REVIEW ARTICLE

Corticosteroids in Septic Shock Treatment: A Systematic Review of Efficacy and Side Effects

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Abstract

Septic shock (SS) is a critical condition with high mortality rates ranging from 27 to 54% in intensive care units (ICU). This systematic review aimed to evaluate the effects of corticosteroids on SS treatment, with a focus on mortality rates, ICU stay duration, shock reversal, and potential side effects. A comprehensive literature search was conducted using PubMed, Scopus, and the Web of Science, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Six studies were selected for the systematic review, including meta-analyses of randomized controlled trials. The results showed that corticosteroids, particularly low-dose hydrocortisone, reduced 28-day mortality, ICU admissions, and hospital mortality. Corticosteroids also improved shock reversal, increased vasopressor-free days, and shortened the ICU stay. However, their use was associated with increased risks of hyperglycemia and hypernatremia. The optimal daily dose for mortality reduction was approximately 260 mg of hydrocortisone or its equivalent. While corticosteroids show promise in managing SS, their use remains controversial due to varied outcomes across studies. Personalized treatment, considering factors such as timing, dosage, and specific corticosteroids, is necessary to optimize the benefits and reduce risks. Further research is required to determine the optimal corticosteroid protocols and effectiveness of adjunct treatments.

Key words: Corticosteroids, intensive care unit stay, mortality, sepsis, septic shock

INTRODUCTION

Sepsis and septic shock (SS) are critical medical conditions resulting in high mortality rates. The sepsis incidence can reach 35%, with mortality rates in intensive care units (ICU) ranging from 27% to 54% for sepsis and SS, respectively.[1] SS involves severe sepsis and sepsis-induced hypotension that persist despite adequate fluid resuscitation, potentially leading to organ perfusion insufficiency and significant morbidity and mortality.[2]

Sepsis is a systemic infection response that can progress to severe sepsis and SS, causing significant morbidity and mortality.[3] This results in high ICU death rates, ranging from 27% for sepsis to 54% for SS, and occurs in approximately 35% of cases.[1] Despite the evaluation of many new treatments, few have been adopted in clinical practice.[1] Management of severe sepsis and SS follows the Surviving Sepsis Campaign guidelines, which emphasize prompt diagnosis, hemodynamic optimization, rapid infection source identification, and appropriate antibiotic use as critical strategies.[1] Recent studies have suggested that microbial burden is the primary factor in mortality and

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shock progression, highlighting the need for optimized antimicrobial therapy for improved results.[4]

The timing of SS onset may indicate the prognosis of severe sepsis. Delayed onset correlates with increased hospital mortality, providing additional mortality risk stratification for patients with specific APACHE II scores.[5] Patients undergoing cardiovascular surgery are at a higher risk of developing SS post-admission, whereas patients undergoing neurosurgery exhibit a lower likelihood.[5]

SS develops when the host's initial response to infection is amplified and dysregulated, causing severe circulatory and cellular/metabolic abnormalities.[6] Its pathophysiology involves complex cascades that release pro and anti-inflammatory mediators, leading to vasodilation, myocardial depression, and microcirculatory dysfunction.[6]

Timely diagnosis and rapid treatment are crucial for improving the outcomes of SS. Management typically includes early goal-directed therapy, infection source control, and hemodynamic support using fluids and vasopressors.[6,7] Despite advancements in critical care, SS mortality remains high, highlighting the need for further research on the underlying mechanisms and innovative therapies.[8]

The treatment of severe sepsis and SS followed the Surviving Sepsis Campaign guidelines, focusing on prompt diagnosis, hemodynamic optimization, rapid focus identification, and appropriate antibiotic administration.[1] Early goal-directed therapy, including fluid resuscitation and timely antimicrobial administration, significantly reduces mortality.[9] Recent advancements include the use of activated protein C in high-risk patients, the evaluation of cortisol responses, and the maintenance of normal glucose levels.[10] An alternative approach suggests that the optimized selection, dosing, and delivery of potent antimicrobial therapy may be more critical, identifying microbial burden as the primary factor driving mortality and progression to irreversible shock.[4]

SS involves circulatory disruption requiring vasopressin to maintain a mean arterial pressure of at least 65 mmHg and a lactate level of >2 mmoL/L or 18 mg/dL.[11] A lactate level of >2 mmoL/L indicates hypoperfusion, highlighting its importance. In sepsis, macrophages are activated by toxins, endotoxins, T cells, interferon-gamma, and superantigens. The role of corticosteroids in sepsis treatment has also been explored.[12] Corticosteroids function by suppressing nuclear factor kappa beta and reducing inflammatory cytokines, such as tumor necrosis factor-α, interleukin (IL-1), and IL-6. They also inhibit inflammatory cell migration and lower the levels of endothelial adhesion molecules, prostaglandins, and chemokines. Despite their anti-inflammatory benefits, the role of corticosteroids in sepsis and SS management remains controversial, with studies reporting inconsistent results regarding their administration, dosage, timing, and type. This review aimed to systematically evaluate the effects of corticosteroids on SS treatment, focusing on their effects on mortality rate, ICU stay duration, shock reversal, and potential side effects.

