Original Contribution

Can corticosteroids reduce the mortality of patients with severe sepsis? A systematic review and meta-analysis

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ABSTRACT

Background: The effects of corticosteroids on clinical outcomes of patients with sepsis remains controversial. We aimed to further determine the effectiveness of corticosteroids in reducing mortality in adult patients with severe sepsis by comparison with placebo.

Methods: Pubmed, Embase, Medline, Cochrane Central Register of Controlled Trials (CENTRAL) as well as the Information Sciences Institute (ISI) Web of Science were searched for all controlled studies that compared corticosteroids and placebo in adult patients with severe sepsis. The primary outcome was the mortality 28-day mortality and the secondary outcomes were mortality at longest follow up, occurrence, and reoccurrence of septic shock.

Results: A total of 19 trials involving 7035 patients were pooled in our analyses. No significant heterogeneity was found in any of the outcome measures. Compared with placebo, corticosteroids were associated with a lower 28-day mortality (RR 0.91, 95% CI 0.85–0.98, Z = 2.57, P = 0.01) both in patients having sepsis and in those who developed septic shock (RR 0.92, 95% CI 0.85–0.99, Z = 2.19, P = 0.03), while no significant difference was found in mortality with the longest follow up in patients either having sepsis (RR 0.94, 95% CI 0.89–1.00, Z = 1.93, P = 0.05), or occurrence (RR 0.83, 95% CI 0.56–1.24, Z = 0.90, P = 0.37) or reoccurrence of septic shock (RR 1.08, 95% CI 1.00–1.16, Z = 1.89, P = 0.06).

Conclusions: Corticosteroids were effective in reducing the 28-day mortality in patients with severe sepsis and in those with septic shock.

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1. Background

Sepsis is a clinical syndrome characterized by systemic inflammation due to infection. Studies showed that, between 2003 and 2015, global incidence of sepsis was about 437 per 100,000 [1]. Vascular dysfunction and systemic inflammatory response contribute to tissue hypoxia, multiple organ dysfunction syndrome (MODS) and death. Thus, sepsis is a syndrome associated with a mortality of 25% and up to 52% once developed to septic shock [2]. Up to now, no effective therapy for sepsis has been developed other than resuscitative therapy, respiratory support, and antibiotic therapy [3].

The hypothalamic-pituitary-adrenal (HPA) axis is usually impaired in patients with sepsis. [4] In these patients, the hypothalamic-pituitary-adrenal axis affects inflammation through white blood cells, cytokines, and nitric oxide production [5]. The same time, inflammatory cytokines may either suppress cortisol response to adrenocorticotropic, resulting in insufficient adrenal output, or compete with intracellular corticosteroids receptor function, resulting in peripheral tissue corticosteroids resistance [6]. Thus, the major theoretical purpose of glucocorticoids in sepsis is to restore balance of the altered HPA axis with the goal of improved outcomes such as mortality.

Nevertheless, the role of corticosteroids in reducing mortality in patients with severe sepsis remains unclear despite numerous published randomized controlled trials (RCTs) and meta-analysis papers. In 2009, a systematic review published in The Journal of American Medical Association reported that low dose corticosteroids might have a beneficial effect on short-term mortality of patients with severe sepsis [7]. However, a meta analysis in 2015 found no advantage in the use of corticosteroids in any dose [8]. Recently, two double-blind RCTs have been published which reported conflicting results about the use of corticosteroids in patients with severe sepsis. In the study of Venkatech et al., hydrocortisone did not result in lower mortality than placebo [9]. On the contrary, in the study of Annane et al., mortality was lower in patients who received hydrocortisone plus fludrocortisone [10].
Considering the controversial findings on corticosteroids in adult patients with severe sepsis, we therefore assumed that corticosteroids may be more effective than placebo in reducing mortality. To identify the role of corticosteroids in improving clinical outcomes of patients with severe sepsis, we conducted a systematic review and meta-analysis of all published trials comparing the mortality of patients with severe sepsis patients who received corticosteroids and those who received placebo.

