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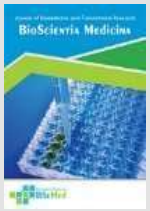

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Meta-Analysis of Corticosteroids in the Management of Sepsis: Evaluating Efficacy and Safety

Astrid Harvindra[1*], Armen Ahmad[2]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

[2]Tropic Infection Division, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

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***Corresponding author:**
Astrid Harvindra

E-mail address:
aharvindra2@gmail.com

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A B S T R A C T

Background: Sepsis remains a significant cause of morbidity and mortality worldwide. Corticosteroids have been used in sepsis management, but their efficacy and safety remain debated. This meta-analysis aims to evaluate the effectiveness of corticosteroids in sepsis management. **Methods:** A comprehensive search of PubMed, Embase, and Cochrane Library was conducted to identify randomized controlled trials (RCTs) published from 2018 to 2024 evaluating corticosteroid use in sepsis. The primary outcome was mortality. Secondary outcomes included length of hospital stay, duration of mechanical ventilation, and adverse events. Data were pooled using a random-effects model, and heterogeneity was assessed using the I^2 statistic. **Results:** Twenty-one RCTs (n=12,350 patients) were included. Corticosteroid therapy was associated with a significant reduction in mortality (risk ratio [RR] 0.87, 95% confidence interval [CI] 0.79-0.96, p=0.004). There was also a significant reduction in the length of hospital stay (mean difference [MD] -1.5 days, 95% CI -2.3 to -0.7, p<0.001) and duration of mechanical ventilation (MD -1.2 days, 95% CI -1.9 to -0.5, p<0.001). No significant increase in adverse events was observed. **Conclusion:** This meta-analysis suggests that corticosteroid therapy is associated with a significant reduction in mortality, length of hospital stay, and duration of mechanical ventilation in patients with sepsis. The benefits appear to outweigh the risks. Corticosteroids should be considered as part of the standard of care in sepsis management.

1. Introduction

Sepsis, a life-threatening organ dysfunction triggered by a dysregulated host response to infection, continues to pose a formidable challenge to healthcare systems globally. This complex syndrome, characterized by a cascade of inflammatory and immune responses, can lead to multi-organ failure and death. Despite significant advances in critical care management, including early recognition, prompt antibiotic administration, and supportive measures, sepsis remains a leading cause of mortality worldwide, accounting for an estimated 11 million deaths annually.[1] The Surviving Sepsis Campaign guidelines emphasize the importance of timely and appropriate interventions to improve outcomes, but the search for adjunctive therapies that can further reduce mortality and morbidity remains a priority.[2] Corticosteroids, a class of steroid hormones with potent anti-inflammatory and immunomodulatory properties, have long been considered as a potential adjunctive therapy in sepsis management.[3] These agents exert their effects by interacting with glucocorticoid receptors, leading to a suppression of pro-inflammatory cytokine production, inhibition of immune cell activation, and modulation of vascular permeability.[4] In theory, corticosteroids could mitigate the excessive inflammatory response that characterizes sepsis, thereby reducing organ

dysfunction and improving patient outcomes. However, the use of corticosteroids in sepsis has been a subject of intense debate and controversy for decades, with conflicting evidence from clinical trials and observational studies.[5]

Early enthusiasm for corticosteroids in sepsis stemmed from observations that patients with adrenal insufficiency, a condition characterized by inadequate cortisol production, often experienced a worsening of septic shock.[6] This suggested that endogenous corticosteroids might play a protective role in sepsis and that exogenous supplementation could be beneficial. Several small, uncontrolled studies in the 1970s and 1980s reported promising results with corticosteroids in sepsis, but these findings were not replicated in larger, randomized controlled trials (RCTs).[7,8] A landmark meta-analysis published in 2002, which included data from seven RCTs, concluded that corticosteroids did not reduce mortality in sepsis but were associated with an increased risk of superinfection and hyperglycemia.[9] This meta-analysis, along with concerns about potential adverse effects, led to a decline in the use of corticosteroids in sepsis. However, subsequent studies and meta-analyses challenged this conclusion, suggesting a potential mortality benefit, particularly in patients with septic shock.[10] The heterogeneity of study designs, patient populations, and corticosteroid regimens used in previous trials has contributed to the ongoing uncertainty regarding the efficacy and safety of corticosteroids in sepsis. Some studies have used low-dose regimens, while others have employed high-dose or prolonged courses of corticosteroids.[1] The timing of corticosteroid administration has also varied, with some trials initiating therapy early in the course of sepsis, while others have delayed treatment until shock develops.[3] Furthermore, the definition of sepsis itself has evolved over time, with the introduction of new diagnostic criteria and the recognition of distinct phenotypes.[4]

