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Low-dose corticosteroids for adult patients with septic shock: a systematic review with meta-analysis and trial sequential analysis

Sofie Louise Rygård[1], Ethan Butler[2], Anders Granholm[1], Morten Hylander Møller[1,3], Jeremy Cohen[4,5], Simon Finfer[6,9], Anders Perner[1,3], John Myburgh[2,6,7], Balasubramanian Venkatesh[5,8] and Anthony Delaney[9,10*]

Abstract

Purpose: To assess the effect of low dose corticosteroids on outcomes in adults with septic shock.

Methods: We systematically reviewed randomised clinical trials (RCTs) comparing low-dose corticosteroids to placebo in adults with septic shock. Trial selection, data abstraction and risk of bias assessment were performed in duplicate. The primary outcome was short-term mortality. Secondary and tertiary outcomes included longer-term mortality, adverse events, quality of life, and duration of shock, mechanical ventilation and ICU stay.

Results: There were 22 RCTs, including 7297 participants, providing data on short-term mortality. In two low risk of bias trials, the relative risk (RR) of short-term mortality with corticosteroid versus placebo was 0.98 [95% confidence interval (CI) 0.89–1.08, $p = 0.71$]. Sensitivity analysis including all trials was similar (RR 0.96; 95% CI 0.91–1.02, $p = 0.21$) as was analysis of longer-term mortality (RR 0.96; 95% CI 0.90–1.02, $p = 0.18$). In low risk of bias trials, the risk of experiencing any adverse event was higher with corticosteroids; however, there was substantial heterogeneity (RR 1.66; 95% CI 1.03–2.70, $p = 0.04$, $I^2 = 78\%$). No trials reported quality of life outcomes. Duration of shock [mean difference (MD) −1.52 days; 95% CI −1.71 to −1.32, $p < 0.0001$], duration of mechanical ventilation (MD −1.38 days; 95% CI −1.96 to −0.80, $p < 0.0001$), and ICU stay (MD −0.75 days; 95% CI −1.34 to −0.17, $p = 0.01$) were shorter with corticosteroids versus placebo.

Conclusions: In adults with septic shock treated with low dose corticosteroids, short- and longer-term mortality are unaffected, adverse events increase, but duration of shock, mechanical ventilation and ICU stay are reduced.

PROSPERO registration no. CRD42017084037.

Keywords: Meta-analysis, Corticosteroids, Sepsis, Septic shock

Background

Corticosteroids, acting to both modulate the immune response to infection [1] and to enhance the cardiovascular response to exogenous catecholamines [2], have been administered to patients with sepsis since the 1950s [3]. Early randomised clinical trials (RCTs), using high-dose corticosteroids in patients with septic shock, demonstrated no beneficial treatment effect, with a suggestion that treatment may even increase mortality [4]. As a result, treatment of septic shock with high-dose corticosteroids declined. Interest in the use of lower-dose corticosteroids, often referred to as "stress-dose" steroids,

*Correspondence: adelaney@med.usyd.edu.au
[9] Malcolm Fisher Department of Intensive Care Medicine, Royal North Shore Hospital, St. Leonards, NSW 2065, Australia
Full author information is available at the end of the article

was revived in the late 1990s when two RCTs reported significant improvements in haemodynamic parameters [5, 6] and suggested improved mortality [6].

Subsequent RCTs have reported divergent results [7, 8], and, to date, systematic reviews [9, 10] have not resolved whether use of corticosteroids in patients with septic shock improves outcomes. The ongoing debate has been fuelled by the recent publication of two large RCTs [11, 12] without clear conclusions. Therefore, to provide an updated summary of the evidence, we conducted a systematic review and meta-analysis with trial sequential analysis to assess the effect of low-dose corticosteroids compared to placebo or usual care on patient-centred outcomes, including mortality, adverse events and quality-of-life in adult patients with septic shock.

Methods

The systematic review was conducted according to a pre-specified protocol registered at the international prospective register of systematic reviews (PROSPERO registration CRD42017084037). The full details of the protocol are available in the Electronic Supplementary Material (ESM).

Search and eligibility criteria

We searched for RCTs of adult patients with septic shock, where a corticosteroid in a dose of less than 500 mg per day of hydrocortisone (or equivalent) was compared to placebo, no corticosteroid or any other control intervention, and at least one of the outcomes outlined below were reported. Studies in which the population was not limited to patients with septic shock, but in which data from an identifiable sub-group of patients with septic shock were included, when authors of the studies could provide data on the group of patients with septic shock, were eligible for inclusion. We excluded studies in which both experimental groups received corticosteroids. We applied no language restriction and we included all reports including studies only reported in abstract form.

We performed a search of electronic databases, Medline (via the PUBMED interface), EMBASE and The Cochrane Central Registry of Controlled Trials (via the Ovid interface). All searches were conducted from inception through to March 3, 2018. We used search terms for septic shock, sepsis and septicaemia combined with terms for corticosteroids and sensitive filters specific to each database to identify randomised clinical trials [13–15]. We also performed an electronic search of conference abstracts and clinical trial registries. The full details of the electronic search strategy are available in the ESM. We also conducted a manual search of reference lists of relevant primary studies and previous review articles, and contacted experts in the field.

Take home message

In adults with septic shock, treatment with corticosteroids does not affect short- or longer-term mortality, adverse events are increased but duration of shock, mechanical ventilation and ICU admission are reduced.

Study selection

Two investigators independently screened articles for inclusion based on study title and abstract. The full text of articles deemed relevant during preliminary screening were retrieved and reviewed for inclusion by two reviewers. Disagreement during the review process was resolved by discussion with a third reviewer and by consensus.

Data extraction

Two investigators independently extracted information from each included trial. We extracted all available data as outlined in the protocol, including characteristics of the included studies, details of the population enrolled, details of the intervention including type of corticosteroid, dose and regimen, mode of discontinuation and whether the comparison group received placebo or usual care. Data specified in the protocol that were not available in trial reports were requested from the corresponding authors of included studies.

