2015	NR	30			105			52	52	100	88	>50			6
Payen	2015	NR	31	942	262	243	26	93	113	113	100	100	>50	>50	1	12
			Mean	4023	1208	574	41	71	275	282	98	58	NA	NA	NA	8.5
			Reported in *n*/24 (%)	18 (75 %)	20 (83 %)	24 (100 %)	19 (79 %)	19 (79 %)	24 (100 %)	24 (100 %)	24 (100 %)	14 (58 %)	14 (58 %)	5 (21 %)	5 (21 %)	

Data items P1–P12 are explained in detail in Table 1

Table 3 Reported data items regarding baseline demographics, intervention, comorbidities, infection, co-interventions, and hemodynamic values during the first 24 h after randomization in 24 randomized controlled trials in adult septic shock patients

RCT	C1	MV	RRT	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17	C18	Base	Co	Hem	Items/18
Lin	1	NR	NR	1	1	1	1	1	0	1	1	0	0	0	0	0	1	1	0	0	5	3	2	10
Annane	1	95 %	9 %	1	1	1	0	0	0	0	1	0	1	0	0	1	0	0	0	0	4	1	2	7
Werdan	1	>80 %	NR	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	5	1	0	6
Sprung	1	86 %	NR	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	5
Stephens	1	81 %	NR	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	5	1	0	6
Russell	1	NR	NR	1	1	1	1	1	1	0	1	0	1	0	0	0	1	1	0	0	5	3	3	11
Dhainaut	1	NR	NR	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	2
Palizas	0	NR	NR	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	1	0	2
Jones	1	26 %	NR	0	1	1	1	1	0	1	1	0	0	1	0	0	0	0	0	0	4	3	1	8
Patel	0	NR	NR	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	2
Annane	0	86 %	22 %	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	3	1	0	4
Huh	0	80 %	35 %	1	1	1	1	1	0	0	0	0	0	0	0	0	1	1	1	0	4	1	3	8
PROWESS-SHOCK	0	82 %	13 %	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0	3	0	1	4
6S	1	61 %	0 %[a]	1	1	0	1	1	1	1	0	1	0	1	1	1	0	0	1	1	4	4	5	13
Schortgen	1	NR	8 %	1	1	1	0	0	1	0	1	0	1	0	0	0	0	0	0	0	4	2	1	7
Annane	1	92 %	28 %	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	5	2	0	7
Joannes-Boyau	1	97 %	0 %	1	1	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0	4	3	0	7
TRISS	1	71 %	11 %	0	1	0	1	1	1	1	0	0	0	0	0	1	0	0	1	1	3	3	3	9
PROCESS	1	15 %	NR	0	1	0	1	1	1	1	1	0	1	0	0	0	0	0	1	0	3	4	2	9
ARISE	1	14 %	NR	1	1	1	1	1	1	1	1	0	1	1	0	1	0	1	1	0	5	4	5	14
PROMISE	1	5 %	NR	0	1	0	0	1	1	1	1	1	1	1	0	1	0	0	1	0	2	5	4	11
SEPSISSPAM	1	74 %	NR	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	5	4	8	17
Lu	0	73 %	NR	1	1	0	0	1	0	0	0	0	1	1	0	1	0	0	1	0	2	1	4	7
Payen	1	97 %	NR	1	1	1	1	1	0	0	0	1	0	0	0	0	0	0	0	0	5	2	0	7
Reported in n/24	18	18	9	17	23	17	15	17	10	8	11	3	8	6	2	7	4	5	9	3				
%	75	75	38	71	96	71	63	71	42	33	46	13	33	25	8	29	17	21	38	13				

Data items C1–C18 are explained in detail in Table 1

MV proportion of patients with mechanical ventilation at baseline, *RRT* proportion of patients with renal replacement therapy at baseline. Sub-scoring for C1–C18: *Base* baseline demographics (C1–C5) — max 5, *Co* co-interventions after randomization (C6–C10) — max 5, *Hem* hemodynamic data items for the first 24 h (C11–C18) — max 8