2. Methods

2.1. Search strategies

From 1946 to March 2018, a comprehensive computer search was conducted in PubMed, Embase, Medline, Cochrane Central Register of Controlled Trials (CENTRAL), and Information Sciences Institute (ISI) Web of Science using the keywords of “glucocorticoid” or “corticosteroid” or “steroid” or “cortisone” or “hydrocortisone” or “prednisolone” or “methylprednisolone” or “prednisone” or “dexamethasone” or “triamcinolone” and “sepsis” or “septic” without limitation in the publication type or language. We also reviewed the references listed in each identified article and manually searched the related articles to identify all eligible studies and minimize any potential publication bias.

2.2. Inclusion and exclusion criteria

Eligible clinical trials were identified based on the following criteria: 1) the subjects enrolled in each study included patients with severe sepsis, which was defined in 1992 [11]; 2) patients were randomly divided into experimental group, in which corticosteroids were applied, and control group, in which patients received placebo; and 3) outcomes included but were not limited to mortality, occurrence, or reoccurrence of septic shock. We excluded studies if they were performed in animals or in patients under 18 years, or published as non-randomized study, reviews, or case reports.

2.3. Study selection

Two independent investigators (YN and BM) performed the study selection in two phases. In the first phase, they discarded duplicated and non-controlled studies by screening titles and abstracts. In the second phase, eligible studies were extracted by reviewing full texts in accordance with the previously designed study inclusion criteria. Any disagreement was resolved by mutual consensus in the presence of a third investigator (ZAL).

2.4. Data extraction

Independently, the two data collectors extracted and recorded desirable information of each enrolled study in a standard form recommended by Cochrane [12], which consisted of authors, publication year, study design, country, NCT No., population, demographic characteristics (age, gender, etc.), disease conditions (The Acute Physiologic and Chronic Health Evaluation II (APACHE II) and Simplified Acute Physiologic Score II (SAPS II)), Sequential Organ Failure Assessment (SOFA), and outcome measures (such as mortality and reoccurrence of septic shock). For any missing data or information, corresponding authors were contacted by email to request the full original data. Different opinions between the two collectors were determined by reaching a consensus or consulting a third investigator.

2.5. Quality assessment

For the assessment of risk of bias in estimating the study outcomes, we used the Cochrane risk of bias tool [12]. Each study was assessed for:

1) random sequence generation (selection bias); 2) allocation concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of related outcomes assessment (detection bias); 5) incomplete outcome data (attrition bias); 6) selective reporting (reporting bias); and 7) other biases. Two investigators conducted the quality assessment for the study methodology, independently and separately. Any divergence was resolved by mutual consensus in the presence of a third investigator.
2.6. Statistical analysis

Statistical analysis of our study was accomplished by an independent statistician using Cochrane systematic review software Review Manager (RevMan; Version 5.3.5; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014). We used Mann-Whitney U test to verify hypothesis and rendered statistical significance as a Z-value and P-value < 0.05, and the results were displayed in Forest plots. Continuous variables were reported as mean and standard derivation (SD), while dichotomous variables were shown as frequency and proportion. An initial test for statistical methodology, and statistical heterogeneities was conducted, and the χ² test with P < 0.1 and I² > 50% were used to indicate significance. We also performed the sensitivity analysis to substitute alternative decisions or ranges of values for decisions that were arbitrary or unclear. Random-effects model was applied in the presence of statistical heterogeneity. For continuous data we calculated mean difference (MD) and 95% confidence interval (CI), while for dichotomous data we calculated Risk ratio (RR) and 95% CI.

3. Results

Initially 5776 records were identified, of which 5772 were extracted from electronic databases and 4 from reference lists review. (Fig. 1) By screening the titles and abstracts, we discarded 5729 studies for duplication (n = 766), animal experiments (n = 1945), non-adult patients (n = 1774), and non-controlled studies (n = 1244). We searched the full-text articles for the remaining 47 studies, and eventually 19 trials [9,10,13-28] entered our final analysis after excluding 21 studies for not reporting related outcomes and 7 for not designed as expected.

3.1. Study description

All 19 studies compared the outcomes of corticosteroids and placebo. The 28-day mortality was recorded in 18 studies [9,10,13-19,21-28], mortality at longest follow up was reported in 19 studies [9,10,13-29], the occurrence of septic shock was reported in 2 studies [21,26], and the reoccurrence of septic shock was reported in 9 studies [9,10,13-16,24,26,27]. Details of each enrolled study were presented in Table 1.