Risk of bias assessment

Two investigators, with no affiliation with any of the included trials, independently assessed risk of bias of the included trials. Disagreements were resolved by discussion with a third reviewer and by consensus. Clarifications regarding additional details of the methods of included studies required to assess risk of bias were sought from corresponding authors where these were not clear in the available reports. We used the Cochrane risk of bias tool [16], along with specific criteria developed for the purpose of this review, to ensure consistency across trials (details supplied in ESM). We adjudicated risk of bias across all predefined outcome measures, and overall risk of bias was adjudicated low only if all domains were assessed as low risk of bias.

Outcomes

The primary outcome was short-term mortality (death within 90 days of randomisation) in trials adjudicated as low risk of bias in all domains of the Cochrane risk of bias tool [16]. Secondary outcomes were longer-term mortality (death occurring within and beyond 90 days of randomisation), patient-reported health-related quality of life at final follow-up and the proportion of patients experiencing at least one adverse event. Tertiary outcomes

were time to resolution of shock, duration of mechanical ventilation, duration of ICU and hospital length of stay, and the incidence of specific adverse events; secondary infection, gastrointestinal bleeding, delirium, hyperglycaemia and hypernatraemia, each recorded as defined in the included trials.

Subgroup analyses

We planned to assess nine subgroups for short-term mortality based upon: adjudication of risk of bias, dose of corticosteroid, bolus or infusion dosing, time allowed from eligibility to randomisation, ICU population (medical, surgical or mixed), pulmonary versus non-pulmonary source of sepsis, type of corticosteroid, duration of intervention and mode of treatment cessation.

Data synthesis

We evaluated statistical heterogeneity by inspecting forest plots and quantitatively by using diversity (D^2) [17] and inconsistency (I^2) [18] statistics. Furthermore, clinical heterogeneity was evaluated by performing subgroup analyses for the primary outcome. For subgroup analyses, we used χ^2 tests to investigate heterogeneity (test-of-interaction or test for subgroup differences), and $p < 0.1$ was considered statistically significant. We assessed reporting bias for outcomes in which 10 or more studies provided data, by funnel plot inspection and the Harbord test [19] for dichotomous outcomes and the regression asymmetry test [20] and adjusted rank correlation [21] for continuous outcomes.

For dichotomous outcomes, we calculated relative risks (RRs) with 95% confidence intervals (CIs). For continuous outcomes, we calculated mean differences (MDs) with 95% CIs.

The primary analysis was conducted using a fixed effect model [22] and included only trials adjudicated as overall low risk of bias. We conducted a sensitivity analysis by pooling data with a random effects model, and by pooling data from all trials regardless of adjudication of risk of bias. We assessed the potential effect of missing outcome data by performing a best and worst case analysis [23], assuming in the best–worst case scenario that all patients lost to outcome assessment (follow-up) in the intervention group had a beneficial outcome, whereas all patients lost to outcome assessment in the control group had a detrimental outcome, and in the worst–best case scenario that all patients lost to outcome assessment in the intervention group had a detrimental outcome, whereas all patients lost to outcome assessment in the control group had a beneficial outcome.

Secondary and tertiary outcomes were pooled using a fixed effect model using pooled RRs for dichotomous outcomes and mean differences for continuous outcomes that were available as means with standard deviations. For continuous measures reported in other metrics, not amenable to statistical pooling, we reported the results from each individual trial.

We assessed statistical significance for the primary outcome at $p < 0.05$. Given the multiple outcomes reported we assessed the statistical significance of results of the secondary outcomes at $p < 0.025$ and tertiary outcomes at $p < 0.01$.

Trial sequential analysis

We conducted trial sequential analysis (TSA) in order to assess the risk of random errors [24]. We used a random effects model for all overall low risk of bias trials included in the primary analyses [24]. We used a family-wise error rate, the probability of making one or more false positive assertions when performing multiple hypothesis tests, of 5% [23] with a statistical significance level of 5% for the primary outcome; 2.5% for the three secondary outcomes, and 1% for the tertiary outcomes. We used a beta of 20% and a diversity (D^2) [17] as suggested by the included trials [23]. For dichotomous outcomes, a prespecified relative risk of 15% was used. We present TSA-adjusted CIs for estimates where these were calculated.

Analyses were conducted using Review Manager v.5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), Trial Sequential Analysis v.0.9.5.10 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, available from www.ctu.dk/tsa) and R v.3.4.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) with the meta package v.4.9-0.

Grading the quality of evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [25] to assess the overall quality of evidence for each outcome measure and present the results in the 'summary of findings' table. The quality of evidence and our confidence in the effect-estimates were evaluated on the basis of study design, study quality, precision, consistency, directness and the risk of reporting bias. Consequently, the overall quality of evidence is rated "high", "moderate", "low" or "very low" for each outcome.

Results

The search for studies was completed on March 3, 2018. Figure 1 shows the results of the search and the reasons for exclusion of studies. A total of 15,588 records were retrieved with 23 studies [5–8, 11, 12, 26–42], including a total of 7688 trial participants, included in the systematic review. One study did not report any outcomes of interest and was not included in the quantitative synthesis

