

Do low-dose corticosteroids improve survival or shock reversal from septic shock in adults? Meta-analysis with trial sequential analysis

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Abstract

Objective: This meta-analysis with trial sequential analysis (TSA) was performed to determine whether low-dose corticosteroids (LDCs) can improve survival or shock reversal from septic shock in adults.

Methods: A literature search was performed using several databases (Medline, Cochrane Library, Embase, and Chinese Biological Medical Database) until 23 October 2017. The systematic review was registered in PROSPERO.

Results: Nine randomized controlled trials (RCTs) ($n = 1182$) were included. LDC intervention improved 7-day shock reversal compared with the control group (relative risk, 1.36; TSA-adjusted 95% confidence interval, 1.20–1.54). LDCs had no statistically significant effects on gastrointestinal bleeding or superinfection. LDCs did not reduce 28-day mortality from septic shock (relative risk, 0.96; TSA-adjusted 95% confidence interval, 0.74–1.24). The TSA indicated that RCTs of about 3000 patients would be needed to draw definitive conclusions; similar results were obtained in a subgroup analysis of nonresponders.

Conclusions: LDCs improve 7-day shock reversal. However, whether LDCs improve 28-day survival from septic shock in adults remains unclear. The results of well-designed larger RCTs are needed.

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Keywords

Septic shock, steroids, meta-analysis, trial sequential analysis, survival, shock reversal

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Introduction

Sepsis is a form of life-threatening organ dysfunction caused by a dysregulated host response to infection. The latest consensus recommends eliminating the concept “severe sepsis,” which makes septic shock more prominent.¹ In fact, septic shock occurs in more than 230,000 patients in the United States each year, and the mortality rate is still 40% despite bundled interventions.² It is very important for clinicians to identify septic shock early and manage it appropriately.²

During the early period of sepsis, corticosteroids are critical to maintain the homeostatic functions of metabolism, the vasculature, and the immune system. However, because of the frequently impaired functions of the adrenal cortex by endotoxins or sepsis, corticosteroid production is assumed to be insufficient to cover the body’s survival requirements, resulting in an inadequate amount of steroids at the tissue and cellular levels.³ Synthetic steroids have been given for more than 50 years to patients with severe infection of various causes. The use of low-dose hydrocortisone is now recommended in patients with septic shock that does not respond to fluid and vasopressor therapy.⁴ However, conflicting results of low-dose corticosteroid (LDC) administration have been obtained.

The effects of LDCs have been assessed in various trials and three recent systematic reviews.^{5–7} Two main questions remain unanswered: Does LDC therapy improve shock reversal and finally survival from septic shock in adults? Is there an ideal LDC treatment regimen?

Septic shock is the result of an infection. In patients with septic shock, sepsis is complicated by low blood pressure, and one or more organ systems subsequently fail when the blood supply to these organs is reduced. Poor recovery or death may occur if septic shock is not rapidly reversed. In previous reviews, overall patients with sepsis were included and not all LDC treatment regimens were the same. Each analysis method used in systematic reviews has its own pitfalls, and conventional meta-analyses fail to provide the required information size (RIS), a threshold for treatment or placebo.⁸ The drive behind systematic reviews is to gain information that helps to guide clinical practice and design improved treatment regimens in future research. In the present systematic review, both a meta-analysis and trial sequential analysis (TSA) of randomized controlled trials (RCTs) were conducted with a special focus on septic shock. The effects of prolonged LDC therapy on 7-day reversal, the incidence of serious adverse events (SAEs), and finally 28-day survival of patients with septic shock were evaluated. A subgroup analysis of responders and nonresponders (patients who did and did not respond to corticotropin testing) was also performed.

Materials and methods**Search strategy**

We conducted this systematic review in accordance with the PRISMA statement.

Our review protocol was registered in PROSPERO with the identification number CRD 42017077531. We searched Medline, the Cochrane Library, Embase, and the Chinese Biological Medical Database up to 23 October 2017. The following search terms were used: septic shock, steroids, corticosteroids, adrenal cortex hormone, and glucocorticoids.

Ethics

The study was exempt from an ethical review because it only involved the use of existing data or records.