A total of 7035 patients were pooled from all the included trials in our final systematic review and meta-analysis, among whom 3517 were treated with corticosteroids and 3518 with placebo. Details of baseline characteristics of patients in each enrolled study were shown in Table 2.

3.2. Quality assessment

Quality assessment of the 19 enrolled studies showed no bias in attribution, detection, blinding, or reporting in 11 studies, but high bias in 2 studies with regard to performance because of the limited number of patients and personnel. (Figs. 2 and 3) No studies were excluded for low quality or dubious decisions in the sensitivity analysis. There was no evidence of reporting bias for the on inspection of the funnel plot (Fig. 4).

### Table 1: Basic characteristics of 18 enrolled studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>RCT no.</th>
<th>Population</th>
<th>Disease</th>
<th>Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annane 2002</td>
<td>Placebo controlled, randomized, double-blind, parallel-group trial</td>
<td>NR</td>
<td>300</td>
<td>Septic shock</td>
<td>50 mg hydrocortisone bolus every 6 h for 7 days and 500 μg fludrocortisone orally per day for 7 days</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Annane 2018</td>
<td>Multicenter, double blind, randomized trial</td>
<td>NCT00625209</td>
<td>1241</td>
<td>Septic shock</td>
<td>50 mg hydrocortisone bolus for every 6 h and 50 μg fludrocortisone tablet daily for 7 days</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Arabi 2010</td>
<td>Randomized controlled study</td>
<td>ISRCTN99675218</td>
<td>75</td>
<td>Septic shock</td>
<td>50 mg hydrocortisone every 6 h and dose reduction by 10 mg every 2 days after shock resolution</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Bellaret 1998</td>
<td>Prospective, randomized, double-blind, placebo-controlled study.</td>
<td>NR</td>
<td>41</td>
<td>Septic shock</td>
<td>100 mg hydrocortisone bolus every 8 h for 5 days then weaned over 6 days</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Brriegel 1999</td>
<td>Prospective, randomized, double-blind, single-center study</td>
<td>NR</td>
<td>40</td>
<td>Septic shock</td>
<td>100 mg hydrocortisone within 30 min and followed by 0.18 mg/Kg/h until shock reversal</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Cicirelli 2007</td>
<td>Prospective randomized clinical trial</td>
<td>NR</td>
<td>29</td>
<td>Septic shock</td>
<td>0.2 mg/Kg dexamethasone, 3 doses at intervals of 36 h</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Confalonieri 2005</td>
<td>A preliminary randomized study</td>
<td>NR</td>
<td>46</td>
<td>Sepsis</td>
<td>200 mg hydrocortisone bolus followed by 10 mg/h for 7 days, and then weaned over 4 days</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Gordon 2014</td>
<td>Prospective open-label randomized controlled pilot trial</td>
<td>ISRCTN66727957</td>
<td>31</td>
<td>Septic shock</td>
<td>50 mg hydrocortisone bolus 6 h for 5 days, 12 h for 3 days, daily for 3 days</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Hu 2009</td>
<td>Randomized controlled study</td>
<td>NR</td>
<td>77</td>
<td>Septic shock</td>
<td>50 mg hydrocortisone bolus every 6 h for 7 days 200 mg/d</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Keh 2016</td>
<td>Double-blind, randomized clinical trial</td>
<td>NCT00670254</td>
<td>380</td>
<td>sepsis</td>
<td>50 mg hydrocortisone bolus, 200 mg for 5 days, 100 mg for 2 days, 50 mg for 2 days, 25 mg for 2 days</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Lv 2017</td>
<td>Placebo controlled, Randomized clinical study</td>
<td>NCT 02580240</td>
<td>118</td>
<td>Septic shock</td>
<td>200 mg/d hydrocortisone for 6 days, then tapered off</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Meduri 2007</td>
<td>Randomized clinical trial</td>
<td>NR</td>
<td>80</td>
<td>Severe sepsis</td>
<td>1 mg/kg/d methylprednisolone for 14 days, 0.5 mg/kg/d for 7 days, 0.25 mg/kg/d for 4 days and 0.125 mg/kg/d for 3 days. If MV free before day 14, patients was advanced to day 15 of drug therapy.</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Oppert 2005</td>
<td>Prospective, randomized, double-blind, single-center study</td>
<td>NR</td>
<td>41</td>
<td>Septic shock</td>
<td>50 mg hydrocortisone bolus followed by a continuous infusion of 0.18 mg/Kg until vasopressor cessation &gt;1 h, then weaned by steps of 0.02 mg/kg/h</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Rinaldi 2006</td>
<td>Randomized prospective study</td>
<td>NR</td>
<td>40</td>
<td>Severe sepsis</td>
<td>300 mg/d hydrocortisone for 6 days, then tapered off 50 mg hydrocortisone every 6 h for 7 days</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Tongyou 2016</td>
<td>Double blind, single center, randomized, placebo-controlled trial</td>
<td>NCT 01284452</td>
<td>197</td>
<td>Sepsis</td>
<td>300 mg/d hydrocortisone for 6 days, then tapered off 50 mg hydrocortisone every 6 h for 7 days</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Venkatesh 2018</td>
<td>International, pragmatic, double-blind, parallel group, randomized, controlled trial</td>
<td>NCT01448109</td>
<td>3658</td>
<td>Septic shock</td>
<td>200 mg/d hydrocortisone for 7 days</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Yildiz2002</td>
<td>Placebo-controlled, randomized, double-blind, single center study</td>
<td>ISRCTN36253388</td>
<td>40</td>
<td>sepsis</td>
<td>5 mg prednisolone at 6:00 and 2.5 mg at 18:00 for 10 days</td>
<td>ΔΔΔ</td>
</tr>
<tr>
<td>Yildiz 2011</td>
<td>Prospective, randomized, double-blind, placebo-controlled trial</td>
<td>NCT01275638</td>
<td>55</td>
<td>sepsis</td>
<td>10 mg Prednisolone at 6:00, 5 mg at 14:00, and 5 mg/d at 22.00 for 10 days</td>
<td>ΔΔΔ</td>
</tr>
</tbody>
</table>

