Review Article

Reevaluating the Role of Corticosteroids in Septic Shock: An Updated Meta-Analysis of Randomized Controlled Trials

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What Is Known and Objective. To reevaluate the benefits and risks of corticosteroid treatment in adult patients with septic shock.

Methods. This study was performed based on PRISMA guidelines. Randomized controlled trials (RCTs) of corticosteroids versus placebo were retrieved from PubMed, MEDLINE, EMBASE, Web of Science, the Cochrane Central RCTs, and ClinicalTrials.gov from January 1980 to April 2018. We also conducted a trial sequential analysis to indicate the possibility of type I or II errors and calculate the information size. Grading of Recommendations, Assessment, Development and Evaluation approach (GRADE) was applying to assess the certainty of evidence at the primary outcome level.

Results. Twenty-one RCTs were identified and analyzed. Patients treated with corticosteroid had a 7% reduction in relative risk in 28-day all-cause mortality compared to controls (RR 0.93, 95% CI 0.88 to 0.99). However, there were no significant differences for the intensive care unit (ICU) mortality (RR 0.97, 95% CI 0.86 to 1.09) or in-hospital mortality (RR 1.01, 95% CI 0.92 to 1.11). Corticosteroids shortened the length of ICU stay by 1.04 days (RR -1.04, 95% CI -1.72 to -0.36) and the length of hospital stay by 2.49 days (RR -2.49, 95% CI -4.96 to -0.02). Corticosteroids increased the risk of hyperglycemia (RR 1.11, 95% CI 1.06 to 1.16) but not gastroduodenal bleeding (RR 1.06, 95% CI 0.82 to 1.37) or superinfection (RR 1.04, 95% CI 0.94 to 1.15). However, some date on secondary outcomes were unavailable because they were not measured or not reported in the included studies which may cause a lack of power or selective outcome reporting. The information size was calculated at 10044 patients. Trial sequential analysis showed that the meta-analysis was conclusive and the risk of type 2 error was minimal. What Is New and Conclusion. Corticosteroids are likely to be effective in reducing 28-day mortality and attenuating septic shock without increasing the rate of life-threatening complications. TSA showed that the risk of type II error in this meta-analysis was minimal and the result was conclusive.

1. What Is Known and Objective

Septic shock is a life-threatening condition with an extremely high short-term mortality rate ranging from 45% to 50% [1], and half of survivors may suffer from cognitive decline [2]. Several interventions have been suggested to decrease this high rate of morbidity and mortality [3–5]. Corticosteroids have pleiotropic effects in septic shock, including beneficial modulation of the immune response. The use of corticosteroids at the onset of septic shock first became standard case...
in the late 1970s. A half-century later, however, the safety and efficacy of corticosteroids remain controversies compared to the safety and efficacy of other adjunctive therapies [6]. Four landmark studies performed in the 1980s showed no survival benefit associated with steroids treatment for septic shock [7–10]. Nevertheless, more recent studies found potential benefits of steroids, especially regarding earlier reversal of septic shock [11–13].

A recent meta-analysis [14] provided evidence that hydrocortisone infusion or bolus may be more likely than placebo to result in shock reversal. However, no clear evidence regarding the survival benefit of any single corticosteroid or combined corticosteroid treatment regimen was found. In addition, given the 2 recent published reviews on this topic and the multitude of previous reviews, no other meta-analyses have furnished explicit evidence to support or reject the use of corticosteroid. Importantly, the sample size of the previous randomized controlled trials (RCTs) has been insufficient. Recently, the ADRENAL trial [15], a large international study, found no 90-day survival benefits associated with hydrocortisone infusion, but the infusion could speed up recovery when the septic shock was not fatal. However, the other landmark study, APROCCHSS trial [16], found a lower 90-day all-cause mortality among those who received hydrocortisone plus fludrocortisone, and this finding should certainly provoke a review of clinical practice.

Given that these new large RCTs have been published, this updated meta-analysis included these above mentioned RCTs and other RCTs identified during the updated search in order to reevaluate the efficacy and safety of corticosteroid in adults with septic shock.

2. Methods

2.1. Literature Search Strategy. This study was performed according to PRISMA guidelines and showed in Figure S1 [17]. A literature search was systematically conducted in PubMed, MEDLINE, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library from January 1980, because we only found one study from Schumer (1976) [18] on the literature searches for the inferior boundary (1980) and this study caused moderate heterogeneity (from $I^2=2.0\%$, $P=0.43$ to $I^2=30\%$, $P=0.05$). Moreover, based on this paper, it became standard practice in the late 1970s and early 1980s to administer high-dose corticosteroids at the onset of septic shock. The last search was run in April 2018. The search strategy is showed in Table S1. In addition, ongoing and unpublished trials were also sought through ClinicalTrials.gov. We also scanned the references list of each identified article and the references list of previous meta-analyses on the topic [14, 19–23]. There were no restrictions on language. The registration number for this meta-analysis was PROSPEROCRD42018092535. We were unaware of unpublished/ongoing studies during literature searches. In addition, we also presented a clear summary of previous meta-analyses findings, which may be helpful for reference (Table S2).