Study eligibility

The study eligibility criteria for this systematic review were as follows: RCTs that included adult patients (age of ≥ 18 years) with septic shock; an explicit description of the septic shock criteria in the relevant trials, with the definitions of septic shock and reversal of shock in compliance with the consensus definitions;⁹ and the intervention consisted of LDC administered intravenously for ≥ 5 days, with LDCs defined as hydrocortisone at ≤ 300 mg/day or equivalents of other corticosteroids.¹⁰ No limitations were imposed regarding the types of corticosteroids or whether administration occurred continuously or intermittently, and co-interventions (e.g., vasopressor therapy, fluid replacement, or antibiotics) were allowed. The exclusion criteria were as follows: non-RCTs, cross-over studies, repeated experiments, studies with high doses of corticosteroids (>300 mg/day), and studies comparing different doses of corticosteroids in different intervention groups.

The study outcomes were 7-day shock reversal, the incidence of corticosteroid-related SAEs (gastrointestinal bleeding and superinfection), and 28-day mortality of patients with septic shock. Subgroups (responders and nonresponders) were

determined according to the response to adrenocorticotrophic hormone (ACTH) stimulation. Nonresponders were defined as patients with a low cortisol response (a ≤ 9 - $\mu\text{g}/\text{dl}$ increase in the cortisol level) to a 250- μg intravenous bolus of corticotropin.¹¹

Data extraction and assessment of risk of bias

The present study was conducted by four groups of researchers: one literature search group, two literature review groups, and one data analysis group. After the literature search, two groups independently reviewed all the literature and excluded clearly irrelevant reports after assessment of their full text. If an inconsistency was encountered, the data extraction was repeated until a consensus was reached. Further disagreements were resolved through discussion. The authors then entered the data into modified tables from the templates of the Cochrane Collaboration. We assessed the risk of bias according to the Cochrane Collaboration's tool (updated June 2014); specifically, a trial was assessed as having a lower risk of bias if it had at least five low-risk rankings in seven domains.²⁰

Statistical analysis

We conducted the meta-analysis using Cochrane Review Manager (RevMan) software, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and conducted the TSA using TSA software, version 0.9.5.5 beta (Copenhagen Trial Unit, Copenhagen, Denmark).²¹ The publication bias was assessed using STATA software (StataCorp, College Station, TX, USA). For each trial, we calculated the relative risk (RR) with 95% confidence interval (CI) to evaluate the relative effect sizes. We used fixed-effects models for

dichotomous outcomes in the meta-analysis. Acceptable heterogeneity was quantified by a p value of >0.1 and inconsistency factor (I^2) of $<50\%$ based on tests for heterogeneity among the identified trials.

In a conventional meta-analysis, repeated significance testing of accumulating data inflates the overall risk of type I error; however, TSA can reduce the risk of type I error inflation and adjust the 95% CI of the RR by taking advantage of the O'Brien-Fleming α -spending function.²¹ Moreover, TSA is analogous to performing an interim analysis in a cumulative meta-analysis. This method can estimate the RIS to achieve preset levels of power, draw benefit boundaries and harm boundaries, and calculate futility. The RIS used with the boundaries can infer whether further trials are needed.²¹ We conducted the TSA with 5% risk of a type I error and a power of 80%, as well as the α -spending adjusted 95% CI for repetitive significance testing.

Results

Search results

We obtained a total of 1972 reports and identified the full texts of 45 articles in our initial review. We excluded 36 reports based on the inclusion and exclusion criteria, and the characteristics of the 9 included studies ($n = 1182$) are listed in Table 1.

Trial characteristics and risk of bias assessment

All nine RCTs evaluated LDC treatment with small variation in the duration (≥ 5 days). Hydrocortisone was used in eight RCTs,^{10,12,13-15,17-19} and dexamethasone was used in one RCT.¹⁶ One trial¹⁷ investigated patients with cirrhosis, and one trial¹⁸ investigated surgical postoperative patients with septic shock. According to the results

assessed by RevMan software, five^{10,12,13,17,19} of the nine trials were determined to have a lower risk of bias.

7-Day shock reversal

All pooled intervention effects with their 95% CIs of all trials and all TSAs are listed in Table 2.