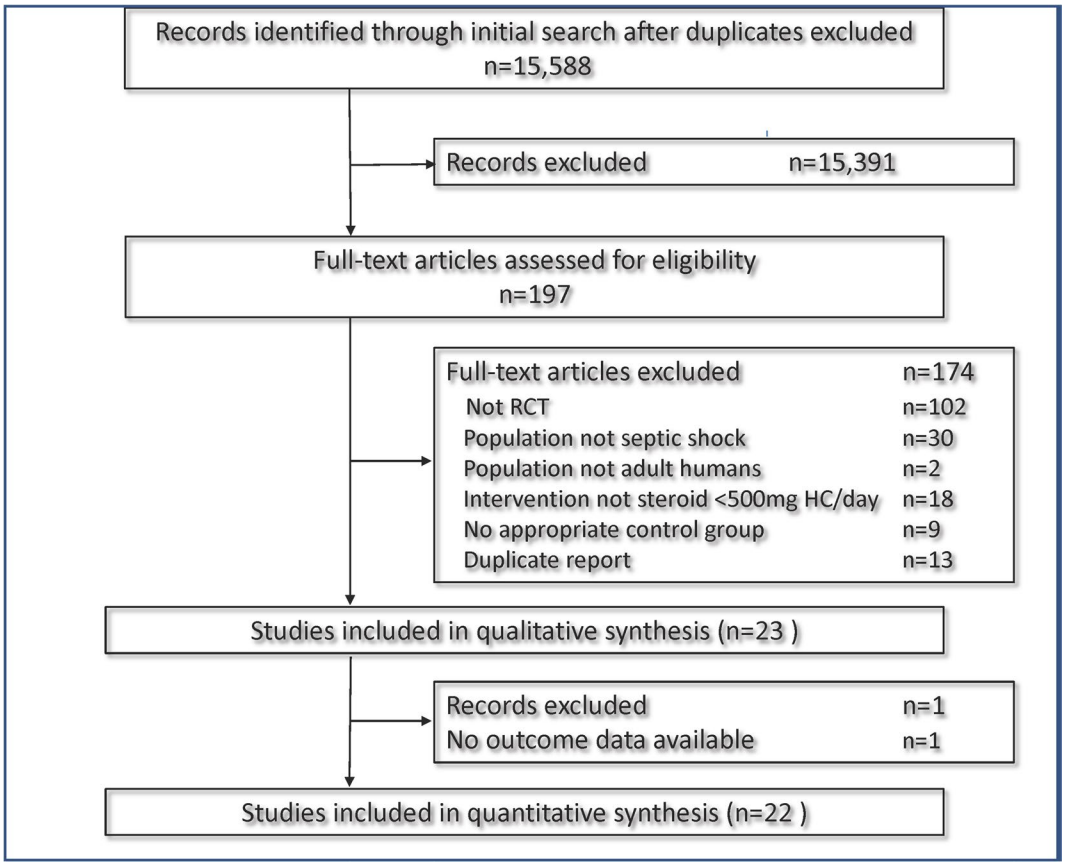

Fig. 1 Results of search and reasons for exclusion of studies. *RCT* randomised clinical trial, *HC* equivalent dose of hydrocortisone

[31]. Additional data and clarifications were obtained from authors of 15 studies [5–8, 12, 26, 27, 29, 32, 33, 37, 38, 41–43]. Data were obtained from two studies [41, 42], in which the primary population was not specifically septic shock but in which a group of patients with septic shock was identifiable at baseline. The characteristics of the included studies are shown in Table 1 and ESM Table 1. There were two studies adjudicated as low risk of bias in all domains [12, 33], with all other studies rated as unclear or high risk of bias in at least one domain of potential bias. The summary of the risk of bias assessments is shown in Fig. 2 and ESM Fig. 1, with the full details of the risk of bias assessments presented in ESM Table 2.

Primary outcome

There was no definitive evidence of reporting bias evident on inspection of the funnel plot (ESM Fig. 2) or via the Harbord test ($p=0.39$). There were 22 studies including a total of 7297 participants with data available regarding short-term (≤ 90 days) mortality [5–8, 11, 12, 26–42]. The pooled estimate of the RR for short-term mortality for corticosteroids compared to placebo in the trials adjudicated as low risk of bias was 0.98 (95% CI 0.89–1.08, $p=0.71$, $I^2=0\%$). The TSA for the primary outcome (shown in ESM Figs. 3, 3a), showed a required information size was exceeded, indicating sufficient events had been accrued in the current trials to exclude a 15% RR (from a baseline event rate of 28.9%), and the TSA adjusted 95% CI remained the same (0.89–1.08). The estimate of the RR for short-term mortality in trials not adjudicated as low risk of bias was similar (RR 0.95, 95% CI 0.88–1.02, $p=0.15$, $I^2=39\%$) to that from the trials estimated as low risk of bias (test for subgroup differences $p=0.58$), as shown in Fig. 3. The results of the sensitivity analyses and subgroup analyses were largely consistent with the primary analysis, with subgroups defined by mode of cessation of the intervention and by type of corticosteroid used showing potentially differential treatment effects, as shown in Table 2. Data were not available to assess the effect of pulmonary versus non-pulmonary source of sepsis.

Table 1 Characteristics of the included trials

Author	Year	Centres	Country	*N*	Severity of illness	Corticosteroid	Dose of corticosteroid	Duration	Control	Primary outcome
Cooperative Study Group [30]	1963	5	USA	194	NR	Hydrocortisone	100 mg q8 h ivi day 1 250 mg q8 h ivi day 2 weaning to 50 mg po day 6	6 days	Placebo	Mortality
Bollaert [6]	1998	2	France	41	SAPS[a] CS 14 ± 3 Control 14 ± 3	Hydrocortisone	100 mg q8 h ivi	≥ 5 days	Placebo	Shock reversal
Briegel [5]	1999	1	Germany	40	APACHE II[b] CS 26 ± 1 Control 27 ± 1	Hydrocortisone	100 mg bolus, 0.18 mg/kg/h then 0.08 mg/kg/h	Duration of vasopressor therapy	Placebo	Time to shock reversal
Chawla [28]	1999	1	USA	44	NR	Hydrocortisone	100 mg q8 h ivi	7 days	Placebo	Duration of vasopressor use
Annane [7]	2002	19	France	300	SAPS II[a] CS 60 ± 19 Control 57 ± 19	Hydrocortisone plus fludrocortisone	HC 50 mg q6 h ivi FC 50 µg daily NGT	7 days	Placebo	28-day survival distribution in non-responders
Oppert [39]	2005	1	Germany	48	APACHE II[c] CS 25 (19–30) Control 25.5 (19.8–29)	Hydrocortisone	50 mg bolus followed by 0.18 mg/kg/h	Until resolution of shock	Placebo	Time to cessation of vasopressor support
Tandan [40]	2005	1	India	28	APACHE II[a] 22 ± 8	"low-dose steroids"	NR	NR	Placebo	28-day survival
Cicarelli [29]	2007	1	Brazil	29	APACHE II[a] CS 20 ± 5 Control 19 ± 4	Dexamethasone	0.2 mg/kg	4.5 days	Placebo	Mortality
Aboab [26]	2008	1	France	23	SAPS II[1a] CS 43 ± 24 Control 48 ± 19	Hydrocortisone plus fludorcortisone	HC 50 mg q6 h ivi FC 50 mg daily NGT	7 days	Placebo	Cardiovascular variability
Kurugundla [35]	2008	1	USA	21	APACHE II[a] CS 24.5 (13–35) Control 26.1 (19–33)	"stress-dose steroids"	NR	NR	Placebo	Mortality and ICU length of stay
Sprung [8]	2008	52	Europe	500	SAPS II[a] CS 49.5 ± 17.8 Control 48.6 ± 16.7	Hydrocortisone	50 mg q6 h ivi for 5 days 50 mg q12 h ivi for 3 days 50 mg daily ivi for 3 days	11 days	Placebo	Mortality at 28 days in corticotropin non-responders
Hu [46]	2009	1	China	77	APACHE II[a] CS 19.5 ± 11.6 Control 18.8 ± 10.5	Hydrocortisone	50 mg q6 h ivi for 7 days 50 mg q8 h ivi for 3 days 50 mg q12 h ivi for 2 days 50 mg daily ivi for 2 days	14 days	Usual care	Mortality
Meduri [37]	2009	1	USA	80	APACHE III[a] CS 74.7 ± 24.7 Control 65.7 ± 11.4	Hydrocortisone	300 mg ivi stat 240 mg/day infusion	7 days	Placebo	Resolution of MODS and shock by day 7
Arabi [27]	2010	1	Saudi Arabia	75	APACHE II[1] CS 30 ± 7.4 Control 29.3 ± 8.0	Hydrocortisone	50 mg q6 h ivi	Shock resolution	Placebo	Mortality at 28 days