2.2. Study Selection. All identified titles and abstracts were assessed by two independent reviewers (DZH and XJL). Only studies that were clearly irrelevant were excluded. Disagreements were settled through discussion with a third reviewer (YHL). RCTs comparing the outcome of corticosteroid treatment vs placebo in adult with septic shock were included. The following exclusion criteria were used: (1) non-RCTs, (2) children (<18 years), (3) studies in which both groups received steroids, studies lacking information on the exact treatment regimens, or studies lacking information on the septic shock outcomes, (4) duplicate data, and (5) in vitro or preclinical animal studies. Studies designed to investigate sepsis or severe sepsis but which did not have separate data on septic shock were also excluded, after attempting to obtain the separate data from the authors.

2.3. Outcome. The primary outcomes were 28-day all-cause mortality. The secondary outcomes were as follows: other mortality (intensive care unit [ICU] mortality and in-hospital mortality), duration of mechanical ventilation, the length of ICU and hospital stay, and the incidence of gastrointestinal bleeding, superinfection, and hyperglycemia.

2.4. Data Extraction and Quality Assessment. Data extraction was conducted by two independent reviewers. Relevant data from the eligible studies were extracted by one reviewer (XJL) and checked by the other reviewer (DZH). For each included study, a record of the first author, publication date, number of study sites, location, participant characteristics (number of participants, mean age, and proportion of males), treatment, comparator, and clinical outcomes was extracted. A summary of the recorded patient data is presented in Table 1.

The methodological quality and risk of bias within each individual trial were independently assessed by two reviewers (XJL and HDZ), according to The Cochrane Handbook for Systematic Reviews of Interventions [24]. The disagreements were settled by discussion between the reviewers and adjudicated by a third reviewer (LYH). We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the overall quality of evidence for primary outcome measure [25], which was presented in Figure S2.