MATERIALS AND METHODS

This study conducted a systematic review of corticosteroid use in SS treatment with the aim of assessing its impact on patient outcomes, such as mortality rates, ICU stay duration, and adverse effects such as hyperglycemia and hypernatremia. The methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13]

A search was performed in PubMed, Scopus, and Web of Science using keywords including "sepsis," "septic shock," "corticosteroids," "vasopressors," "treatment," and "mortality," limited to 2019–2024. A refined search added terms like "emergency" and "corticosteroid," focusing on case reports, randomized controlled trial (RCTs), meta-analyses, and systematic reviews. Filters for the English language and trials comparing corticosteroid therapy to placebo in patients aged 18–60 were applied.

Inclusion criteria included articles published from 2019 to 2024, RCTs evaluating corticosteroid treatments against placebo, participants aged 18–60 years, use of systemic corticosteroids (e.g., hydrocortisone, methylprednisolone), English language publications, and different article types such as case reports, systematic reviews, and meta-analyses.

Exclusion criteria included studies on topical or inhaled corticosteroids, articles without relevant keywords in the title or abstract, health-related commentaries or guidelines, technical reports, and trials combining corticosteroids with Vitamin C or other medications (e.g., ascorbic acid and thiamine).

Two independent reviewers screened the titles and abstracts for eligibility, and full-text articles were further examined. Extracted data included study design, participant demographics, corticosteroid regimen details (dose, type, and duration), and outcomes, such as mortality, ICU stay length, shock reversal, and side effects (hyperglycemia, hypernatremia).

The Cochrane risk of bias tool was used to evaluate potential bias in the selected studies. This assessment covered various aspects including selection, performance, detection, attrition, reporting, and other biases. Each aspect was rated on a scale of 1–5, where 1 represented minimal risk and five indicated the highest risk. The evaluation process involved two independent reviewers examining each study, and any disagreements were resolved by discussion to reach a consensus.

RESULTS

The initial literature search yielded 206 results filtered by specific inclusion and exclusion criteria, eliminating 167 articles due to accessibility issues. The remaining 39 articles were subjected to comprehensive analysis, excluding 29 articles with inadequate data or conclusions. Of the 10 remaining, three were unavailable for download, leaving six studies for the systematic review.[14-19] Figure 1 illustrates the selection process. Table 1 lists the six studies selected for the systematic review.

A meta-analysis by Fang *et al*. on 37 randomized controlled trials (RCTs) (n=9,564) revealed that corticosteroid use reduced mortality at 28 days (Risk Ratio [RR], 0.90, 95% Confidence Interval (CI), 0.82-0.98; I2 = 27%), ICU admission (RR, 0.85, 95% CI, 0.77-0.94; I2 = 0%), and during hospital stays (RR, 0.88, 95% CI, 0.79-0.99; I2 = 38%).[14] Corticosteroids improved shock reversal, increased vasopressor-free days, shortened ICU stay, reduced sequential organ failure assessment scores, and hastened shock resolution. However, corticosteroid treatment increased risks of hyperglycemia (RR, 1.19, 95% CI, 1.08-1.30) and hypernatremia (RR, 1.57, 95% CI, 1.24-1.99).[14]

Yao *et al*.'s meta-analysis of 16 studies found no significant improvement in 14-day or 90-day mortality rates, but extended low-dose corticosteroid treatment notably reduced 28-day mortality, as highlighted by four studies.[15] Fang *et al*.'s meta-analysis provided the strongest evidence per the Jadad decision algorithm, showing that prolonged low-dose corticosteroid regimens reduce 28-day mortality, ICU and hospital death rates, and shorten ICU stays.[14]

Lin *et al*.'s meta-analysis of 30 RCTs (n = 8,836) suggests that prolonged low-dose corticosteroid use may improve 28-day (RR, 0.90, 95% CI: 0.84–0.97), ICU (RR, 0.87, 95% CI: 0.79–0.95), and in-hospital mortality (RR, 0.88, 95% CI: 0.79–0.997) in SS and vasopressor-dependent patients with SS.[16]