Data regarding 7-day shock reversal were provided and analyzed in six RCTs^{10,12,13-15,17} ($n = 996$).

Heterogeneity was acceptable ($I^2 = 22\%$), and there was a statistically significant difference in the test for the overall effect (fixed-effects model: RR, 1.36; 95% CI, 1.22-1.52; TSA-adjusted 95% CI, 1.20-1.54, $p < 0.00001$) (Figure 1(a), Table 2). The TSA showed that the cumulative z-curve crossed the boundary for futility (Figure 1(b)).

SAEs

There was no statistically significant difference in gastrointestinal bleeding ($I^2 = 16\%$; RR, 1.34; 95% CI, 0.86-2.08; TSA-adjusted 95% CI, 0.22-8.16) (Figure 2(a)). Similarly, the meta-analysis for superinfection showed no significant difference ($I^2 = 8\%$; RR, 1.05; 95% CI, 0.87-1.27; TSA-adjusted 95% CI, 0.72-1.54) (Figure 2(b)). However, the TSAs of two adverse events showed that the cumulative z-curves did not cross any of the boundaries. Thus, further studies are needed to draw a deliberate conclusion.

28-Day mortality

No significant difference was found in 28-day mortality (RR, 0.96; 95% CI, 0.85-1.09; TSA-adjusted 95% CI, 0.74-1.24) (Figure 3(a)). TSA [relative risk reduction (RRR), 10%; power, 80%] demonstrated that the RIS (4661) was larger than the number of subjects included in the analysis ($n = 1182$), indicating that about 3000 randomized patients would be needed

Table 1. Characteristics of the randomized controlled trials included in the systematic review

Trials	Number of patients	Inclusion criteria	Interventions	Outcomes
Bollaert et al., 1998 ¹³	41	Patients with vasopressor-dependent septic shock	All patients accepted the short corticotropin test using a 250- μ g IV bolus of tetraacosactrin. Treatment group: hydrocortisone at 100 mg IV three times daily for 5 d. Control group: NS was used as a placebo.	28-day mortality, 7-day shock reversal, superinfection, GI bleeding
Briegleb et al., 1999 ¹⁴	40	Patients with vasopressor-dependent septic shock	Treatment group: hydrocortisone was started at a loading dose of 100 mg given within 30 min, followed by continuous infusion of 0.18 mg/kg/h. When septic shock was reversed, the dose of hydrocortisone was reduced to 0.08 mg/kg/h for 6 d. Control group: NS was used as a placebo.	28-day mortality, 7-day shock reversal, superinfection
Annane et al., 2002 ¹⁰	300	Patients with vasopressor-dependent septic shock	All patients accepted the short corticotropin test using a 250- μ g IV bolus of tetraacosactrin. Treatment group: hydrocortisone at 50 mg was administered by IV injection every 6 h, and 50 μ g of fludrocortisone was administered orally once daily for 7 d. Control group: NS was used as a placebo.	28-day mortality, 7-day shock reversal, superinfection, GI bleeding
Oppert et al., 2005 ¹⁵	48	Patients with vasopressor-dependent septic shock	Treatment group: hydrocortisone (50-mg IV bolus, then 0.18 mg/kg/h continuous infusion until vasopressor cessation for > 1 h, then weaning by steps of 0.02 mg/kg/h every day). Control group: NS was used as a placebo.	28-day mortality, 7-day shock reversal
Cicarelli et al., 2007 ¹⁶	29	Patients with septic shock	Treatment group: dexamethasone (0.2 mg/kg, three doses at intervals of 36 h). Placebo group: NS was used as a placebo.	28-day mortality
Sprung et al., 2008 ¹²	499	Patients with septic shock	All patients accepted the short corticotropin test performed using a 250- μ g IV bolus of tetraacosactrin. Treatment group: hydrocortisone given as a 50-mg IV bolus every 6 h for 5 d. Control group: NS was used as a placebo.	28-day mortality, 7-day shock reversal, superinfection, GI bleeding

(continued)