(1) Mortality at longest follow up; (2) 28-day mortality; (3) Occurrence of septic shock; (4) Reoccurrence of septic shock. RCT, randomized controlled trial.
3.3. Heterogeneity

No significant statistical heterogeneity was found in any of the comparisons between corticosteroids and placebo: 28-day mortality ($I^2 = 11\%, \chi^2 = 19.13, P = 0.32$); mortality at longest follow up ($I^2 = 22\%, \chi^2 = 23.15, P = 0.18$), occurrence of shock ($I^2 = 0\%, \chi^2 = 0.25, P = 0.62$), or reoccurrence of septic shock ($I^2 = 0\%, \chi^2 = 4.99, P = 0.76$).

3.4. Mortality

Significant differences in the 28-day mortality (RR 0.91, 95% CI 0.85–0.98, Z = 2.57, P = 0.01) were found in corticosteroids compared with placebo but not in the mortality at longest follow up (RR 0.94, 95% CI 0.89–1.00, Z = 1.93, P = 0.05). (Figs. 5 and 6).

3.5. Occurrence of septic shock

No significant difference was identified either in occurrence of septic shock between treatment with corticosteroids and placebo (RR 0.83, 95% CI 0.56–1.24, Z = 0.90, P = 0.37) (Fig. 7) or reoccurrence of septic shock (RR 1.08, 95% CI 1.00–1.16, Z = 1.89, P = 0.06). (Fig. 8).

3.6. Post hoc analysis

Subgroup analysis of corticosteroids in patients with septic shock ($n = 6209$) was performed, and corticosteroids were associated with a significantly lower 28-day mortality (RR 0.92, 95% CI 0.85–0.99, Z = 2.19, P = 0.03) than placebo. (Supplemental File 1).

4. Discussion

In this meta-analysis, we found that corticosteroids could reduce the 28-day mortality of both patients with severe sepsis and those with septic shock. However, in terms of the occurrence and reoccurrence of septic shock, corticosteroids did not show any advantage.