Zhang *et al*.'s meta-analysis of 35 RCTs (n = 8,859) found methylprednisolone and dexamethasone more effective than placebo in reducing short-term sepsis mortality (relative risk, 0.65, 95% credible interval: 0.40–0.93; relative risk, 0.42, 95% CI: 0.24–0.84, respectively). Hydrocortisone and hydrocortisone with fludrocortisone reduced shock resolution time (mean difference [MD], −1.70, 95% CI: −2.83–−0.92; MD, −2.54, 95% CI: −4.19–−0.84, respectively) and ICU stays (MD, −1.43, 95% CI: −3.36–−0.15) compared to placebo. Methylprednisolone also increased ventilation-free days (MD, 7.71, 95% CI: 1.15–14.42).[17]

Lu *et al*.'s meta-analysis of nine RCTs involving 1,298 participants found that corticosteroid treatment did not significantly reduce short-term mortality in SS patients (RR, 0.95, 95% CI 0.85–1.06, I^2 = 0%; trial sequential analysis-adjusted CI 0.83–1.09, moderate-certainty evidence). However, corticosteroids significantly shortened the time for shock reversal (MD −21.56 h; 95% CI: −32.95–−10.16, I^2 = 0%; trial sequential analysis-adjusted CI −33.33–−9.78, moderate-certainty evidence). This advantage was achieved without increasing the risks of infection or gastrointestinal bleeding, though hyperglycemia was more likely.[18]

Pitre *et al*. analyzed 45 RCTs (n = 9,563), concluding that corticosteroids probably reduced short-term mortality (RR, 0.93, 95% CI, 0.88–0.99; moderate certainty) and improved shock reversal within 7 days (RR, 1.24, 95% CI: 1.11–1.38; high certainty). Treatment may not significantly impact ICU stay length (MD, −0.6, 95% CI: 1.48–0.27; low

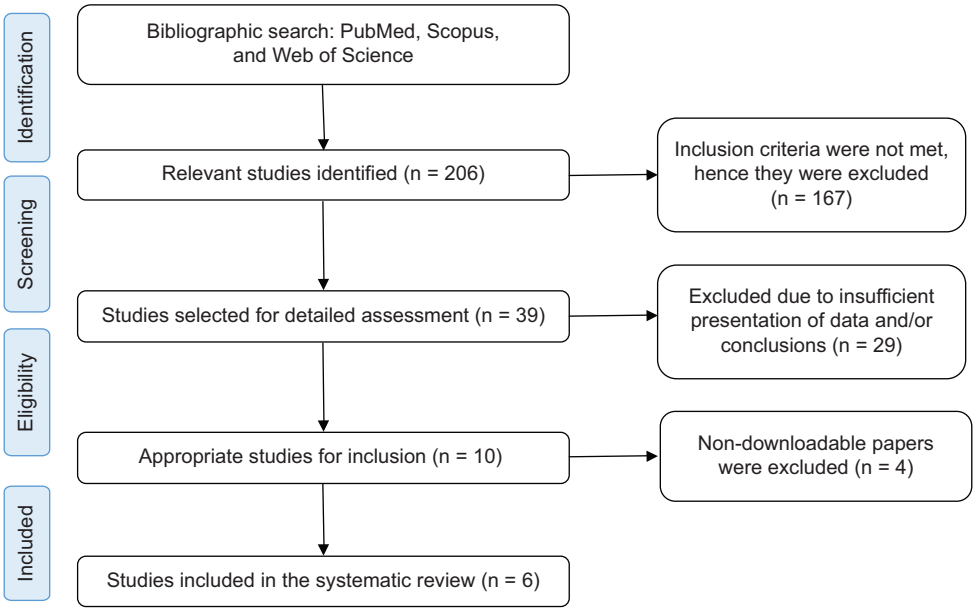

Figure 1: Flow diagram of literature search and study of selection for systematic review (Preferred reporting items for systematic review and meta-analysis flow chart)

Table 1: Characteristics of selected studies on the effects of corticosteroids on SS treatment