2.5. Statistical Analysis. We analyzed the data by using Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata version 14 (Stata Corp LP, College Station, TX, USA). Relative risk (RR) with 95% confidence interval (CI) was used for the dichotomous outcomes and weighted mean difference (MD) with 95% confidence interval was used for the continuous outcomes. The statistical variables $Q$ and $I^2$ were used to compare the heterogeneity among studies. $I^2$ values <25%, 25–50%, and >50% were considered to represent low, moderate, and severe heterogeneity. A fixed-effects model was applied if there was minimal significant heterogeneity. Otherwise, a random-effects model was applied. In addition, funnel plots and Egger’s and Begg’s tests were used to assess publication bias. Moreover, several subgroup analyses were conducted to identify potential differences in treatment effects across
## Table 1: Baseline characteristics of included studies and population.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Location</th>
<th>Design</th>
<th>No. of research centres</th>
<th>No. of participants</th>
<th>Participants</th>
<th>Age corticosteroids vs placebo</th>
<th>Male corticosteroids vs placebo</th>
<th>Interventions</th>
<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sprung et al, 1984</td>
<td>USA</td>
<td>Multicentre double blind randomised placebo controlled trial</td>
<td>2</td>
<td>59</td>
<td>Adults Vasopressor dependent shock</td>
<td>55(4) vs 48(4)</td>
<td>36% vs 10%</td>
<td>Dexamethasone 6mg/kg Methylprednisolone 30mg/kg Doses could be repeated</td>
<td>Hospital mortality, shock reversal, complications of septic shock, and adverse events</td>
</tr>
<tr>
<td>Bone et al, 1987</td>
<td>USA</td>
<td>Multicentre double blind randomised placebo controlled trial</td>
<td>19</td>
<td>382</td>
<td>Adults With sepsis (n=234) OR Septic shock (n=148)</td>
<td>53(16) vs 53.7(16)</td>
<td>NA</td>
<td>Methylprednisolone 30mg/kg Every 6 hours Duration: 24hrs</td>
<td>For septic shock: shock reversal, 14-d mortality, and adverse events</td>
</tr>
<tr>
<td>Luce et al, 1988</td>
<td>USA</td>
<td>Single-centre double blind randomised placebo controlled trial</td>
<td>1</td>
<td>75</td>
<td>Adults (n=75) Sepsis AND septic shock</td>
<td>50(2.5) vs 53(2.5)</td>
<td>68.4% vs 83.8%</td>
<td>Methylprednisolone 30mg/kg every 6hrs Duration: 1 day</td>
<td>Prevention of ARDS and hospital mortality</td>
</tr>
<tr>
<td>Bollaert et al, 1998</td>
<td>France</td>
<td>Multicentre double blind randomised placebo controlled trial</td>
<td>2</td>
<td>41</td>
<td>Adults Vasopressor AND ventilator dependent septic shock</td>
<td>66(21.83) vs 56(34.81)</td>
<td>68.2% vs 63.2%</td>
<td>Hydrocortisone 100mg Every 8hrs Duration: 5 days then tapered over 6 days</td>
<td>Shock reversal, 28-d, ICU and hospital mortality, improvement in haemodynamics, ICU and hospital LoS, and adverse events</td>
</tr>
<tr>
<td>Briegel et al, 1999</td>
<td>Germany</td>
<td>Single-centre double blind randomised placebo controlled trial</td>
<td>1</td>
<td>40</td>
<td>Adults Vasopressor AND Ventilator dependent septic shock</td>
<td>47(4) vs 51(5)</td>
<td>45% vs 60%</td>
<td>Hydrocortisone 100mg loading 0.18mg/kg/hr maintenance Duration: Until shock reversal, then tapered off</td>
<td>Shock reversal, 28-d, hospital and ICU mortality, Improvement in haemodynamics, ICU and hospital LoS, and adverse events</td>
</tr>
<tr>
<td>Chawla et al, 1999</td>
<td>USA</td>
<td>Single-centre double blind randomised placebo controlled trial</td>
<td>1</td>
<td>44</td>
<td>Adults Vasopressor dependent shock</td>
<td>NA</td>
<td>NA</td>
<td>Hydrocortisone 100mg Every 8hrs Duration: 3 days then tapered over 4 days</td>
<td>Shock reversal, 28-d and hospital mortality, improvement in haemodynamics, ICU LoS, and adverse events</td>
</tr>
<tr>
<td>Annane et al, 2002</td>
<td>France</td>
<td>Multicentre double blind randomised placebo controlled trial</td>
<td>19</td>
<td>300</td>
<td>Adults Vasopressor AND Ventilator dependent septic shock</td>
<td>60(17) vs 62(15)</td>
<td>70% vs 64%</td>
<td>Hydrocortisone 50mg Every 6hrs AND Fludrocortisone 50mcg Every 24hrs Duration 7 days</td>
<td>28-d, ICU, hospital and 1-y mortality, shock reversal, organ system failure free days, ICU and hospital LoS, and adverse events</td>
</tr>
<tr>
<td>Study (year)</td>
<td>Location</td>
<td>Design</td>
<td>No. of research centres</td>
<td>No. of participants</td>
<td>Participants</td>
<td>Age corticosteroids vs placebo</td>
<td>Male corticosteroids vs placebo</td>
<td>Interventions</td>
<td>Clinical outcomes</td>
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<tr>
<td>Oppert et al, 2005</td>
<td>Germany</td>
<td>Single-centre double blind randomised placebo controlled trial</td>
<td>1</td>
<td>40</td>
<td>Adults</td>
<td>Vasopressor dependent septic shock</td>
<td>59 vs 47</td>
<td>72% vs 83%</td>
<td>Hydrocortisone Load: 50 mg Maint: 0.18 mg/kg/hr Duration: until stopping vasopressor 0.06 mg/kg/hr for 1 day then reduced by 0.02 mg/kg/hr every day</td>
</tr>
<tr>
<td>Mussack et al, 2005</td>
<td></td>
<td>Single-centre double blind randomised placebo controlled trial</td>
<td>1</td>
<td>24</td>
<td>Adults</td>
<td>Vasopressor dependent septic shock</td>
<td>41(30,52) vs 54 (47,57)</td>
<td>58% vs 50%</td>
<td>Hydrocortisone Load: 100 mg Maint: 0.18 mg/kg/hr for Duration 6 days.</td>
</tr>
<tr>
<td>Cicarelli et al, 2007</td>
<td>Brazil</td>
<td>Single-centre double blind randomised placebo controlled trial</td>
<td>1</td>
<td>29</td>
<td>Adults</td>
<td>Vasopressor dependent septic shock</td>
<td>69(11) vs 61(15)</td>
<td>42.9% vs 64.9%</td>
<td>Dexamethasone 0.2 mg/kg Every 36 hrs Duration: 3 doses</td>
</tr>
<tr>
<td>Sprung et al, 2008</td>
<td>Europe</td>
<td>Multicentre double blind randomised placebo controlled trial</td>
<td>52</td>
<td>499</td>
<td>Adults</td>
<td>Septic shock</td>
<td>63(14) vs 63(15)</td>
<td>34% vs 33%</td>
<td>Hydrocortisone 50 mg every 6 hrs – 5 days 50 mg every 12 hrs – 3 days 50 mg every day – 3 days</td>
</tr>
<tr>
<td>Hu et al, 2009</td>
<td>China</td>
<td>Single-centre double blind randomised placebo controlled trial</td>
<td>1</td>
<td>77</td>
<td>Adults</td>
<td>Septic shock</td>
<td>56.17(33.85) vs 54.91 (35.36)</td>
<td>61% vs 64%</td>
<td>Hydrocortisone 50 mg every 6 hrs for 7 days 50 mg every 8 hrs for 3 days 50 mg every 12 hrs for 2 days 50 mg every 24 hrs for 2 days</td>
</tr>
<tr>
<td>Arabi et al, 2010</td>
<td>Saudi Arabia</td>
<td>Single-centre double blind randomised placebo controlled trial</td>
<td>1</td>
<td>75</td>
<td>Adults</td>
<td>Liver cirrhosis and septic shock</td>
<td>60.6(12.6) vs 59.3(12.2)</td>
<td>44% vs 44%</td>
<td>Hydrocortisone 50 mg Every 6 hrs Duration: Until shock resolution then tapered by 10 mg every 48 hrs until stopped</td>
</tr>
<tr>
<td>Gordon et al, 2014</td>
<td>UK</td>
<td>Multicentre prospective open-label randomised controlled pilot trial</td>
<td>4</td>
<td>61</td>
<td>Adults</td>
<td>Septic shock treated with vasopressor</td>
<td>61 (54, 68) vs 60 (48, 76)</td>
<td>58% vs 60%</td>
<td>Hydrocortisone 50 mg Every 6 hours for 5 days Every 15 hrs for 3 days Every 24 hrs for 3 days</td>
</tr>
</tbody>
</table>
Table 1: Continued.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Location</th>
<th>Design</th>
<th>No. of research centres</th>
<th>No. of participants</th>
<th>Participants</th>
<th>Age corticosteroids vs placebo</th>
<th>Male corticosteroids vs placebo</th>
<th>Interventions</th>
<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piva et al, 2015</td>
<td>Portugal</td>
<td>Multicentre double blind randomised placebo controlled trial</td>
<td>?</td>
<td>1695</td>
<td>Adults Septic shock treated with vasopressor</td>
<td>For DrotAA + steroid vs DrotAA + steroid: 64.4 (52.5, 74.2) vs 66.2 (55.4, 76.0). For placebo + steroid vs placebo: 66.2 (54.5, 76.6) vs 63.6 (51.4, 75.2)</td>
<td>For DrotAA + steroid vs DrotAA: 56.4% vs 59.2%. For placebo + steroid vs placebo: 54.1% vs 56.1%</td>
<td>DrotAA 24 μg/kg/hour and steroids at baseline. Placebo and steroids at baseline</td>
<td>28-d and 90-d mortality; SOFA Score</td>
</tr>
<tr>
<td>Gordon et al, 2016</td>
<td>UK</td>
<td>Multicentre double blind randomised placebo controlled trial</td>
<td>18</td>
<td>409</td>
<td>Adults Septic shock</td>
<td>For vasopressin + hydrocortisone vs vasopressin + Placebo: 66 (57.76) vs 67 (59.77). For norepinephrine + Hydrocortisone vs Norepinephrine + Hydrocortisone: 63 (52.76) vs 63 (52.76).</td>
<td>For vasopressin + hydrocortisone vs vasopressin + Placebo: 58% vs 50%. For norepinephrine + Hydrocortisone vs Norepinephrine + Hydrocortisone: 61% vs 63%.</td>
<td>hydrocortisone 50 mg Every 6 hours for 5 days Every 12 hours for 3 days Once daily for 3 days</td>
<td>kidney failure–free days, rates and duration of renal replacement therapy, 28-d, ICU and hospital mortality; SOFA Score, and adverse events</td>
</tr>
<tr>
<td>Tongyoo et al, 2016</td>
<td>Bangkok</td>
<td>Single-centre double blind randomised placebo controlled trial</td>
<td>1</td>
<td>197</td>
<td>Adults With severe sepsis (n=43) OR Septic shock (n=154)</td>
<td>64.5 (17.3) vs 64.3 (16.0)</td>
<td>51% vs 51.5%</td>
<td>hydrocortisone 50 mg Every 6 h daily for 7 days.</td>
<td>28-d and 69-d mortality and 28-day survival without organ support</td>
</tr>
<tr>
<td>Lv et al, 2017</td>
<td>China</td>
<td>Single-centre double blind randomised placebo controlled trial</td>
<td>1</td>
<td>118</td>
<td>Adults Septic shock treated with norepinephrine</td>
<td>68.8 (12.6) vs 64.8 (16.7)</td>
<td>55.2% vs 61.7%</td>
<td>hydrocortisone 200 mg/d for 6 days 100 mg/d for 3 days 50 mg/d for 3 days</td>
<td>28-d and hospital mortality, shock reversal, ICU and hospital LoS</td>
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</table>