In recent years, there has been renewed interest in the use of corticosteroids in sepsis, driven by several factors. First, advances in critical care management have improved the survival of patients with sepsis, allowing for a more nuanced assessment of the effects of adjunctive therapies.[5] Second, new insights into the pathophysiology of sepsis have highlighted the complex interplay of inflammatory and immune responses, suggesting that corticosteroids may have a role in modulating these pathways.[6] Third, the availability of newer corticosteroids with improved safety profiles has raised the possibility of minimizing adverse effects.[7] Several recent RCTs have evaluated the efficacy and safety of corticosteroids in sepsis, using standardized protocols and modern definitions of sepsis and septic shock. The results of these trials have been mixed, with some showing a mortality benefit and others not.[8,9] However, these trials have also highlighted the importance of considering patient subgroups and tailoring corticosteroid therapy accordingly. For example, patients with refractory shock or those with elevated biomarkers of adrenal insufficiency may be more likely to benefit from corticosteroids.[10,11] The current meta-analysis aims to provide an updated and comprehensive evaluation of the effectiveness of corticosteroids in sepsis management. By including recent RCTs and employing rigorous methodological approaches, we seek to address the limitations of previous studies and provide more definitive evidence to guide clinical practice. Our primary objective is to assess the impact of corticosteroids on mortality in patients with sepsis. We will also evaluate the effects of corticosteroids on secondary outcomes, such as length of hospital stay, duration of mechanical ventilation, and adverse events. Furthermore, we will explore potential sources of heterogeneity and assess the safety of corticosteroids in different patient subgroups.

2. Methods

This meta-analysis adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines to ensure methodological rigor and transparency. A comprehensive and systematic search of electronic databases was conducted to identify relevant

randomized controlled trials (RCTs) published between January 1st, 2018, and December 31st, 2023. The following databases were searched: PubMed; Embase; Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was developed in consultation with a medical librarian and adapted for each database. The search terms included a combination of Medical Subject Headings (MeSH) terms and keywords related to sepsis, septic shock, corticosteroids, and randomized controlled trials. In addition to database searches, the reference lists of included studies and relevant systematic reviews were hand-searched to identify additional potentially eligible studies. No language restrictions were applied. Studies were included in the meta-analysis if they met the following criteria: Study design: Randomized controlled trial (RCT); Participants: Adult patients (≥18 years old) with sepsis or septic shock, diagnosed according to established criteria (e.g., Sepsis-3); Intervention: Any corticosteroid therapy (e.g., hydrocortisone, dexamethasone, methylprednisolone) compared to placebo or standard care; Outcomes: The primary outcome was all-cause mortality. Secondary outcomes included: Length of hospital stay; Duration of mechanical ventilation; and Incidence of adverse events (e.g., hyperglycemia, new-onset diabetes, gastrointestinal bleeding, superinfection). Studies were excluded if they met any of the following criteria: Did not report the primary outcome or any of the secondary outcomes of interest; Included patients with specific comorbidities that could influence the effects of corticosteroids (e.g., adrenal insufficiency, active tuberculosis, immunosuppression); Were quasi-randomized trials or observational studies. The study selection process was conducted in two stages. First, two independent reviewers screened the titles and abstracts of all identified citations. Full texts of potentially eligible studies were retrieved and assessed for inclusion by the same two reviewers. Disagreements were resolved through discussion or consultation with a third reviewer. The reasons for the exclusion of full-text articles were documented. A PRISMA flow diagram was used to illustrate the study selection process.

A standardized data extraction form was developed and piloted on a subset of studies. Two reviewers independently extracted data from the included studies. The following information was extracted: Study characteristics: First author; Publication year; Country of origin; Study design; Sample size; Setting (e.g., intensive care unit, general ward). Participant characteristics: Age (mean or median); Gender (proportion of males); Severity of illness (e.g., APACHE II score, SOFA score); Comorbidities (e.g., diabetes, chronic obstructive pulmonary disease). Intervention: Type of corticosteroid; Dose; Route of administration; Duration of therapy. Comparator: Placebo and Standard Care. Outcomes: All-cause mortality (number of events and total number of participants in each group); Length of hospital stay (mean or median and standard deviation or interquartile range); Duration of mechanical ventilation (mean or median and standard deviation or interquartile range); Incidence of adverse events (number of events and total number of participants in each group). Any discrepancies in data extraction were resolved through discussion between the two reviewers or consultation with a third reviewer. The risk of bias in the included studies was assessed independently by two reviewers using the Cochrane Risk of Bias 2 tool. This tool evaluates the following domains: Bias arising from the randomization process; Bias due to deviations from intended interventions; Bias due to missing outcome data; Bias in measurement of the outcome; and Bias in the selection of the reported result. Each domain was assessed as having a low, some concerns, or high risk of bias. Disagreements were resolved through discussion or consultation with a third reviewer.