Study details	28-Day mortality	ICU stay duration	Study design	Participants (*n*)	Corticosteroid type/ dose	Main findings
Fang *et al.* (2019)[14]	RR, 0.90, CI: 0.82–0.98	Reduced (RR, 0.85, 95% CI, 0.77–0.94)	Systematic review and meta-analysis of randomized, placebo-controlled, or standard care-controlled clinical trials.	9564	Hydrocortisone, low-dose	This study indicates that corticosteroid therapy reduces 28-day ICU and hospital mortality rates in patients with sepsis. It is linked to better outcomes, such as faster shock reversal, more vasopressor-free days, shorter ICU stays, improved sequential organ failure assessment scores, and quicker shock resolution. However, studies have suggested that it may also increase the risk of hyperglycemia and hypernatremia.
Yao *et al.* (2019)[15]	No significantchange	-	Systematic review and meta-analysis of RCTs on the use of corticosteroids for sepsis and SS.	-	Low-dose corticosteroids	Extended low-dose corticosteroid use in patients with sepsis and SS lowered the 28-day ICU and hospital mortality rates and shortened ICU stays. However, it exacerbated hyperglycemia and hypernatremia adverse effects without improving the 90-day mortality rates.
Lin *et al.* (2019)[16]	RR, 0.90, CI: 0.84–0.97	Reduced(RR, 0.87, 95% CI: 0.79–0.95)	Randomized, placebo-controlled or standard therapy-controlled trial.	8836	Prolonged low-dose regimen	Prolonged low-dose corticosteroid therapy increased short-term survival rates, including deaths within 28 days, in the ICU, and during hospital stay, but did not affect long-term survival rates at 90 days, 180 days, and 1 year. This method is particularly advantageous for patients with SS and vasopressor-dependent SS.
Zhang *et al.* (2020)[17]	Reduced (Relative Risk, 0.65, 95% credible interval: 0.40–0.93)	Shortened (Mean Difference, −1.43, 95% credible interval: −3.36–−0.15)	Bayesian network meta-analysis of 35 RCTs on the use of corticosteroids in sepsis.	8859	Methylprednisolone, dexamethasone	In patients with sepsis, methylprednisolone and dexamethasone reduced short-term mortality rates more effectively than the placebo. Hydrocortisone, alone or with fludrocortisone, improved shock recovery and shortened ICU stay more successfully than placebo.

(*Contd...*)

Table 1: (*Continued*)

Study details	28-Day mortality	ICU stay duration	Study design	Participants (*n*)	Corticosteroid dose	Corticosteroid type/	Main findings
Lu *et al*. (2021)[18]	No significant change	-	Systematic review and meta-analysis of RCTs	1298	-		Corticosteroid therapy did not significantly affect short-term mortality rates compared with the control group. However, this notably reduced the time required for shock reversal. Although corticosteroid use was linked to a higher incidence of hyperglycemia, it did not increase the infection risk or gastrointestinal bleeding.
Pitre *et al*. (2024)[19]	RR, 0.93, CI: 0.88–0.99	No significant change	Systematic review and meta-analysis of RCTs	9563	Hydrocortisone or equivalent		Corticosteroids are likely to reduce short-term mortality and enhance shock resolution in patients with sepsis. The duration of ICU stay may remain largely unaffected by the corticosteroid treatment. Patients with sepsis on corticosteroids may experience increased risks of hyperglycemia, hypernatremia, and potentially greater muscle weakness.

ICU: Intensive care unit, SS: Septic shock, RCTs: Randomized Controlled Trials, RR: Risk Ratio, CI: Confidence interval

certainty), but likely increased hyperglycemia (RR, 1.13; 95% CI: 1.08–1.18; moderate certainty), hypernatremia (RR, 1.64, 95% CI: 1.32–2.03; moderate certainty), and possibly neuromuscular weakness (RR, 1.21, 95% CI: 1.01–1.45; low certainty). Dose-response analysis suggests an optimal daily dose of about 260 mg hydrocortisone or equivalent for mortality reduction (RR, 0.90, 95% CI: 0.83–0.98).[19]

The bias risk assessment showed varying levels across the studies [Figure 2]. Fang *et al*. had minimal selection and attrition biases but considerable other biases (score: 5).[14] Yao *et al*. and Lin *et al*. displayed moderate bias in most areas,[15,16] whereas Zhang *et al*. showed increased performance and detection bias risks.[17] Lu *et al*. demonstrated medium to high risk in numerous categories,[18] and Pitre *et al*. presented the greatest bias risk, especially in selection and reporting aspects.[19]

DISCUSSION

Corticosteroids do not significantly impact 28-day mortality in patients with SS,[20,21] though some studies indicate a minor reduction in short-term mortality with an optimal dose of around 260 mg/day of hydrocortisone or its equivalent.[19]

The effect on ICU stay duration is mixed, with some studies reporting a significant decrease, whereas others find no notable impact.[19] Corticosteroids consistently improve shock reversal, reducing the time to shock reversal and increasing the rate of shock reversal by day seven.[19,20,22]

Patients with high vasopressor needs and severe illness scores may benefit from this treatment.[22] Potential adverse effects include increased risks of hyperglycemia, hypernatremia, and neuromuscular weakness;[19] however, some studies have reported no significant differences in the rates of superinfection.[21,23]

This systematic review examined multiple studies on corticosteroid use, focusing on mortality rates, ICU stay duration, and side effects, such as hyperglycemia and hypernatremia.