[a] An exclusion criteria

Table 4 Reported mortality outcomes (O1–O3) (control group and experimental group) and total data completeness scores in 24 randomized controlled trials in adult septic shock patients

RCT	O1-Controls hospital (%)	O2-Controls 28/30 day (%)	O3-Controls 90 days (%)	Experimental Hospital (%)	Experimental 28/30 day (%)	Experimental 90 days (%)	Patients (P1–P12)	Controls (C1–C18)	Outcomes (O1–O3)	Total score/36
Lin							6	10	0	16
Annane	49	34	50	52	40	52	8	8	6	22
Werdan		37			39		6	6	2	14
Sprung	41	32		44	34		4	5	3	12
Stephens	25			27			10	6	1	17
Russell		39	50		35	44	9	11	5	25
Dhainaut		32			40		5	2	2	9
Palizas		30			28		4	2	2	8
Jones	23			17			8	8	1	17
Patel		43			50		6	2	2	10
Annane							8	4	0	12
Huh	35	34		42	37		8	8	3	19
PROWESS-SHOCK		24	33		26	34	9	4	5	18
6S		36	43		39	51	9	13	5	27
Schortgen	48			43			12	7	1	20
Annane	44	35	46	45	37	48	12	7	6	25
Joannes-Boyau			51			50	12	7	3	22
TRISS			43			45	12	9	3	24
PROCESS	19		34	21		32	10	9	4	23
ARISE	16		19	15	15	19	10	14	6	30
PROMISE			29			30	9	11	3	23
SEPSISSPAM		34	42		37	44	10	17	5	32
Lu	29			25			6	7	1	14
Payen		20	24		28	34	12	7	5	24
Mean	33	32	39	33	35	40	8.5	7.7	3.1	19.3
Reported in *n* (%)	10 (42 %)	14 (58 %)	12 (50 %)	10 (38 %)	14 (58 %)	12 (50 %)	Max 12	Max 18	Max 6	

Data items for reporting (P1–P12, C1–C18, and O1–O3) are explained in detail in Table 1

using high norepinephrine with regard to targeted MAP [29]. Thus, 2 of 24 (8 %) trials provided adequate data to confirm that their control group treatment was adherent to recommended usual care.

Control group outcomes

Each of the mortality outcomes was reported in 42–58 % of trials (Table 4). The mean sub-score for mortality outcomes was 3 (range 0–6) of 6. Three studies reported all three mortality outcomes [5, 12, 26]. The mean of 28-/30-day mortality was 32 % and ranged 2.5-fold from 16 % [5] to 43 % [20]. The mean (range) of reported 90-day mortality was 39 % (19–51 %) (12 studies). In 4 of 5 studies where >50 % fulfilled the Sepsis -3 criteria for septic shock [32], the reported 90-mortality (mean, range) was 41 % (24–51 %).

Completeness of the reported data

The average total data completeness score was 19 (range 8–32) of 36. The data completeness scores for each trial are presented in Table 4. Studies published between 2012 and 2015 (12 studies) had higher scores than studies published between 2006 and 2011 (12 studies): mean 24 (range 14–32) versus 15 (range 8–25), $p = 0.001$. The 10 studies (5 from 2006 to 2011 [11, 12, 16, 19, 20] and 5 from 2012 to 2015) [4–6, 29, 30] focusing on hemodynamic management in septic shock patients did not have higher scores than the studies not focusing on hemodynamic treatment: mean 21 (range 10–32) versus 18 (8–27), $p = 0.37$. Three studies reported at least 75 % (corresponding to 27 items) of the required data [5, 21, 29]. The trials with lower ($n = 9$) than mean mortality

rates (Table 4) reported a comparable amount of data to that of trials ($n = 13$) with a higher mortality rates (19.6 vs. 20.1/36). The five trials with >50 % septic shock patients (Table 2, P11, Sepsis-3-definition) had a mean completeness score of 23/36.

In summary, of the 33 items evaluated, 15 were reported in less than 50 % of the trials. Data were frequently missing for relevant comorbidities, co-interventions (renal replacement therapy, red blood cell transfusion, inotropes, total fluids, fluid balance), norepinephrine dose for the first 24 h (reported in 17 % of trials) and its duration, basic hemodynamic values achieved for the first 24 h (MAP reported in 33 %, urine output in 8 %, lactate in 29 % of trials) and development of organ dysfunction.