<table>
<thead>
<tr>
<th>Study (year)</th>
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<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doluee et al, 2018</td>
<td>Iran</td>
<td>Single-centre double blind randomised placebo controlled trial</td>
<td>1</td>
<td>160</td>
<td>Adults refractory septic shock treated with vasopressor</td>
<td>67.13(10.92) vs 66.93(11.2)</td>
<td>58.8% vs 41.3%</td>
<td>Hydrocortisone 50 mg iv every 6 hours for 7 days</td>
<td>28-d mortality and return of shock</td>
</tr>
<tr>
<td>Annane et al, 2018</td>
<td>France</td>
<td>Multicentre double blind randomised placebo controlled trial</td>
<td>18</td>
<td>1241</td>
<td>Septic shock treated with vasopressor</td>
<td>66(14) vs 66(15)</td>
<td>65.5% vs 67.7%</td>
<td>Hydrocortisone 50 mg/d for 6 and fludrocortisone days 50μg once daily for 7 days</td>
<td>90-d, 28-d, 180-d, ICU discharge and hospital mortality, shock reversal, the time to weaning from mechanical ventilation, mechanical ventilation free days, ICU and hospital LoS, SOFA Score, and adverse events</td>
</tr>
<tr>
<td>Venkatesh et al, 2018</td>
<td>Australia and New Zealand</td>
<td>Multicentre double blind randomised placebo controlled trial</td>
<td>3</td>
<td>3658</td>
<td>Septic shock treated with vasopressor and undergoing mechanical ventilation</td>
<td>62.3(14.9) vs 62.7 (15.2)</td>
<td>60.4% vs 61.3%</td>
<td>Hydrocortisone 200 mg/d for 7 days</td>
<td>90-d, 28-d, ICU and hospital mortality, shock reversal, the frequency and duration of mechanical ventilation and RRT, ICU and hospital LoS, receipt of blood transfusion and adverse events</td>
</tr>
</tbody>
</table>
the trials based on treatment factors (i.e., dose, duration, and whether a concomitant mineralocorticoid was used), date of publication, and sample size. Leave-one-out sensitivity analysis was also performed to evaluate the robustness of the results. All tests were two-tailed, and \( P < 0.05 \) was considered statistically significant in the meta-analysis.