Studies have indicated that corticosteroid therapy reduces the 28-day mortality and ICU admissions. Fang *et al*. meta-analysis of 37 RCTs revealed corticosteroids significantly decreased 28-day mortality and ICU admissions.[14] Lin *et al*. also reported lower 28-day and ICU mortality with low-dose corticosteroids.[16]

However, corticosteroid use in SS is related to adverse effects, such as hyperglycemia and hypernatremia. Pitre *et al*. noted an increased risk of hyperglycemia and hypernatremia in patients on corticosteroids.[19] These side effects necessitate careful monitoring during treatment to mitigate their risks.

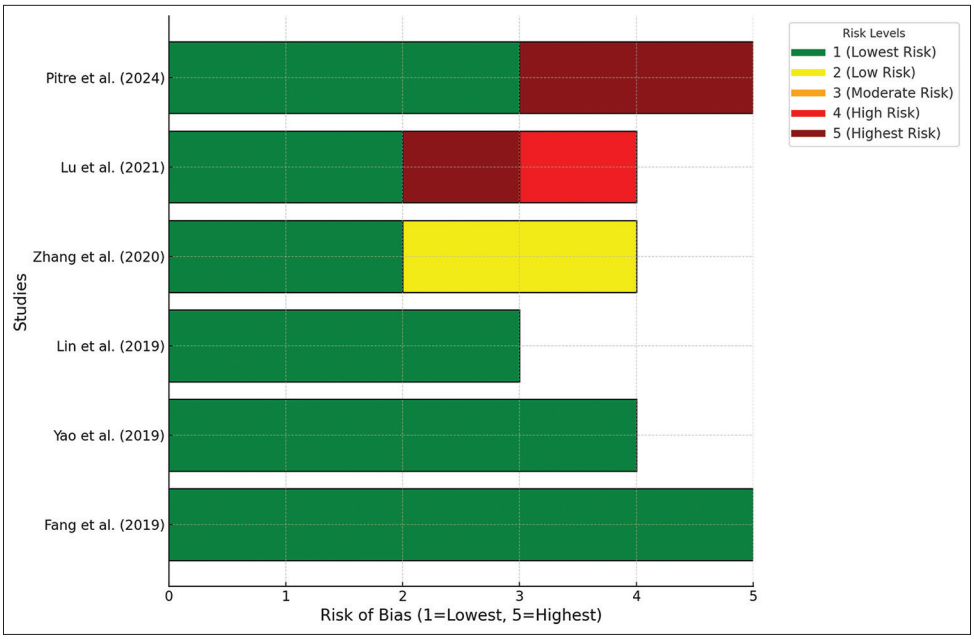

Figure 2: Assessment of individual risk of bias in studies included in a systematic review of corticosteroids in patients with SS

While Zhang *et al*. reported that methylprednisolone and dexamethasone improved short-term mortality and shock resolution,[17] Lu *et al*. found no significant reduction in short-term mortality despite faster shock reversal.[18] These variations highlight that the timing, dosage, and type of corticosteroid significantly impact outcomes in patients with SS.

Studies combining fludrocortisone with hydrocortisone did not show significant improvements in hospital mortality or duration of ICU stay. Yao *et al*. meta-analysis indicated no significant improvement in 14-day or 90-day mortality.[15] However, this combination increased vasopressor-free days and sped up shock resolution, without consistently reducing mortality.

A critical observation is the variation in corticosteroid dosing protocols. Most studies support low-dose corticosteroid treatment (200–300 mg/day of hydrocortisone or equivalent) for 4–7 days, which is linked to better outcomes and fewer side effects. High-dose regimens are associated with more complications, including immunosuppression and secondary infections.

CONCLUSION

Low-dose corticosteroids, particularly hydrocortisone, have been extensively studied for treating SS. This review showed significant benefits, including reduced 28-day mortality, shorter ICU stays, and improved shock reversal. While corticosteroids show promise in managing SS, their use in sepsis remains controversial. The varied outcomes across studies necessitate personalized treatment, considering factors such as timing, dosage, and specific corticosteroids, to optimize benefits and reduce risks. Despite the potential benefits, further research is required to determine optimal corticosteroid protocols, particularly in terms of dosage and duration. In addition, the effectiveness of adjunct treatments, such as fludrocortisone or ascorbic acid, remains uncertain and warrants further investigation.

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