Table 1. Continued

Trials	Number of patients	Inclusion criteria	Interventions	Outcomes
Arabi et al., 2010 ¹⁷	75	Patients with cirrhosis and septic shock	Treatment group: hydrocortisone at 50 mg was administered by IV injection every 6 h until hemodynamic stability was achieved, followed by steroid tapering over 8 d. Control group: NS was used as a placebo.	28-day mortality, 7-day shock reversal, superinfection, GI bleeding
Wan et al., 2014 ¹⁸	89	Postoperative surgical patients with septic shock	All patients accepted the short corticotropin test performed using a 250- μ g IV bolus of tetracosactrin. Treatment group: A 50-mg IV hydrocortisone bolus was administered every 6 h for 5 or 7 d. Control group: NS was used as a placebo.	28-day mortality, 7-day shock reversal, superinfection, GI bleeding
Gordon et al., 2014 ¹⁹	61	Patients with vasopressor-dependent septic shock	All patients were allocated to receive vasopressin (titrated up to 0.06 U/min). Treatment group: IV hydrocortisone (50-mg IV bolus every 6 h for 5 d, every 12 h for 3 d, and then once daily for 3 d). Control group: NS was used as a placebo.	28-day mortality

GI, gastrointestinal; NS, normal saline; IV, intravenous.

Table 2. Conventional meta-analysis and TSA-adjusted RRs with 95% CIs for all outcomes

	Number of patients	Conventional meta-analysis RR (95% CI)	TSA-adjusted 95% CI
7-day shock reversal	996	1.36 (1.22–1.52)	1.20–1.54
Serious adverse events			
Gastrointestinal bleeding	1010	1.34 (0.86–2.08)	0.22–8.16
Superinfection	970	1.05 (0.87–1.27)	0.72–1.54
28-day mortality			
All trials	1182	0.96 (0.85–1.09)	0.74–1.24
Subgroup: ACTH response			
Nonresponders	529	0.92 (0.76–1.10)	0.44–1.93
Responders	387	0.96 (0.75–1.24)	ID
Nonresponders vs. responders	916	0.95 (0.76–1.18)	ID

TSA, trial sequential analysis; RR, relative risk; CI, confidence interval; ACTH, adrenocorticotropic hormone; ID, insufficient data to obtain adjusted confidence interval.

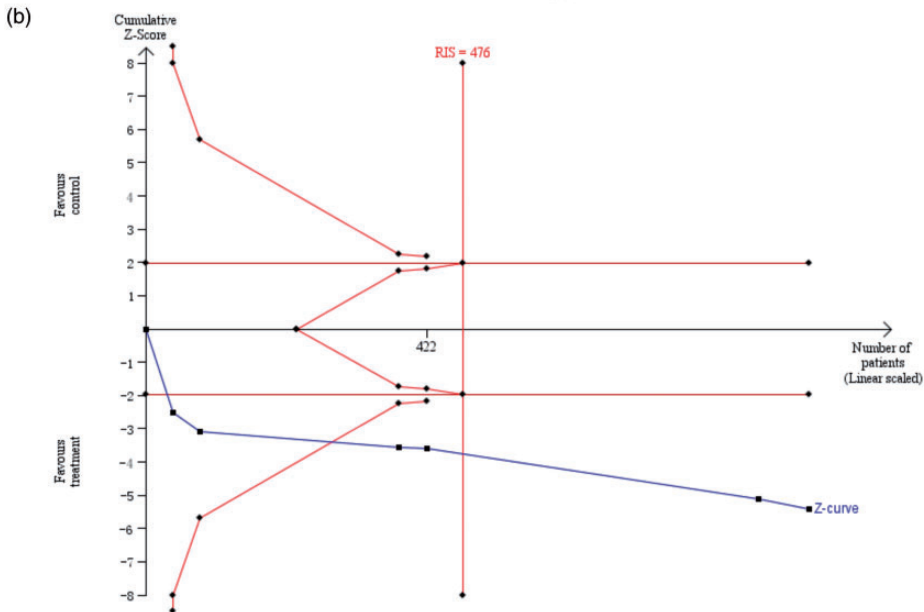
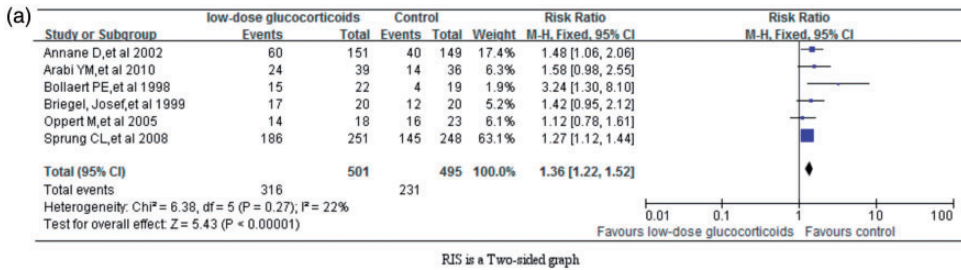