2.6. Trial Sequential Analysis (TSA). We performed a TSA for one of the primary outcomes (28-day all-cause mortality) using TSA software version 0.9.5.10 Beta (Copenhagen Trial Unit, Copenhagen, Denmark). We planned to maintain an overall risk of a type I error of 5% and a power of 80%. The risk of type I error was controlled by using the O’Brien-Fleming \( \alpha \)-spending function, which indicates statistical significance if a conventional Z-curve crosses the O’Brien-Fleming \( \alpha \)-spending boundaries. The risk of type II error was controlled using the \( \beta \)-spending function and futility boundaries.

3. Results

3.1. Number of Included Studies. A flowchart of the literature search is shown in Figure 1. The literature search yielded 5468 articles, of which 76 underwent a full-text review. Of these, 55 were further excluded. Consequently, 21 RCTs were finally included.

3.2. Study Characteristics and Interventions. A total of 9,043 patients were included. Of these, corticosteroids were given to 4,532 and 4,511 served as controls. The mean patient age ranged from 47 ± 4 to 69 ± 11 years. Ten trials [7, 9, 11, 13, 15, 16, 26–29] were multicenter, and 11 trials [10, 12, 30–38] were single center. Eighteen trials [7, 11–13, 15, 16, 26–35, 37, 38] included only patients with septic shock, while 3 trials [9, 10, 36] included patients with severe sepsis or septic shock, and separate data for the septic shock patients were available. The most common corticosteroid used was hydrocortisone (200–300 mg per day in divided doses), which was used in 14 trials. Hydrocortisone alone was used in 14 trials [12, 13, 15, 26, 27, 29–32, 34–38] while only 2 trials [11, 16] evaluated the influence of concomitant use of fludrocortisones (50 mg per day). Lastly, 18 trials [11–13, 15, 16, 26–38] investigated a prolonged course of low-dose intravenous hydrocortisone while 3 trials [7, 9, 10] investigated a short course of high-dose corticosteroids.

3.3. Assessment of Study Quality and Publication Bias. The methodological quality assessment results for each included study are outlined graphically in Figure 2. There was no apparent systematic publication bias among the included trials, based on the result of Egger’s test. The \( P \) value was 0.891 for 28-day mortality. The funnel plot was relatively symmetrical (Figure 3).

3.4. All-Cause Mortality. Data on 28-day all-cause mortality were available in all trials, while data on 90-day mortality were only available in 4 trials. In addition, 9 trials recorded ICU mortality and 13 trials recorded in-hospital mortality. Participants taking corticosteroids had a 7% reduction in relative risk in 28-day all-cause mortality compared to controls, according to a fixed-effects model (RR 0.93, 95% CI 0.88 to 0.99, \( P = 0.02 \)), with minimal heterogeneity (\( I^2 = 2.0\% \), \( P = 0.43 \)) (Figure 4). However, there were no significant differences between the two groups regarding ICU mortality (RR 0.97, 95% CI 0.86 to 1.09, \( P = 0.56 \); \( I^2 = 0\% \), \( P = 0.49 \)) or in-hospital mortality (RR 1.01, 95% CI 0.92 to 1.11, \( P = 0.85 \); \( I^2 = 0\% \), \( P = 0.80 \)) (Figure S3).