We found a significantly lower 28-day mortality in patients with severe sepsis treated with corticosteroids. This may have resulted from several factors, among which the improvement of hemodynamics was the main mechanism. By binding to mineralocorticoid receptors in the kidney, corticosteroids could improve glomerular function [30], free water clearance, and sodium renal excretion [31]. Thus, patients with sepsis can restore effective blood volume through sodium and water re-entention. Second, corticosteroids are known to regulate the contractility of vascular smooth muscle through controlling alpha 1-adrenoceptor-mediated second-messenger, adenosine triphosphate-sensitive potassium channels and depressing pressor sensitivity to noradrenaline [32]. Third, endothelial glucocorticoid receptors is a critical regulator for Acute Physiologic Score; SOFA, Sequential Organ Failure Assessment; SD, standard derivation.

| Table 2 |
| Basic characteristics of patients |

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Hydrocortisone</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>APACHE II Mean (SD)</td>
<td>SOFA N (%)</td>
</tr>
<tr>
<td></td>
<td>Age, year Mean (SD)</td>
<td>or Median (IQR)</td>
</tr>
<tr>
<td>Annane 2002</td>
<td>NR</td>
<td>62 ± 15</td>
</tr>
<tr>
<td>Annane 2018</td>
<td>NR</td>
<td>66 ± 14</td>
</tr>
<tr>
<td>Arabi 2010</td>
<td>30.0 ± 7.4</td>
<td>NR</td>
</tr>
<tr>
<td>Bollaert 1998</td>
<td>NR</td>
<td>66 (21–83)</td>
</tr>
<tr>
<td>Briel 2019</td>
<td>26 ± 1</td>
<td>NR</td>
</tr>
<tr>
<td>Cicarelli 2007</td>
<td>20 ± 5</td>
<td>NR</td>
</tr>
<tr>
<td>Confalonieri 2005</td>
<td>17.2 ± 4.1</td>
<td>NR</td>
</tr>
<tr>
<td>Gordon 2014</td>
<td>19 (14–22)</td>
<td>NR</td>
</tr>
<tr>
<td>Hu 2009</td>
<td>18.75 ± 19.54</td>
<td>NR</td>
</tr>
<tr>
<td>Keh 2016</td>
<td>19.5 ± 6.9</td>
<td>NR</td>
</tr>
<tr>
<td>Lv 2017</td>
<td>25.5 ± 9.5</td>
<td>NR</td>
</tr>
<tr>
<td>Meduri 2007</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Oppert 2005</td>
<td>25 (19–30)</td>
<td>NR</td>
</tr>
<tr>
<td>Rinaldi 2006</td>
<td>20 ± 6.9</td>
<td>NR</td>
</tr>
<tr>
<td>Tongyo 2016</td>
<td>21.7 ± 5.7</td>
<td>NR</td>
</tr>
<tr>
<td>Venkatesh 2014</td>
<td>24 ± 19–29</td>
<td>NR</td>
</tr>
<tr>
<td>Yildiz 2002</td>
<td>15.4 ± 5.5</td>
<td>NR</td>
</tr>
<tr>
<td>Yildiz 2011</td>
<td>75 (35–90)</td>
<td>NR</td>
</tr>
</tbody>
</table>

APACHE, The Acute Physiologic and Chronic Health Evaluation; IQR, interquartile range; NR, not report; SAPS, Simplified Acute Physiologic Score; SOFA, Sequential Organ Failure Assessment; SD, standard derivation.
organ function through a peripheral vascular circulation recovery [35]. Fourth, corticosteroids also improve micro-circulation and tissue perfusion in septic shock [36]. This effect may be mediated by non-transcriptional activation of endothelial nitric oxide synthase [37] and stabilization of capillary permeability. Corticosteroids have been shown to increase renal blood flow, inhibit inducible nitric oxide synthase activation in the renal cortex, prevent the appearance of cortical microcirculatory hypoxic areas, improve renal oxygen delivery, and significantly restore oxygen consumption, kidney function and tubular sodium reabsorption to baseline values [38]. Fifth, corticosteroids attenuate inflammation in various organs in patients with sepsis. For example, they have been shown to dramatically inhibit the nuclear factor-kappa B in peripheral blood and pulmonary mononuclear cells [38]. They also stimulate the albumin synthesis and decrease pro-inflammatory mediators such as interleukin-1 and interleukin-6 [39].

As for mortality at longest follow up, we did not find any significant advantage of corticosteroids over placebos. The longest follow up time in the included studies varied from right out of hospital to 1 year after hospital discharge, during which we could not sure the exact reason for death.