Figure 1. Effects of low-dose corticosteroids on 7-day shock reversal in patients with septic shock. (a) Meta-analysis. (b) Trial sequential analysis (Alpha, 5%; Beta, 10%; Diversity, 43%; CEP, 47.0%; Relative risk reduction, 36%; Power, 80%). CEP, control event proportion.

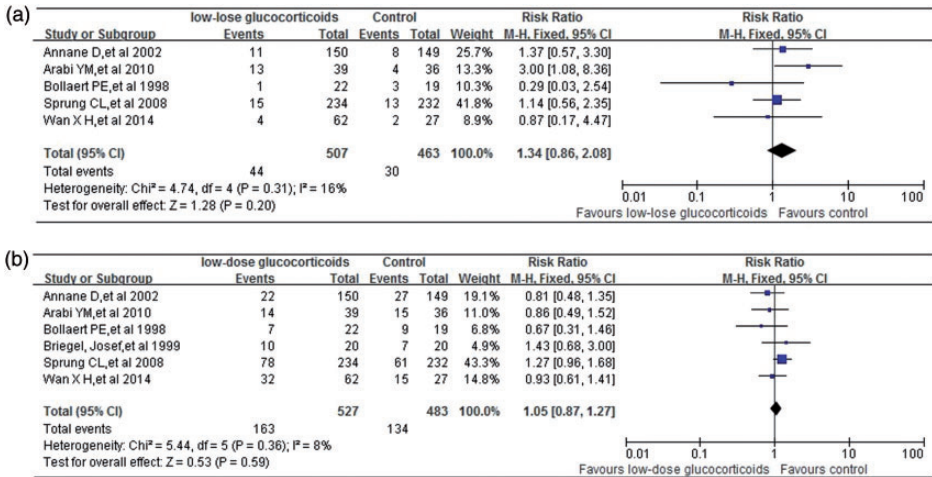


Figure 2. Serious adverse events of low-dose corticosteroids in patients with septic shock.

(a) Gastrointestinal bleeding. (b) Superinfection.

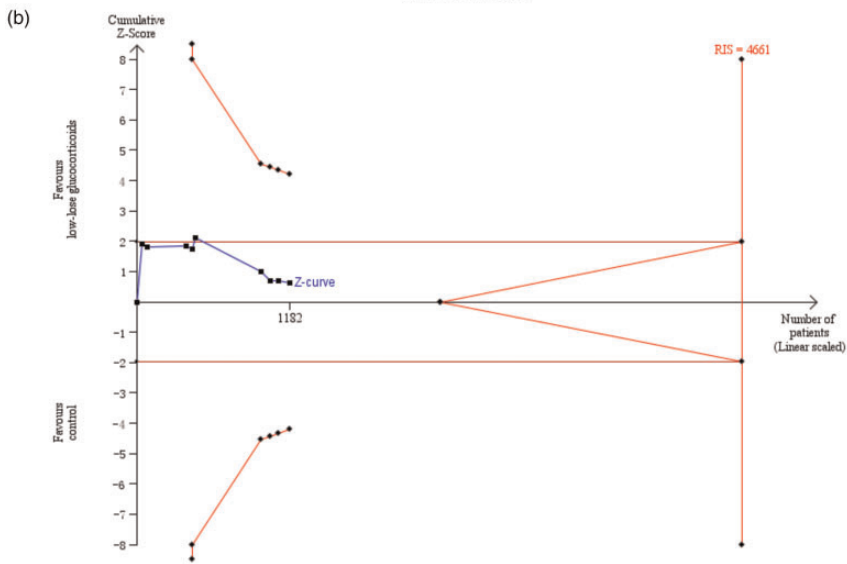
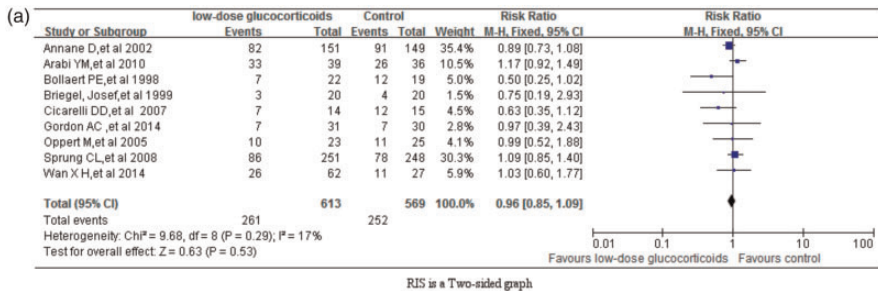