After the first evaluation, there was disagreement on 41 of 794 (5.1 %) registered data items, most frequently regarding the method of calculation of eligible patients and the adequacy of reported data for estimating the proportion of patients fulfilling the Sepsis-3 septic shock criteria. All these discrepancies were reconciled in the final evaluation.

Discussion

Main findings

In this systematic review comprising recent large RCTs in septic shock, we found that about one-half of the data considered necessary for evaluation of the control group were reported. Only one-fifth of RCTs provided data on baseline vasopressor use and on lactate levels needed to evaluate septic shock presence according to the Sepsis-3 definition. Basic hemodynamic variables for day 1 after randomization were reported in up to one-third of trials. Only 2 of 24 trials provided adequate data to confirm that their control group treatment was adherent to usual care according to the current guidelines.

Patient populations

We assessed the representativeness of the patient population based on the ratio of randomized per eligible patients. The representativeness of four trials [5, 12, 16, 29] was limited due to less than 50 % of eligible patients being randomized. In addition, three recent large studies [4–6] included septic shock patients, less than one-fifth of whom met the recent definition of septic shock [32]. Thus, most available data from previous RCTs might not be applicable to septic shock patients with the exception of two studies [26, 27] in which more than 75 % had septic shock according to the Sepsis-3 definition published in 2016 after all the RCTs.

Control group characteristics, interventions, and co-interventions

For assessment of trial results, data on baseline characteristics, intervention, infection, and co-interventions are crucial. More than one-fourth of the trials did not report microbiological findings, co-morbidities, or co-interventions (Table 3). Increased transparency regarding administered concomitant interventions would allow improved interpretation of the results of individual trials. Additionally, by carefully documenting the treatment given and analyzing the compliance–effect ratio by site, potential impact misattribution may be minimized [33]. None of the assessed trials included a clear risk of misalignment [2]. Less than half of the papers reported inotropes, and one-third reported use of RBCs. Of note, the hemodynamic data for the first 24 h were reported in the minority of studies, with only one study reporting all eight items [29]. We argue that, when septic shock is treated, the variables characterizing septic shock and hemodynamic treatment given should be reported, including duration of vasoactive treatment, both the values and timing of lactate measurements (due to its time-dependency), and duration of hyperlactatemia (not reported in any trial; see the ESM Table). In general, we found it surprising that only two trial reports provided adequate data to show their control group adherence to usual care. Thus, the reporting of future trials can improve markedly.

Completeness of the reported data

Unexpectedly, especially the data regarding basic hemodynamic variables (such as MAP, central venous pressure, urine output, blood lactate) and treatment given over time (such as total fluids, fluid balance achieved, vasopressor dose and duration) were inadequate in most cases. Notably, reporting was not affected by whether vasoactive treatment or hemodynamic management in general was studied. Similarly, the standard mortality outcome measures were reported in only half of the studies. Suggested international standardization of clinical outcomes measurement [34] when extended to septic shock trials, as recently suggested for perioperative trials [35], would provide better comparison of future trials' results.

Limitations and strengths

Our systematic review has some limitations. First, due to the heterogeneity and missing hemodynamic data, a meta-analysis of published data was not possible. Additionally, the registered data of previous trials were inadequate for post hoc analysis classifications according to the recent septic shock definition. Second, the proposed dataset has not been used or validated previously. Thus, several important aspects may deserve to be added to the dataset. Among these are documentation of adequacy and time to antimicrobial therapy, duration of septic shock before randomization and/or vasopressor therapy, adjunctive immunomodulation treatments administered,

and surrogate and patient-related important outcomes other than mortality. In general, the reporting of the abovementioned additional data was infrequent. Third, the aims of each RCT may have an effect on the decision as to which data are important and should be registered. However, we did not find any differences in the completeness of hemodynamic items in RCTs focusing on hemodynamics or those with higher mortality rates compared to other RCTs in septic shock patients. Therefore, the demonstrated variation in the registered data in the quite large RCTs analyzed in septic shock patients seems to be determined by factors other than the aims of the RCTs. Finally, the number of RCTs included was limited, and their patient populations, severity of illness, and studied treatments differed. Thus, we did not include analysis of inclusion or exclusion criteria, sample size calculations, randomization process, the effect of treatments or other important items included in the CONSORT checklist for RCTs [36]; instead, we focused on the reporting of data on patients, interventions, and mortality in control groups.