Table 1 continued

Author	Year	Centres	Country	*N*	Severity of illness	Corticosteroid	Dose of corticosteroid	Duration	Control	Primary outcome
Deng [31]	2011	1	China	38	NR	Methylprednisolone	40 mg ivi daily	6 days	Usual care	Blood coagulation
Gordon [32]	2014	4	England	63	APACHE II[c] CS 19 (14–22) Control 20 (17–25)	Hydrocortisone	50 mg ivi q6 h for 5 days 50 mg ivi q12 h for 3 days 50 mg ivi daily for 3 days	11 days	Placebo	Vasopressin concentrations
Mirea [38]	2014	1	Romania	181	APACHE II[a] CS (Bolus) 21.5 ± 9.9 CS (infusion) 24 ± 7.8 Control 22.5 ± 9.7	Hydrocortisone	A. 50 mg ivi q6 h bolus B. 200 mg ivi infusion	7 days	Usual care	Mean serum sodium values over 7 days
Torres [42]	2015	3	Spain	120	NR	Methylprednisolone	0.5 mg/kg/q12 h	5 days	Placebo	Rate of treatment failure for severe CAP
Gordon [33]	2016	18	United Kingdom	421	APACHE II[c] 24 (19–30)[d]	Hydrocortisone	50 mg ivi q6 h for 5 days 50 mg ivi q12 h for 3 days 50 mg ivi daily for 3 days	11 days	Placebo	Kidney failure free days to day 28
Tongyoo [41]	2016	1	Thailand	206	APACHE II[a] CS 21.7 ± 5.7 Control 21.9 ± 5.7	Hydrocortisone	50 mg ivi q6 h	7 days	Placebo	28 day mortality
Lv [36]	2017	1	China	120	APACHE II[c] CS 25.5 ± 9.5 Control 21.3 ± 6.9	Hydrocortisone	200 mg ivi infusion	6 days then tapered	Placebo	28 day mortality
Venkatesh [12]	2018	69	Australia, New Zealand, UK, Saudi Arabia, Denmark	3800	APACHE II[c] CS 24 (19–29) Control 23 (18–29)	Hydrocortisone	200 mg ivi infusion	7 days	Placebo	90 day mortality
Annane [11]	2018	34	France	1241	SAPS II[a] CS 56 ± 19 Control 56 ± 19	Hydrocortisone plus fludrocortisone	HC 50 mg ivi q6 h FC 50 mg NGT daily	7 days	Placebo	90 day mortality

N number of participants randomised, *USA* United States of America, *ivi* intravenous, *po* per oral, *NR* not reported, *SD* standard deviation, *SEM* standard error of the mean, *SAPS* simplified acute physiology score, *CS* corticosteroid, *HC* hydrocortisone, *FC* fludrocortisone, *NGT* nasogstric tube, *MODS* multiple organ dysfunction syndrome, *UK* United Kingdom, *CAP* community acquired pneumonia

[a] Mean ± standard deviation

[b] Mean ± standard error of the mean

[c] Median (interquartile range)

[d] Results from overall trial population, as results for hydrocortisone/placebo not available separately

Secondary outcomes

For longer-term mortality, there were a total of 5667 trial participants from three trials that reported mortality at 12 months [5–7] and two trials that reported mortality at 180 days [11, 44]. The pooled RR for longer-term mortality for corticosteroids compared to placebo (ESM Fig. 4) was 0.96 (95% CI 0.90–1.02, $p=0.18$, $I^2=0\%$). The proportion of trial participants reporting any adverse event was available in 10 trials [5–7, 11, 12, 27, 29, 32, 33, 37]. The fixed effect estimated RR of reporting an adverse event for trial participants randomised to receive corticosteroids compared to control in trials adjudicated as low risk of bias was 1.66 (1.03–2.70, $p=0.04$, $I^2=78\%$). The TSA analysis (ESM Fig. 5a), included too few events to calculate TSA-adjusted CI. When the pooled RR of reporting an adverse event was estimated from all trials (ESM Fig. 5), the estimated RR was 0.98 (95% CI 0.90–1.08, $p=0.73$, $I^2=54\%$, test for subgroup difference $p=0.02$). The results of the sensitivity analyses for the secondary outcomes are shown in ESM Table 3. No trial included in this review reported health-related quality of life outcomes.