Figure 3. Effects of low-dose corticosteroids on 28-day mortality in patients with septic shock. (a) Meta-analysis. (b) Trial sequential analysis (Alpha, 5%; Beta, 10%; Diversity, 33%; CEP, 50.0%; Relative risk reduction, 10%; Power 80%).

CEP, control event proportion.

before firm conclusions can be drawn (Figure 3(b)).

Subgroup analysis

There was no significant difference among nonresponders ($I^2=0\%$; RR, 0.92; 95% CI, 0.76–1.10; TSA-adjusted 95% CI, 0.44–1.93). The TSA of four trials (RRR, 8%; power, 80%) showed that further studies of several thousand patients were needed. Similar results were obtained in additional subgroup analyses.

Publication bias analysis

We only conducted a publication bias analysis of 28-day mortality in all of the patients and 7-day shock reversal among survivors because of the small number of RCTs included for other outcomes. Begg's funnel plots were applied for qualitative analysis. No statistical significance was found in the analysis of either 28-day mortality or 7-day shock reversal. The funnel plots also qualitatively showed no remarkable publication bias for the included RCTs.

Discussion and conclusions

On the basis of the results of our analysis, LDC therapy improves shock reversal. LDC treatment did not influence safety in this study, and the TSA indicates that more research is needed to confirm this finding. Definitive conclusions regarding whether LDC improves survival in patients with septic shock cannot be drawn. RCTs of about 3000 patients are needed to provide sufficient evidence, or an optimal LDC regimen that maximizes therapeutic benefits while reducing adverse events should be designed in the future.

The present review focused exclusively on septic shock trials. To our knowledge, this is the first study to combine a traditional meta-analysis with TSA and confirm that LDC treatment improves 7-day shock

reversal in all adults with septic shock. The meta-analysis results in another review⁷ showed that the incidence of 7-day shock reversal was significantly different between the treatment group and control group. Furthermore, our TSA results indicated that the available samples were sufficient and confirmed that firm evidence was reached. In fact, we found strong evidence that corticosteroids attenuate inflammation in various organs during sepsis, resulting in less organ dysfunction. They also contribute to restoration of an effective blood volume, notably via sodium and water retention. Finally, corticosteroids enhance vascular contractile and blood pressure responses to α -1 agonists. This effect likely occurs through a non-genomic effect and a genomic transrepression effect if there is prolonged improvement in vascular responsiveness; endothelial cells play important roles in this process.²²

Although corticosteroids have many benefits in patients with septic shock, they may also suppress immune function and cause adverse events. The incidence of SAEs (e.g., gastrointestinal bleeding and superinfection) may increase when large doses of corticosteroids are used, thus affecting patients' safety and possibly increasing mortality. Like other reviews,^{6,7} our meta-analyses indicated that LDCs did not significantly affect the incidence of SAEs. In fact, adrenal dysfunction is related to the hypothalamic-pituitary-adrenal axis, steroid hormones, and glucocorticoid receptors; recent research has shown that the main manifestations of adrenal dysfunction during sepsis are decreased steroidogenesis, cortisol delivery to tissue, sensitivity of tissue to cortisol, and decreased metabolism and clearance from plasma.²³ LDCs are administered as replacement therapy to overcome a relative deficiency of cortisol and to compensate for decreased tissue sensitivity to corticosteroids. Because of the five-fold longer

half-life of hydrocortisone,²⁴ hydrocortisone doses of ≤ 300 mg/day (referred to as a “low dose” in the literature) may expectedly result in high cortisol levels with high risks of adverse effects.