Despite its limitations, we consider this systematic review valuable in describing the variability and potential flaws in reporting data on control groups in large-scale septic shock trials. We are not aware of any previous systematic review with this purpose and patient population. A previous systematic review in septic patients [37], which included 2 of the 24 RCTs in this review, had a different objective, aiming at improving the success rate of future septic shock trials, and focused on the design and methodology of trials.

Future directions

In addition to the Sepsis-3 definition of septic shock, we need more detailed and standardized reporting of RCTs. In this paper, we propose a minimum set of items to be reported as a first step toward standardizing the reporting, and not as a complete and final dataset. A generally accepted common electronic septic shock dataset for all large-scale RCTs would improve the clinical utility of trial results, and provide better options for individual-patient meta-analysis to combine the data from separate trials more easily. Inclusion of data on time-related values, such as lactate and MAP, interventions, and changes in potential surrogate outcomes, such as daily Sequential Organ Failure Assessment (SOFA), not only in RCTs but also in cohort studies among septic shock patients, would allow use of new statistical time-dependent outcome analyses. We consider that inclusion of septic shock patients (on vasopressors and with elevated lactate) should take place as early as possible, but may not be feasible 24/7, unless an option for deferred consent is available.

Conclusions

In this systematic review including recent large RCTs among septic shock patients, we found that the reported data regarding patient populations, control group characteristics, co-interventions, administered hemodynamic treatments, and hemodynamic values achieved, varied considerably and were inadequate in many trials. However, the completeness of reported data has improved during the last decade. Few RCTs have included patients that fulfilled the current septic shock definition, and very few provide adequate data to confirm that the control group treatment represents usual care. Thus, we suggest that a standardized dataset will be created, generally agreed upon, and validated, after which it may be used for reporting in future septic shock trials.

Electronic supplementary material

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Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflicts of interest regarding this contribution. AP was the principal investigator of 6S and TRISS trials, PH co-authored the TRISS trial, and VP co-authored TRISS and ARISE trials and contributed as an investigator to EXTENDED APC, PROWESS-SHOCK, and 6S trials.

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References

1. Shankar-Hari M, Phillips GS, Levy ML et al (2016) Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315:775–787
2. Deans KJ, Minneci PC, Suffredini AF et al (2007) Randomization in clinical trials of titrated therapies: unintended consequences of using fixed treatment protocols. Crit Care Med 35:1509–1516
3. Takala J (2009) Better conduct of clinical trials: the control group in critical care trials. Crit Care Med 37(1 Suppl):S80–S90
4. Investigators PROCESS, Yealy DM, Kellum JA et al (2014) A randomized trial of protocol-based care for early septic shock. N Engl J Med 370:1683–1693
5. ARISE Investigators, ANZICS Clinical Trials Group, Peake S et al (2014) Goal-directed resuscitation for patients with early septic shock. N Engl J Med 371:1496–1506