Tertiary outcomes

Tertiary outcomes were assessed on all trials regardless of adjudication of risk of bias. The time to resolution of shock was shorter in trial participants assigned to receive corticosteroids, with data available from 7 trials in a metric suitable for pooling [12, 29, 34, 36–38, 41]; the results of this pooled analysis are shown in Table 3 and ESM Fig. 6. There were an additional 9 trials [5–8, 11, 28, 32, 33, 39] that reported time to resolution of shock using metrics that were not amenable to statistical pooling; all but one [33] showed a shorter duration of shock in the group assigned corticosteroids (ESM Table 4).

Based on 5 trials [5, 12, 29, 37, 41] with data available in a format that allowed pooling, duration of mechanical ventilation was shorter in patients assigned to steroid treatment (Table 3; ESM Fig. 7). An additional 4 trials [11, 27, 32, 33] reported data in metrics that were not amenable to statistical pooling (ESM Table 4); in these the duration of ventilation was similar in the two groups.

In 13 trials [6–8, 12, 27, 28, 33, 34, 36–38, 42] that reported duration of ICU admission in a manner that allowed pooling of data, duration was shorter in patients assigned steroids (Table 3; ESM Fig. 8). There was no evidence of reporting bias on inspection of the funnel plot (ESM Fig. 9) or the regression asymmetry test ($p=0.24$) or the adjusted rank correlation test ($p=0.33$). An additional 3 trials [11, 32, 35] reported data in metrics that did not allow pooling, two reported a shorter duration

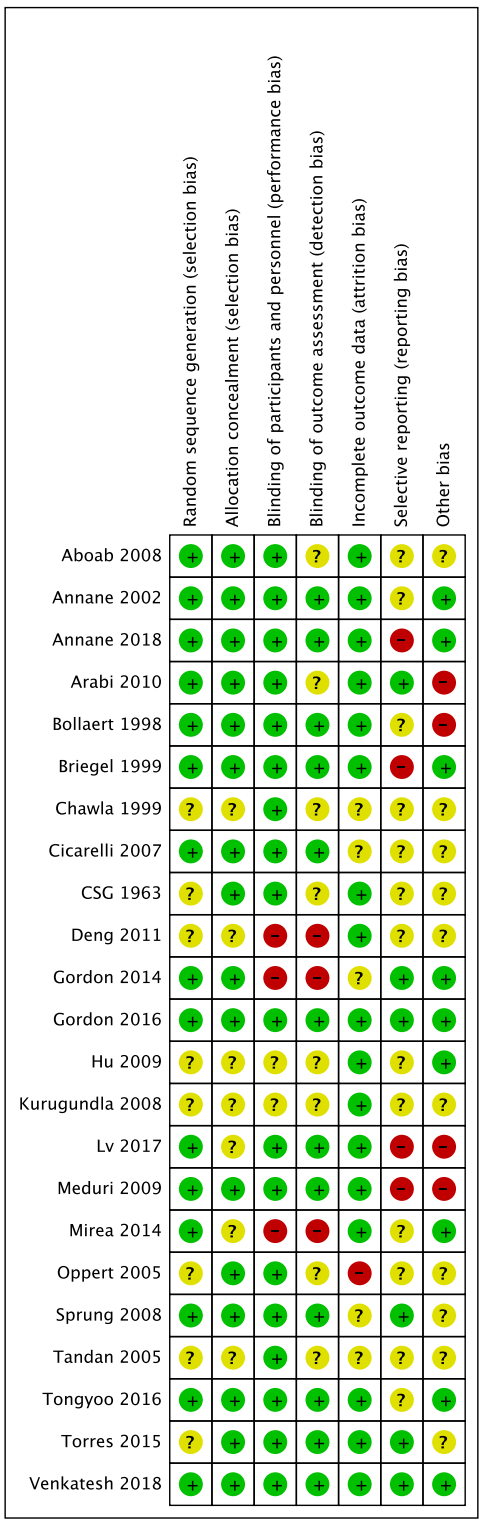

Fig. 2 Summary of risk of bias assessments for all randomised clinical trials of corticosteroids compared to placebo or usual care in patients with septic shock