Finally, our meta-analysis results did not indicate that LDC therapy increased 28-day survival in patients with septic shock, although this was anticipated. However, the TSA indicated that drawing a conclusion was premature and that about 3000 randomized patients were needed. Another recent review also showed that LDC therapy could not reduce mortality in patients with sepsis;⁶ however, the authors included overall patients with sepsis and even those with systemic inflammatory response syndrome. The latter may be milder in severity and too inclusive. Additionally, “low-dose corticosteroids” was defined as hydrocortisone of ≤ 500 mg/day or equivalent, which was higher than the dosage in our review. However, in their updated review with a meta-analysis, Annane et al.⁷ found that administration of LDCs for a longer duration might favorably impact all-cause 28-day mortality in patients with sepsis and further suggested that patients with more severe forms of sepsis, such as septic shock or adrenal insufficiency, were more likely to derive a survival benefit from LDCs. In fact, they included children. Notably, the hypothalamic-pituitary-adrenal axis of children is different from that of adults and develops across childhood, and pediatric sepsis is distinct from adult sepsis.²⁵ Annane et al.⁷ also used data from the last half century, while treatment strategies used in sepsis have changed with time. In another review, the effects of different doses of corticosteroids were analyzed using a Bayesian approach.⁵ In meta-analyses, a frequentist approach is often used for pairwise techniques. The results of all of the above-mentioned studies were also inconclusive in terms of mortality, as was our analysis. The Bayesian

meta-analysis, like our analysis, also showed that low-dose hydrocortisone had high efficacy, especially in shock reversal, which again supports propagating the use of LDCs in patients with septic shock despite the different analysis method.

Nonresponders are patients with adrenal dysfunction and even insufficiency.²⁶ In our review, the percentage of nonresponders reached 57.8% (529/916) among patients with septic shock, and the 28-day mortality of nonresponders was numerically higher in the control group; however, there was no significant difference in 28-day mortality among the nonresponders (49.4% vs. 43.9%). In fact, a sensitive and specific diagnostic tool for adrenal insufficiency remains to be found. During the stimulation test, a dose of 250 mg of ACTH leads to supraphysiologic ACTH levels and could therefore overcome any ACTH resistance, and a low incremental plasma cortisol response gives little information about the adequacy of cortisol production when cortisol metabolism is reduced. TSAs of all subgroups showed that further studies of additional samples are needed.

This systematic review has some limitations. In this TSA, the RRR for the intervention effect was estimated according to our included RCTs, and the power of the statistical test in the TSA was only 80%. Additionally, substantial clinical heterogeneity existed among the included trials. Finally, although whether LDCs could reduce 28-day mortality was uncertain, the regimen of corticosteroid administration (i.e., dosing, timing, duration, methods, and other parameters) was closely correlated with treatment efficacy, and this is critical for survival from septic shock. However, we did not analyze these parameters in the present review. On the basis of stable isotope studies,²⁷ it appears that even a dose of 60 mg of hydrocortisone may be sufficient. A pulsatile pattern of receptor binding was recently found during critical illness, and

the glucocorticoid receptor may be continually activated.²⁸ Continuous infusions of corticosteroids may yield more benefits than intermittent administration. The underlying mechanisms of adrenal dysfunction have been clarified more recently, and new RCTs with improved regimens should be carried out in the future.

Author contributions

Rui Xu and Chengfu Zhou performed the systematic literature search. Two groups of authors (Yan Huang and Ling Wu; Qi Liu and Wei Hu) were responsible for the literature review and extracting data from the selected articles. Qian Wang and Quan Du analyzed the data. Quan Du and Rui Xu planned and wrote the review.

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Declaration of conflicting interest

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