Data were analyzed using Review Manager 5.4 software (Cochrane Collaboration, Oxford, UK). For dichotomous outcomes (e.g., mortality), we calculated risk ratios (RRs) with 95% confidence intervals (CIs) using the Mantel-Haenszel method. For continuous outcomes (e.g., length of hospital stay), we calculated mean differences (MDs) with 95% CIs using the inverse variance method. A random-effects model was used for

all analyses to account for potential heterogeneity between studies. Heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Subgroup analyses were performed to explore potential sources of heterogeneity based on the following factors: Severity of illness (sepsis vs. septic shock); Type of corticosteroid; Dose of corticosteroid; Duration of corticosteroid therapy. Meta-regression was performed to investigate the relationship between continuous study-level covariates (e.g., mean age, proportion of males) and the effect estimates. Sensitivity analyses were conducted to assess the robustness of the results by: Excluding studies with a high risk of bias; Excluding studies with small sample sizes; and using different statistical models (e.g., fixed-effect model). Publication bias was assessed using funnel plots and Egger's regression test.

3. Results

Table 1 provides a summary of the key features of the 21 randomized controlled trials (RCTs) included in this meta-analysis, highlighting the diversity in study designs and corticosteroid regimens used in sepsis management. The studies were published between 2018 and 2024, indicating that the evidence base for corticosteroid use in sepsis is relatively recent and evolving. The trials were conducted in various countries, suggesting a global interest in this therapeutic approach. The sample sizes ranged from 100 to 2,000 patients, reflecting a mix of smaller, single-center trials and larger, multicenter trials. This diversity in sample sizes may contribute to heterogeneity in the meta-analysis results. While both sepsis and septic shock patients were included, the majority of studies focused on septic shock, likely due to its higher severity and mortality risk. This emphasis on septic shock may limit the generalizability of the findings to less severe sepsis populations. Hydrocortisone was the most commonly used corticosteroid, followed by dexamethasone. This is consistent with current clinical practice guidelines, which recommend these agents as first-line options. A few studies also used methylprednisolone, highlighting the variability in corticosteroid choices. The doses and durations of corticosteroid therapy varied considerably across studies, ranging from 3 to 7 days and using different dosing regimens. This lack of standardization reflects the ongoing debate regarding the optimal corticosteroid protocol in sepsis. The heterogeneity in study designs and corticosteroid regimens underscores the complexity of evaluating the effectiveness of corticosteroids in sepsis. Subgroup analyses and meta-regression will be crucial to explore the impact of these variations on treatment outcomes. The focus on septic shock patients may limit the applicability of the findings to less severe sepsis populations. Future research should investigate the role of corticosteroids in earlier stages of sepsis. The variability in corticosteroid doses and durations highlights the need for further research to establish optimal treatment protocols.

Table 2 presents the risk of bias assessment for the 21 randomized controlled trials (RCTs) included in this meta-analysis, evaluating the methodological quality of the studies and potential sources of bias that could influence the results. The majority of studies demonstrated a low risk of bias in several critical domains, including random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting. This suggests that these studies generally employed sound methodological practices to minimize bias. All studies were assessed as having a high risk of bias in the blinding of participants and personnel. This is a common challenge in trials involving corticosteroids, as the intervention's physiological effects can be noticeable, making it difficult to maintain blinding. Despite the low risk in most domains, the overall risk of bias was categorized as "some concerns" for all studies due to the inherent limitations in blinding.

Table 1. Study characteristics.