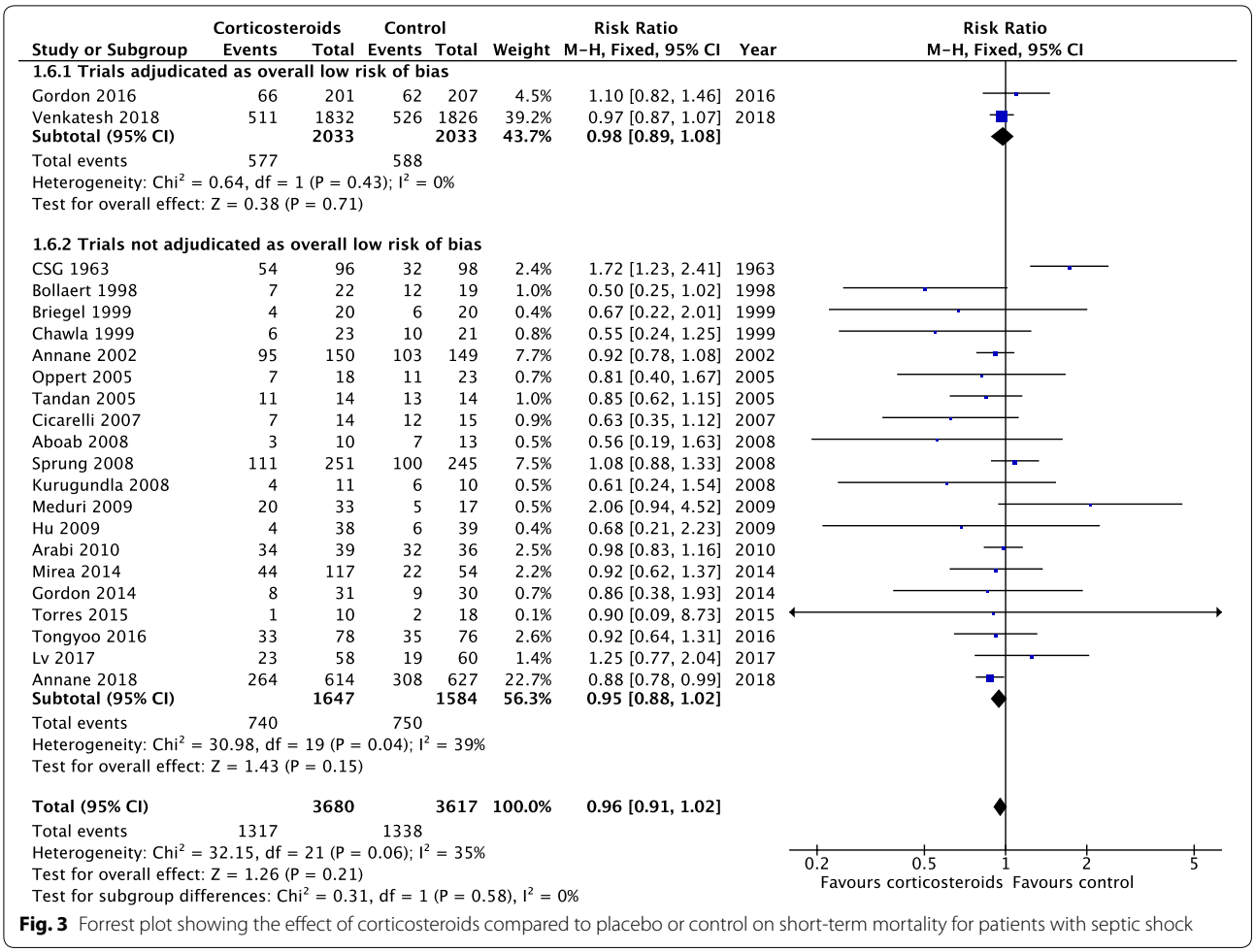

Fig. 3 Forrest plot showing the effect of corticosteroids compared to placebo or control on short-term mortality for patients with septic shock

of ICU admission in the corticosteroid group (ESM Table 4).

In 11 trials that reported data that could be pooled [6–8, 12, 26–28, 33, 36–38, 42] there was no significant difference in duration of hospital admission (Table 3; ESM Fig. 10). There was no evidence of reporting bias on inspection of the funnel plot (ESM Fig. 11) or via the regression asymmetry test ($p=0.19$) or the adjusted rank correlation test ($p=0.93$). There were two additional trials that reported duration of hospital admission in metrics not amenable to statistical pooling [11, 31], neither showed a significant difference between the two groups.

The effect of corticosteroids on the incidence of individual adverse events, as defined in the included studies, is reported in Table 3 and ESM Figs. 12, 14–17. Corticosteroid treatment was associated with increased reporting of hypernatraemia and hyperglycaemia but not secondary infection (Table 3). There was no evidence of reporting bias for the incidence of secondary infection on inspection of the funnel plot (ESM Fig. 13) or from the Harbord test, 0.99.

Summary of findings and recommendations

The quality of evidence for all outcomes (summary of findings) is presented in Table 4.

Discussion

The results of this systematic review provide an evidence summary to inform clinicians regarding decisions to use corticosteroids in adult patients with septic shock. We found that assignment to treatment with corticosteroids had no effect on either short-term or longer-term mortality. To date, health-related quality of life has not been reported by any trial. Adverse events were increased in patients assigned to corticosteroids. The time to resolution of shock was shorter, as was duration of mechanical ventilation, and ICU admission. The use of corticosteroids was not associated with increased incidence of secondary infection.

This systematic review and meta-analysis has a number of methodological strengths. The research question was focussed to include a specific clinically relevant population and a specific intervention. The study was conducted

Table 2 Sensitivity and subgroup analysis of the effect of corticosteroids compared to placebo or usual care on short-term mortality in patients with septic shock

	Number of trials	Number of participants	Relative risk	95% CI	*p*	I^2 (%)	Test of subgroup difference
Primary analysis							
Low risk of bias trials, fixed effect model	2	4066	0.98	0.89–1.08	0.71	0	NA
Sensitivity analyses							
Random effects model	2	4066	0.98	0.89–1.08	0.72	0	NA
All trials regardless of risk of bias assessment	22	7297	0.96	0.91–1.02	0.21	35	NA
Best case scenario[a]	2	4221	0.87	0.79–0.95	0.002	5	NA
Worst case scenario[a]	2	4221	1.11	1.01–1.22	0.03	0	NA
Subgroup analyses for short term mortality							
Risk of bias							
Trials adjudicated low risk of bias	2	4066	0.98	0.89–1.08	0.71	0	0.58
Trials not adjudicated low risk of bias	20	3231	0.95	0.88–1.02	0.15	39	
Dose of corticosteroid[b,c]							
< 200 mg/day	9	5218	0.99	0.92–1.07	0.84	0	0.12
201–300 mg/day	5	1642	0.89	0.81–0.98	0.02	41	
301–500 mg/day	6	388	1.11	0.87–1.42	0.41	69	
Bolus or infusion[c]							
Bolus	15	3255	0.95	0.88–1.02	0.19	44	0.70
Infusion	3	3862	0.98	0.89–1.08	0.65	0	
Bolus and infusion	3	131	1.14	0.72–1.83	0.57	49	
Timing of randomisation[c,d]							
≤ 24 h	11	6368	0.96	0.90–1.03	0.27	43	0.56
> 24 h	6	731	1.01	0.87–1.17	0.87	53	
ICU population[c]							
Medical	4	388	0.99	0.83–1.20	0.95	0	0.33
Surgical	1	29	0.63	0.35–1.12	0.11	NA	
Mixed medical/surgical	13	6593	0.95	0.89–1.01	0.12	9	
Type of corticosteroid[c]							
Hydrocortisone	16	5649	1.01	0.93–1.08	0.87	38	0.09
Hydrocortisone plus fludrocortisone	3	1563	0.88	0.80–0.97	0.01	0	
Dexamethasone	1	29	0.63	0.35–1.12	0.11	NA	
Methylprednisolone	1	28	0.90	0.09–8.73	0.93	NA	
Duration of intervention[c]							
Fixed duration	17	7092	0.97	0.91–1.03	0.30	47	0.58
Variable[e]	3	156	0.91	0.73–1.12	0.38	0	
Cessation of treatment[c]							
Abrupt	9	5653	0.93	0.87–1.00	0.05	3	0.04
Tapered	11	1595	1.08	0.96–1.21	0.22	46	