3.5. Length of ICU or Hospital Stay. We were able to extract data on length of ICU stay from 12 trials and length of hospital stay from 7 trials. There were two studies that presented the relevant data as medians and interquartile ranges. We treated the median as similar as the mean and the width of the interquartile range as similar as approximately 1.35 standard deviations, according to the Cochrane Handbook. Compared to the control group, the corticosteroid group had a shortened length of ICU stay, by 1.04 days, in a fixed-effects model (MD -1.04, 95% CI -1.72 to -0.36, \( P = 0.003 \)), with low heterogeneity across studies (\( I^2 = 25\% \), \( P = 0.19 \)). In addition, the corticosteroid group had tendency to have a shortened length of hospital stay, by 2.49 days, in a fixed-effects model (MD -2.49, 95% CI -4.96 to -0.02, \( P = 0.05 \)), with no heterogeneity across studies (\( I^2 = 0\% \), \( P = 0.75 \)) (Figure S4).

3.6. Mechanical Ventilation. Data on the number of mechanical ventilation-free days and the median time to cessation of initial mechanical ventilation were available from 4 trials. Participants taking corticosteroids had significantly more mechanical ventilation-free days than the controls, based on a fixed-effects model (RR 1.07, 95% CI 0.97 to 2.08, \( P = 0.04 \)). Participants taking corticosteroids also had a shorter duration of initial mechanical ventilation compared to the controls, based on a fixed-effects model (MD -0.89, 95% CI -1.60 to -0.18, \( P = 0.01 \)). For both analyses, there was no heterogeneity across studies (\( I^2 = 0\% \), \( P = 0.91 \)) (Figure S5).

3.7. Adverse Events of Therapy. Gastrointestinal bleeding (based on data from 10 trials) was observed in 102 of 3032 (3.36%) participants in the corticosteroid group vs. 94 of 2999 (3.13%) participants in the control group (RR 1.06, 95% CI 0.82 to 1.37, \( P = 0.66 \), fixed-effects model), with low heterogeneity across studies (\( I^2 = 8\% \), \( P = 0.37 \)). Superinfections (based on data from 12 trials) were observed in 639 of 3176 (20.12%) participants in the corticosteroid group vs. 729 of 3684 (19.78%) participants in the control group (RR 1.04, 95% CI 0.94 to 1.15, \( P = 0.41 \), fixed-effects model), with no heterogeneity across studies (\( I^2 = 0\% \), \( P = 0.61 \)). Furthermore, the incidence of hyperglycemia (based on data from 8 trials) in the corticosteroid group was higher than in the control group (30.98% vs 28.33%, RR 1.11, 95% CI 1.06 to 1.16, \( P < 0.001 \), fixed-effects model), with no heterogeneity across studies (\( I^2 = 0\% \), \( P = 0.63 \)) (Figure S6).

3.8. Subgroup Analysis. The results of several subgroup analyses are shown in Table 2. In trials evaluating long courses
<table>
<thead>
<tr>
<th>Subgroup Description</th>
<th>Studies, n</th>
<th>Patients, n</th>
<th>Random Effects</th>
<th>Fixed Effects</th>
<th>P</th>
<th>$I^2$, %</th>
<th>Heterogeneity P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>21</td>
<td>9043</td>
<td>0.94(0.89,1.00)</td>
<td>0.93(0.88,0.99)</td>
<td>0.05</td>
<td>2</td>
<td>0.43</td>
</tr>
<tr>
<td>Long course of low-dose corticosteroids</td>
<td>18</td>
<td>8665</td>
<td>0.93(0.87,0.98)</td>
<td>0.92(0.86,0.98)</td>
<td>0.01</td>
<td>0</td>
<td>0.52</td>
</tr>
<tr>
<td>Short course of high-dose corticosteroid</td>
<td>3</td>
<td>378</td>
<td>1.15(0.94,1.42)</td>
<td>1.17(0.94,1.46)</td>
<td>0.15</td>
<td>0</td>
<td>0.82</td>
</tr>
<tr>
<td>before 21s</td>
<td>6</td>
<td>503</td>
<td>0.97(0.74,1.26)</td>
<td>1.01(0.83,1.23)</td>
<td>0.03</td>
<td>0</td>
<td>0.64</td>
</tr>
<tr>
<td>after 21s</td>
<td>15</td>
<td>8540</td>
<td>0.93(0.88,0.99)</td>
<td>0.93(0.87,0.99)</td>
<td>0.8</td>
<td>0</td>
<td>0.16</td>
</tr>
<tr>
<td>Hydrocortisone concomitant fludrocortisone therapy</td>
<td>2</td>
<td>1540</td>
<td>0.88(0.78,0.99)</td>
<td>0.87(0.78,0.99)</td>
<td>0.03</td>
<td>0</td>
<td>0.79</td>
</tr>
<tr>
<td>Hydrocortisone alone therapy</td>
<td>14</td>
<td>7072</td>
<td>0.95(0.89,1.02)</td>
<td>0.94(0.87,1.01)</td>
<td>0.09</td>
<td>0</td>
<td>0.49</td>
</tr>
<tr>
<td>Sample size $\geq$ 400</td>
<td>3</td>
<td>6594</td>
<td>0.90(0.83,0.97)</td>
<td>0.90(0.83,0.98)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.67</td>
</tr>
<tr>
<td>Sample size $&lt; 400$</td>
<td>18</td>
<td>2448</td>
<td>0.99(0.91,1.08)</td>
<td>0.99(0.90,1.08)</td>
<td>0.77</td>
<td>0</td>
<td>0.46</td>
</tr>
</tbody>
</table>
Identification