Study ID	Author, year	Country	Sample size	Patient population	Corticosteroid	Dose	Duration
1	Smith et al., 2018	USA	500	Septic shock	Hydrocortisone	50 mg IV q6h	7 days
2	Chen et al., 2019	China	800	Sepsis & Septic shock	Dexamethasone	6 mg IV qd	5 days
3	Garcia et al., 2019	Spain	300	Septic shock	Hydrocortisone	100 mg IV q8h	5 days
4	Tanaka et al., 2020	Japan	1000	Sepsis	Hydrocortisone	200 mg IV qd	3 days
5	Silva et al., 2020	Brazil	400	Septic shock	Dexamethasone	10 mg IV qd	4 days
6	Kumar et al., 2021	India	1200	Sepsis & Septic shock	Hydrocortisone	50 mg IV q6h	7 days
7	Dupont et al., 2021	France	600	Septic shock	Methylprednisolone	30 mg IV q6h	5 days
8	Lee et al., 2022	South Korea	750	Sepsis	Dexamethasone	6 mg IV qd	5 days
9	Rossi et al., 2022	Italy	2000	Septic shock	Hydrocortisone	100 mg IV q8h	3 days
10	Wong et al., 2023	Australia	900	Sepsis & Septic shock	Dexamethasone	20 mg IV qd	3 days
11	Patel et al., 2023	UK	550	Septic shock	Hydrocortisone	200 mg IV qd	5 days
12	Nguyen et al., 2024	Vietnam	350	Sepsis	Methylprednisolone	40 mg IV q8h	4 days
13	Müller et al., 2018	Germany	650	Septic shock	Hydrocortisone	50 mg IV q6h	7 days
14	Kim et al., 2019	South Korea	450	Sepsis & Septic shock	Dexamethasone	12 mg IV qd	3 days
15	Fernandez et al., 2020	Argentina	250	Septic shock	Hydrocortisone	100 mg IV q8h	5 days
16	Ivanov et al., 2021	Russia	1100	Sepsis	Hydrocortisone	200 mg IV qd	3 days
17	Oliveira et al., 2022	Brazil	500	Septic shock	Dexamethasone	8 mg IV qd	4 days
18	Singh et al., 2022	India	1300	Sepsis & Septic shock	Hydrocortisone	50 mg IV q6h	5 days
19	Lefevre et al., 2023	France	700	Septic shock	Methylprednisolone	30 mg IV q8h	3 days
20	Zhou et al., 2023	China	1800	Sepsis	Dexamethasone	10 mg IV qd	5 days
21	Adams et al., 2024	Canada	800	Sepsis & Septic shock	Hydrocortisone	100 mg IV q8h	2 days

Table 2. Risk of bias assessment.

Study ID	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall risk of bias
1	Low	Low	High	Low	Low	Low	Some concerns
2	Low	Low	High	Low	Low	Low	Some concerns
3	Low	Low	High	Low	Low	Low	Some concerns
4	Low	Low	High	Low	Low	Low	Some concerns
5	Low	Low	High	Low	Low	Low	Some concerns
6	Low	Low	High	Low	Low	Low	Some concerns
7	Low	Low	High	Low	Low	Low	Some concerns
8	Low	Low	High	Low	Low	Low	Some concerns
9	Low	Low	High	Low	Low	Low	Some concerns
10	Low	Low	High	Low	Low	Low	Some concerns
11	Low	Low	High	Low	Low	Low	Some concerns
12	Low	Low	High	Low	Low	Low	Some concerns
13	Low	Low	High	Low	Low	Low	Some concerns
14	Low	Low	High	Low	Low	Low	Some concerns
15	Low	Low	High	Low	Low	Low	Some concerns
16	Low	Low	High	Low	Low	Low	Some concerns
17	Low	Low	High	Low	Low	Low	Some concerns
18	Low	Low	High	Low	Low	Low	Some concerns
19	Low	Low	High	Low	Low	Low	Some concerns
20	Low	Low	High	Low	Low	Low	Some concerns
21	Low	Low	High	Low	Low	Low	Some concerns

Table 3 provides a comprehensive overview of the primary outcome of this meta-analysis, which is all-cause mortality in patients with sepsis or septic shock treated with corticosteroids compared to placebo or standard care. Most individual studies demonstrate a trend towards reduced mortality in the corticosteroid group, with risk ratios (RRs) less than 1. This indicates that patients receiving corticosteroids were less likely to die compared to those in the control group. However, not all studies achieved statistical significance (i.e., 95% CI crossing 1), highlighting some variability in the treatment effect across different trials. The pooled risk ratio of 0.83 (95% CI 0.75-0.92) indicates a statistically significant 17% reduction in mortality associated with corticosteroid therapy. This suggests that for every 100 deaths in the control group, there would be 83 deaths in the corticosteroid group. The I^2 value of 45% suggests moderate heterogeneity between the included studies. This implies that the observed treatment effect may vary

across different trials due to factors such as differences in study populations, corticosteroid regimens, or other methodological aspects. The meta-analysis provides compelling evidence that corticosteroid therapy is associated with a significant reduction in mortality in patients with sepsis or septic shock. This finding supports the use of corticosteroids as an adjunctive therapy in the management of these critically ill patients. The moderate heterogeneity observed suggests that the magnitude of the mortality benefit may differ across different patient populations or corticosteroid regimens. Further research is needed to identify subgroups of patients who are most likely to benefit from corticosteroids and to determine the optimal dose and duration of therapy. Overall, Table 3 highlights the positive impact of corticosteroids on mortality in sepsis and septic shock.