CI confidence intervals, *NA* not applicable, *ICU* intensive care unit

[a] Analysis based on trials adjudicated as low risk of bias

[b] Based of equivalent daily dose of hydrocortisone

[c] All trials regardless of adjudication of risk of bias

[d] Maximum allowed time from eligibility to randomisation

[e] Intervention continued until resolution of shock or ICU discharge

Table 3 The effect of corticosteroids compared to placebo or usual care on tertiary outcomes in patients with septic shock

	Number of trials	Number of participants	Estimate of treatment effect	95% CI	*p*	I^2 (%)
Time to resolution of shock	7	4302	MD −1.52 days	−1.71 to 1.32	< 0.0001	51
Duration of mechanical ventilation	5	3986	MD −1.38 days	−1.96 to 0.80	< 0.0001	24
Duration of ICU admission	13	5204	MD −0.75 days	−1.34 to 0.17	0.01	11
Duration of hospital admission	11	5099	MD −0.87 days	−2.17 to 0.44	0.19	14
Incidence of secondary infection	11	6036	RR 1.05	0.95–1.16	0.31	0
Incidence of gastrointestinal bleeding	12	6158	RR 1.09	0.80–1.46	0.59	8
Incidence of delirium or encephalopathy	3	3991	RR 1.99	0.37–10.84	0.43	47
Incidence of hyperglycaemia	9	5882	RR 1.11	1.07–1.16	< 0.0001	0
Incidence of hypernatraemia	5	4640	RR 1.67	1.35–2.07	< 0.0001	0

CI confidence interval, *MD* mean difference, *ICU* intensive care unit, *RR* relative risk

in accordance with current best research practice and followed a pre-published protocol. A trial sequential analysis was used to assess the risk of random errors (spurious findings), with results supporting the contention that a 15% relative increase or decrease in short-term mortality can be confidently excluded. The risk of bias assessment was conducted in a robust fashion, by using reviewers not involved in any of the included studies. There are also a number of limitations. As with all meta-analyses, the strength of conclusions that can be drawn are dependent on the strength of the included trials. What is less often recognised is the problems that may arise from differing definitions of outcomes used by studies. The two largest trials reported incidences of hyperglycaemia in the control groups as 3/1829 (0.16%) [12] and 520/626 (83.1%) [11], respectively. Pooling data that is clearly as disparate as these leads to reduced confidence in the results of the analysis, as can be seen in the GRADE summary of findings table. Pooling time-to-event outcomes, such as time to resolution of shock and duration of mechanical ventilation is also difficult in a trial-level meta-analysis. These outcomes are prone to bias due to competing risk [45], and the data included in this systematic review and meta-analysis highlights the particular difficulty of pooling trial-level data for time to event outcomes in critically ill patients. We anticipated reporting data on health-related quality of life, but found these data were not reported by the included trials.

The results of this systematic review and meta-analysis differ from the previous review published in the Cochrane Database of Systematic Reviews, which found a reduction in mortality when corticosteroids were used in patients with sepsis [46]. In contrast, our study was restricted to trials in which the study population was septic shock, excluding trials in which corticosteroids were used for other indications such as pneumonia [47], trials in which both experimental groups received corticosteroids [9, 48], and trials which used larger doses of corticosteroids [49]. The inclusion of the two recently published, largest trials [11, 12] aids the interpretation of the results of these trials to allow clinicians, researchers and those directing health policy to make decisions regarding the use of corticosteroids in this population.

The results of this systematic review and meta-analysis indicate that, while there is no discernible mortality benefit, a significant reduction in duration of ventilation, if confirmed with more specific analyses, may represent a patient-centred outcome. Subsequent confirmation of the benefits related to a reduction in duration of ICU admission in specific cost-effectiveness and health economic analyses might provide justification for recommending the use of corticosteroids in future clinical practice guidelines, if these analyses confirm that these benefits outweigh the potential effects related to increased risk of adverse events. It was notable that the risk of experiencing any adverse event was higher in trial participants assigned to corticosteroids. The data would suggest that this effect was greatest on biochemical events such as hyperglycaemia and hypernatraemia, but the clinical significance of these events is not clear. The subgroup of trials which used hydrocortisone and fludrocortisone did suggest the possibility of a mortality benefit but, given this was based on trials not adjudicated as low risk of bias and was of marginal significance, we cannot draw strong inferences from this result.

Further research is needed to clarify some issues. The publication of the longer-term outcomes from all trials included in this review may add some clarity regarding the effect of corticosteroids on long-term mortality. Pooling all the trial data in an individual patient data meta-analysis would allow more accurate assessment of the effect of corticosteroids on time-to-event outcomes as

Table 4 Summary of findings table

Corticosteroids compared to placebo or usual care for adults with septic shock

Patient or population: adults with septic shock
Setting: intensive care unit
Intervention: corticosteroids (< 500 mg per day)
Comparison: placebo or usual care