However, our meta-analysis also indicated that corticosteroids could not further prevent the occurrence and reoccurrence of septic shock. First of all, only two studies involving 494 patients were eligible for the analysis of occurrence of septic shock; and type II error might exist because of the limited number of patients. Second, the sensitization of the vasculature to vasopressors could be increased by corticosteroids [32]. For this reason, vasopressors were less needed in patients treated with corticosteroids. Because hydrocortisone was tapered in some patients while vasopressors were still necessary, hemodynamic deterioration may be underestimated if the patients were treated with corticosteroids.

Third, the use of corticosteroids might lead to increased risk of secondary infection and sepsis because of inhibiting inflammation, which is commonly known as adverse events [40]. Finally, studies showed that short term use of corticosteroids would lead to a rebound of the systematic inflammatory response [41]. These disadvantages might offset the advantages of corticosteroids, which may account for the result that no significant difference between corticosteroids and placebos was found in the rate of occurrence and reoccurrence of septic shock.

Although all enrolled studies used low dose corticosteroids (<300 mg per day), the exact dose and duration of corticosteroids still varied. Nevertheless, we did not find the optimal dose or duration for reducing the mortality of sepsis. Moreover, our study did not explore the exact initiating time of corticosteroids. However, Studies showed that in patients with septic shock, receiving hydrocortisone for, early initiation of corticosteroids was associated with improved survival. [42]

The conclusions we drew from our meta analysis differed from those of previous analyses. This may be attributed to the fact that we included
more large-sample RCTs published recently [43]. Moreover, we excluded all the studies conducted before 1992 for two reasons. The first reason was that the earliest definition and diagnosis criteria of sepsis were not confirmed until 1992 [11]. In the clinical studies published before 1992, the definition of “sepsis” was not consistent with the one made in 1992. The other reason was that the methods used widely in clinical settings in recent years such as early-goal-directed therapy, which could reduce the mortality of sepsis, were not popular 20 years ago [44]. Moreover, compared with the ones published in 2015 [45] we excluded the studies involving patients with community-acquired pneumonia but not stating clearly whether these patients met the diagnosis criteria of sepsis.

Recently, two large-sample, multicenter RCTs have been published but reported contradictory findings [9,10]. In Annane’s study, hydrocortisone-plus-fludrocortisone could reduce the 90-day mortality, while Venkatesh found no significant difference in the 90-day mortality.

Fig. 5. The 28-day mortality. CI, confidence interval; SD, standard deviation.

Fig. 6. Mortality at longest follow up.

Fig. 7. The occurrence of septic shock.
even though a trend of lower mortality in the hydrocortisone group was identified. Meanwhile, hydrocortisone-plus-fludrocortisone might be more powerful than hydrocortisone alone.

Despite our findings, the present study still has some limitations that needed to be addressed. First of all, no significant heterogeneity was identified in any of the comparisons, but clinical heterogeneity still existed. Although low dose corticosteroids (<300 mg per day) were administrated in all the studies, the exact dose and duration of corticosteroids still varied. We did not find the optimal dose or duration for reducing the mortality of sepsis. Second, in spite of the subgroup analysis on patients with septic shock, the severity of sepsis differed by studies, which could be seen from the APACHE II and SOFA score. Third, our analysis showed that, in general, patients with sepsis could benefit from corticosteroids, but not all patients responded to corticosteroids. Thus, more studies should be done to profile the characteristics of sepsis patients who respond well to corticosteroids.

5. Conclusions

Corticosteroids could reduce the 28-day mortality of both patients with severe sepsis and those with septic shock. However, it did not show any advantage in preventing the occurrence and reoccurrence of septic shock.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2018.11.040.

Abbreviations

APACHE The Acute Physiologic and Chronic Health Evaluation
CENTRAL Cochrane Central Register of Controlled Trials
CI confidence interval
ISI Information Sciences Institute
MD mean difference
RR risk ratio
RCT randomized controlled trial
SAPS Simplified Acute Physiologic Score
SD standard derivation
SOFA Sequential Organ Failure Assessment

Consent for publication
Not applicable.

Availability of data and material
Not applicable.

Competing interests
None of all authors have any financial or non-financial competing interests in this manuscript.

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Author contributions
Y-NN and Y-WW designed the study, drafted the manuscript, conducted literature search and data analysis; Y-NN, Y-ML and B-ML revised the manuscript critically for important intellectual content; Z-AL made the decision to submit the report for publication. All authors read and approved the final manuscript.

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References