6. Mouncey PR, Osborn T, Power GS, Trial Investigators PROMISE et al (2015) Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 372:1301–1311
7. Caironi P, Tognoni G, Masson S, Albios Study Investigators et al (2014) Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 370:1412–1421
8. De Backer D, Biston P, Devriendt J et al (2010) Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 362:779–789
9. Brunkhorst FM, Oppert M, Marx G et al (2012) Effect of empirical treatment with moxifloxacin and meropenem vs. meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial. JAMA 307:2390–2399
10. Vincent JL, Marshall JC, Dellinger RP et al (2015) Talactoferrin in severe sepsis: results from the phase II/III Oral tAlactoferrin in Severe sepsIS Trial. Crit Care Med 43:1832–1838
11. Lin SM, Huang CD, Lin HC, Liu CY, Wang CH, Kuo HP (2006) A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial. Shock 26:551–557
12. Annane D, Vignon P, Renault A et al (2007) Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet 370:676–684
13. Werdan K, Pilz G, Bujdoso O et al (2007) Score-based immunoglobulin G therapy of patients with sepsis: the SBITS study. Crit Care Med 35:2693–2701
14. Sprung CL, Annane D, Keh D et al (2008) Hydrocortisone therapy for patients with septic shock. N Engl J Med 358:111–124
15. Stephens DP, Thomas JH, Higgins A et al (2008) Randomized, double-blind, placebo-controlled trial of granulocyte colony-stimulating factor in patients with septic shock. Crit Care Med 36:448–454
16. Russell JA, Walley KR, Singer J et al (2008) Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 358:877–887
17. Dhainaut JF, Antonelli M, Wright P et al (2009) Extended drotrecogin alfa (activated) treatment in patients with prolonged septic shock. Intensive Care Med 35:1187–1195
18. Palizas F, Dubin A, Regueira T et al (2009) Gastric tonometry versus cardiac index as resuscitation goals in septic shock: a multicenter, randomized, controlled trial. Crit Care 13:R44
19. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA (2010) Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA 303:739–746
20. Patel GP, Grahe JS, Sperry M et al (2010) Efficacy and safety of dopamine versus norepinephrine in the management of septic shock. Shock 33:375–380
21. Annane D, Cariou A, Maxime V et al (2010) Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. JAMA 303:341–348
22. Huh JW, Choi HS, Lim CM et al (2011) Low-dose hydrocortisone treatment for patients with septic shock: a pilot study comparing 3 days with 7 days. Respirology 16:1088–1095
23. Ranieri VM, Thompson BT, Barie BS, PROWESS-SHOCK study group et al (2012) Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med 366:2055–2064
24. Perner A, Haase N, Guttormsen AB, Scandinavian Critical Care Trials Group (2012) Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 367:124–134
25. Schortgen F, Clabault K, Katsahian S et al (2012) Fever control using external cooling in septic shock: a randomized controlled trial. Am J Respir Crit Care Med 185:1088–1095
26. Annane D, Timsit JF, Megarbane B et al (2013) Recombinant human activated protein C for adults with septic shock: a randomized controlled trial. Am J Respir Crit Care Med 187:1091–1097
27. Joannes-Boyau O, Honore PM, Perez P et al (2013) High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. Intensive Care Med 39:1535–1546
28. Holst LB, Haase N, Wetterslev J, TRISS trial group, Scandinavian Critical Care Trials Group et al (2014) Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 371:1381–1391
29. Asfar P, Meziani F, Hamel JF, Investigators Sepsispam et al (2014) High versus low blood-pressure target in patients with septic shock. N Engl J Med 370:1583–1593
30. Lu NF, Zheng RQ, Lin H, Shao J, Yu JQ, Yang DG (2015) Improved sepsis bundles in the treatment of septic shock: a prospective clinical study. Am J Emerg Med 33:1045–1049
31. Payen DM, Guilhot J, Launey Y et al (2015) Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial. Intensive Care Med 41:975–984
32. Singer M, Deutschman CS, Seymour CW et al (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315:801–810
33. Kavanagh BP, Nurok M (2015) Standardized intensive care—protocol misalignment and impact misattribution. Am J Respir Crit Care Med 193:17–22
34. Porter ME, Larsson S, Lee TH (2016) Standardizing patient outcomes measurement. N Engl J Med 374:504–506
35. Myles PS, Grocott MP, Boney O, Moonesinghe SR, COMPAC-StEP Group (2016) Standardizing end points in perioperative trials: towards a core and extended outcome set. Br J Anaesth 116:586–589
36. Schulz KF, Altman DG, Moher D, For the CONSORT group (2010) CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. J Clin Epidem 63:834–840
37. Annane D (2009) Improving clinical trials in the critically ill: unique challenge—sepsis. Crit Care Med 37:S117–S128