Outcomes	Anticipated absolute effects[e] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with corticosteroids				
All cause short-term (< 90 days) mortality (short-term mortality)	370 per 1000	355 per 1000 (337–377)	Rate ratio 0.96 (0.91–1.02)	7297 (22 RCTs)	⊕⊕⊕⊕ HIGH	
All cause long-term (> 90 days) mortality (long-term mortality)	405 per 1000	377 per 1000 (348–405)	Rate ratio 0.96 (0.90–1.02)	5667 (5 RCTs)	⊕⊕⊕◯ MODERATE[a]	Smaller number of included studies and fewer studies with low risk of bias lead to concerns regarding risk of bias.[a]
Proportion of patients with > 1 adverse outcome (adverse outcomes)	154 per 1000	151 per 1000 (139–167)	Rate ratio 0.98 (0.90–1.08)	5908 (10 RCTs)	⊕⊕◯◯ LOW[a,c]	When stratified by risk of bias in the sensitivity analyses the pooled point estimate and confidence intervals significantly changed.[a] Heterogeneity is likely present (including, but not limited to a large I^2 statistic)[c]
Health-related quality of life—not reported	–	–	–	–	–	No study reported patient-reported outcome measures including health rated quality of life.
Time to resolution of shock (days)	The mean time to resolution of shock (days) ranged from 2.8 to 6.8 days	The mean time to resolution of shock (days) in the intervention group was 1.52 days lower (1.71–1.32 lower)	–	4302 (7 RCTs)	⊕⊕⊕◯ MODERATE[d]	Considered a surrogate outcome rather than a patient-centred outcome.[d]
Duration of mechanical ventilation (days)	The mean duration of mechanical ventilation (days) ranged from 4 to 26 days	The mean duration of mechanical ventilation (days) in the intervention group was 1.38 days lower (1.96–0.8 lower)	–	3986 (5 RCTs)	⊕⊕⊕◯ MODERATE[a]	Smaller number of included studies and fewer studies with low risk of bias lead to concerns regarding risk of bias.[a]
ICU length of stay (days)	The mean ICU length of stay (days) ranged from 2.48 to 24 days	The mean ICU length of stay (days) in the intervention group was 0.75 days lower (1.34–0.17 lower)	–	5204 (13 RCTs)	⊕⊕⊕◯ MODERATE[d]	Considered a surrogate outcome rather than a patient-centred outcome.[d]

Table 4 continued

Outcomes	Anticipated absolute effects[e] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with corticosteroids				
Hospital length of stay (days)	The mean hospital length of stay (days) ranged from 11.71 to 39.4 days	The mean hospital length of stay (days) in the intervention group was 0.87 days lower (2.17–0.44 higher)	–	5099 (11 RCTs)	⊕⊕⊕◯ MODERATE[b]	Confidence intervals are wide and include appreciable benefit and harm.[b]
Proportion of patients with > 1 episode of secondary infection	188 per 1000	197 per 1000 (178–218)	Rate ratio 1.05 (0.95–1.16)	6036 (11 RCTs)	⊕⊕⊕◯ MODERATE[b]	Confidence intervals are wide and include appreciable benefit and harm.[b]
Proportion of patients with > 1 episode of gastrointestinal bleeding	25 per 1000	27 per 1000 (20–36)	Rate ratio 1.09 (0.80–1.46)	6158 (12 RCTs)	⊕⊕◯◯ LOW[a]	Majority of the weight of the point estimate was attributed to trials not adjudicated as low risk of bias.[a] Confidence intervals are wide and include appreciable benefit and harm.[b]
Proportion of patients with > 1 episode of cerebral impairment	1 per 1000	1 per 1000 (0–5)	Rate ratio 1.99 (0.37–10.84)	3991 (3 RCTs)	⊕◯◯◯ VERY LOW[b,c]	Confidence intervals are very wide and include appreciable benefit and harm.[b] Heterogeneity is likely present (including, but not limited to a large I^2 statistic)[c]
Proportion of patients with > 1 episode of hyperglycaemia	285 per 1000	316 per 1000 (305–331)	Rate ratio 1.11 (1.07–1.16)	5882 (9 RCTs)	⊕⊕◯◯ LOW[c,d]	Large disparity in the reported incidence of this outcome leads to concerns regarding consistency.[c] Considered a surrogate outcome rather than a patient-centred outcome.[d]
Proportion of patients with > 1 episode of hypernatraemia	42 per 1000	70 per 1000 (57–87)	Rate ratio 1.67 (1.35–2.07)	4640 (5 RCTs)	⊕⊕◯◯ LOW[c,d]	Large disparity in the reported incidence of this outcome leads to concerns regarding consistency.[c] Considered a surrogate outcome rather than a patient centred outcome.[d]

CI confidence interval; *MD* mean difference

GRADE working group grades of evidence

High certainty we are very confident that the true effect lies close to that of the estimate of the effect; *Moderate certainty* we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; *Low certainty* our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; *Very low certainty* we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

[b] Downgraded for serious risk of bias

[c] Downgraded for serious imprecision

[d] Downgraded for serious inconsistency

[e] Downgraded for serious indirectness.

well as subgroups pf patients based on clinical characteristics, such as time to commencement of the intervention or possibly response to a corticotropin stimulation test. It may also allow for a more nuanced assessment of the role of corticosteroids in those with more severe shock, defined by dose of vasopressor, while accounting for confounders in this relationship such as volume of fluid administered and sedative regimen. More information regarding the effect of corticosteroids on longer-term quality of life is required.

In conclusion, there is high-quality evidence that, in adult patients with septic shock, corticosteroids compared to placebo or control therapy had no significant effect on short-term or longer-term mortality. Among patients treated with corticosteroids, there was an increased incidence of adverse events and an association with shorter duration of shock, mechanical ventilation and ICU admission, but these latter conclusions are based on lower-quality evidence.

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Author details
[1] Department of Intensive Care, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark. [2] University of New South Wales, Kensington, NSW, Australia. [3] Centre for Research in Intensive Care, Copenhagen, Denmark. [4] Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia. [5] University of Queensland, Brisbane, QLD, Australia. [6] Division of Critical Care and Trauma, The George Institute for Global Health, University of New South Wales, Sydney, Australia. [7] Department of Intensive Care Medicine, St. George Hospital, Kogarah, NSW, Australia. [8] Department of Intensive Care, Wesley Hospital, Brisbane, QLD, Australia. [9] Malcolm Fisher Department of Intensive Care Medicine, Royal North Shore Hospital, St. Leonards, NSW 2065, Australia. [10] Northern Clinical School, Sydney Medical School, University of Sydney, St. Leonards, NSW, Australia.

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Professors Venkatesh, Finfer, Myburgh, Perner and Associate Professor Cohen were all members of the management committee of the ADRENAL study. The other authors have no conflicts of interest to declare.

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