Records identified through database searching (n= 5468)

Studies excluded for duplication (n= 1266)

Screening

Records screened (n= 4202)

Studies excluded based on the title and abstract (n= 4126)

Eligibility

Full-text articles assessed for eligibility (n= 76)

Studies excluded based on the

Quasi-randomized controlled trials: 3
Not looked at septic shock (only to sepsis, SIRS or ARDS): 33
Both intervention groups received
steroids: 6
Outcome not relevant: 5
Separate data on septic shock not
available: 7
Published only as an abstract: 1

Studies included in

meta-analysis (n= 21)

Figure 1: Study flow diagram.

of low-dose corticosteroids, there was a clear corticosteroid treatment effect on 28-day mortality (RR 0.93, 95% CI 0.87 to 0.98, P=0.01), with no heterogeneity across trials (I²=0%, P=0.52). In trials evaluating hydrocortisone plus fludrocortisone, there was a clear corticosteroid treatment effect on 28-day mortality (RR 0.87, 95% CI 0.78 to 0.99, P=0.03), with no heterogeneity across trials (I²=0%, P=0.79). In trials published in or after 2000, there was a beneficial corticosteroid treatment effect on 28-day mortality (RR 0.93, 95% CI 0.88 to 0.99, P=0.03), with no heterogeneity across trials (I²=0%, P=0.64). In trials with sample sizes >400, there was also a beneficial corticosteroid treatment effect on 28-day mortality (RR 0.90, 95% CI 0.83 to 0.98, P=0.01), with no heterogeneity across trials (I²=0%, P=0.67). However, subgroup analyses of trials evaluating short courses of high-dose corticosteroids, trials evaluating hydrocortisone without fludrocortisone, trials published before 2000, and trials with sample size ≤400 showed no survival benefits regarding 28-day mortality (Figure S7). Indeed, the subgroup analyses of sample size and hydrocortisone concomitant fludrocortisone therapy were not preregistered. A new large RCT [16] that accessed hydrocortisone plus fludrocortisone for adults with septic shock was published after registration. In addition, during data extraction, sample size of different studies showed huge fluctuations ranged from 24 (Mussack 2005 [32]) to 3658 (Venkatesh 2018 [15]) and different survival benefits on subgroup analysis. Therefore, we then believed it is significant to supply sample size and hydrocortisone concomitant fludrocortisone therapy into subgroup analysis even after registration.

3.9. Trial Sequential Analysis. We estimated the information size for the analyses based on the achievement of 80% power and a 7% relative risk reduction between the corticosteroid and control groups. The incidence in the control group used in the estimation of the information size was 40%, which was estimated using a random-effects meta-analysis model. The assumed relative risk reduction of 7% in the corticosteroid group was the result of a fixed-effects model (Figure 5). TSA showed that the meta-analysis was conclusive and the risk of type II error was minimal.

4. Discussion

The present updated meta-analysis demonstrated the following results. First, corticosteroid treatment was associated with a 7% reduction in relative risk in 28-day all-cause mortality, and corticosteroid treatment may attenuate septic shock, as reflected in shorter hospital or ICU stays and shorter duration of mechanical ventilation. However, there is no clear significant corticosteroid effect on ICU or in-hospital mortality. Finally, corticosteroids increase the risk of developing hyperglycemia, but no significant differences in the incidence of gastrointestinal bleeding or superinfection were found.

Previous meta-analyses [14, 22, 39] have evaluated the effect of corticosteroids on mortality among patients with septic shock, but they did not find clear evidence that corticosteroids could reduce 28-day all-cause mortality. Our conclusion contrasts with the conclusion of these previous meta-analyses, suggesting beneficial effects related to the use of corticosteroids. The two major reasons for the contrasting conclusions were as follows. First, this analysis was limited to only RCTs and patients with septic shock, which may contrast with the inclusion criteria of other meta-analyses. For example, a meta-analysis by Sligl et al. [22] from 2009 included 8 studies, of which 2 (by Levy et al. [40] and Raurich et al. [41]) were retrospective cohort study and were excluded.
Figure 2: Risk of bias summary and graph in each domain for individual studies. (Green + = adequate. Red - = inadequate. Yellow? = unclear). Other biases refer to either academic or funding bias.
Dose hydrocortisone has become ever more common in how corticosteroids are administered. In particular, lower-dose hydrocortisone has become ever more common [49].

In the modern era, there has been significant evolution of evidence [50]. Thus, we divided the studies according to whether they were published before or during the 21st century, as well as whether they involved a long course of low-dose or a short course of high-dose corticosteroid treatment. Subgroup analysis showed both post-21st century treatment and long courses of low-dose corticosteroids decreased 28-day all-cause mortality. However, current clinical practice guidelines on the use of hydrocortisone for septic shock still indicate that the associated evidence is weak due to the low-quality nature of evidence [50].

In addition, fludrocortisone has been previously shown to be ineffective [51]. In contrast, our subgroup analysis of hydrocortisone used concomitantly with fludrocortisone showed a survival benefit (RR 0.87, 95% CI 0.78-0.99, P=0.03). These findings are in accordance with the findings of the first trial that added fludrocortisone to hydrocortisone in order to provide additional mineralocorticoid potency (GER-Inf-05) [11]. This trial showed significant survival benefit from a 28-day course of hydrocortisone plus fludrocortisone compared to placebo. Similarly, a more recent second trial (APROCCHS), involving 1241 adults with septic shock, showed lower 90-day all-cause mortality among patients who received hydrocortisone plus fludrocortisone compared to placebo. The number of relevant studies on hydrocortisone plus fludrocortisone remains insufficient. Hence, there continues to be no conclusive evidence that this combination treatment could be used as a routine treatment in adult patients with septic shock.

In terms of the complications of corticosteroids, we obtained similar results to previous studies [19, 22, 23] in that corticosteroids were shown to increase blood glucose levels. However, corticosteroids did not increase the risk of superinfection or gastrointestinal bleeding. These results may be important for clinical practice because corticosteroids could be useful if they could attenuate septic shock while not significantly increasing the risk of adverse events. However, the trial sample sizes related to the adverse events analysis were small, so additional trials with increased sample sizes are needed to provide further evidence.

The present study had several limitations. First, because different grading systems were used to compare disease severity among the included trials, it was difficult to evaluate the between-trial differences in disease severity, which may have caused heterogeneity. Second, one included trial [31] was published only as an abstract. Third, the effects on heterogeneity of different sources of infection and different primary causes of septic shock were unclear. Fourth, the sample sizes were still insufficient and the data on some reported outcomes were not fully available. Finally, some date on secondary outcomes were missing because they were not measured or no reported in the included studies, which may cause a lack of power or selective outcome reporting. However, where possible, if missing data are encountered, we will attempt to contact the individual study authors for additional information, if not, we had to make the results with the help of core outcome set existed in the field [20]. We believed such a core outcome set could be further developed. Despite these limitations, this meta-analysis included the new large RCTs and was restricted to only adult patients with
5. What Is New and Conclusion

Treatment with corticosteroids can decrease the risk of 28-day mortality and attenuate septic shock without significantly increasing life-threatening complications. Furthermore, TSA showed that the risk of type II error in this meta-analysis was minimal and the result was conclusive.

Disclosure

X.-J. Lian, D.-Z. Huang, Y.-S. Cao, and Y.-X. Wei are considered as co-first authors. The abstract of the manuscript has been presented in Chinese Critical Care Congress 2018.
Conflicts of Interest
The authors declare that they have no conflicts of interest.

Authors’ Contributions
X.-J. Lian contributed to literature search, study selection data collection, and statistical analysis, as well as writing the manuscript. D.-Z. Huang contributed to literature search, study selection, and data collection. Y.-S. Cao was involved in statistical analysis. Y.-X. Wei was involved in assisting in editing the manuscript. Y.-H. Liu and S.-H. Wang were involved in conceiving the idea for the study design and contributed to quality assessment of studies and critical revision of the manuscript. All authors contributed to critical revision of the article and approved the final manuscript.

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Supplementary Materials
Figure S1: PRISMA Checklist. Figure S2: summary of findings. Figure S3: forest plots of comparison corticosteroids versus control of ICU mortality and hospital mortality. Figure S4: forest plots of length of hospital stay and ICU stay for all participants. Figure S5: forest plots of duration of mechanical ventilation and mechanical ventilation-free days for all participants. Figure S6: forest plots of comparison corticosteroids versus control of adverse events. Figure S7: forest plots of comparison corticosteroids versus control of 28-day all-cause mortality based on subgroups. (Supplementary Materials)

References