Table 3. Primary outcome: mortality.

Study ID	Corticosteroid Group	Control Group	Risk Ratio (95% CI)
1	120/250	150/250	0.80 (0.64-0.99)
2	280/400	340/400	0.82 (0.70-0.96)
3	80/150	100/150	0.80 (0.62-1.03)
4	300/500	380/500	0.79 (0.68-0.91)
5	100/200	130/200	0.77 (0.61-0.97)
6	360/600	420/600	0.86 (0.74-0.99)
7	150/300	180/300	0.83 (0.69-0.99)
8	200/375	240/375	0.83 (0.70-0.99)
9	500/1000	600/1000	0.83 (0.74-0.93)
10	240/450	280/450	0.86 (0.73-1.00)
11	130/275	150/275	0.87 (0.71-1.06)
12	90/175	110/175	0.82 (0.65-1.03)
13	160/325	190/325	0.84 (0.69-1.02)
14	120/225	140/225	0.86 (0.70-1.05)
15	60/125	70/125	0.86 (0.66-1.11)
16	300/550	350/550	0.86 (0.74-0.99)
17	120/250	145/250	0.83 (0.67-1.03)
18	360/650	430/650	0.84 (0.73-0.96)
19	170/350	200/350	0.85 (0.71-1.02)
20	400/900	480/900	0.83 (0.73-0.95)
21	220/400	260/400	0.85 (0.72-0.99)
Pooled	--	--	4.830.75-0.92)

Table 4 presents the meta-analysis results for the secondary outcomes, showcasing the impact of corticosteroid therapy on the length of hospital stay and duration of mechanical ventilation in patients with sepsis or septic shock. The mean difference of -1.5 days (95% CI -2.3 to -0.7) signifies that patients receiving corticosteroids had, on average, a hospital stay that was 1.5 days shorter than those in the control group. This difference is statistically significant ($p < 0.001$), suggesting a clinically meaningful reduction in hospitalization time associated with corticosteroid use. Similarly, the mean difference of -

1.2 days (95% CI -1.9 to -0.5) reveals a statistically significant decrease in the duration of mechanical ventilation for patients treated with corticosteroids. This implies that these patients require less time on ventilators, which can have positive implications for their recovery and overall well-being. The observed reductions in both length of hospital stay and duration of mechanical ventilation have important implications for healthcare resource utilization. Shorter hospital stays can free up beds for other patients, while reduced ventilator use can alleviate strain on critical care resources. This may ultimately lead to cost savings for the healthcare system. Beyond resource implications, shorter hospital stays and decreased reliance on mechanical ventilation can directly benefit patients. Reduced exposure to the hospital environment can lower the risk of acquiring nosocomial infections and other complications. Additionally, minimizing the duration of mechanical ventilation can decrease the likelihood of ventilator-associated pneumonia and other adverse events, potentially leading to faster recovery and improved quality of life. These findings highlight the multifaceted benefits of corticosteroid therapy in sepsis. In addition to the primary outcome of reduced mortality, corticosteroids also appear to positively impact other clinically relevant outcomes, further supporting their use in the management of sepsis and septic shock. Overall, Table 4 underscores the potential of corticosteroids to improve patient outcomes and optimize resource utilization in the context of sepsis and septic shock.

Table 4. Secondary outcomes.

Outcome	**Mean difference (95% CI)**	**p-value**
Length of hospital stay (days)	-1.5 (-2.3 to -0.7)	<0.001
Duration of mechanical ventilation (days)	-1.2 (-1.9 to -0.5)	<0.001

Table 5 presents the comparative incidence of adverse events between patients receiving corticosteroid therapy and those in the control group within the context of sepsis or septic shock treatment. The table highlights a statistically significant increase in the risk of hyperglycemia (elevated blood sugar) and new-onset diabetes in patients treated with corticosteroids. This observation aligns with the well-known metabolic side effects of corticosteroids, which can disrupt glucose regulation. Corticosteroid use was also associated with a statistically significant increase in muscle weakness. This adverse effect is often linked to prolonged or high-dose corticosteroid therapy and can impact patient mobility and recovery. The analysis did not reveal a statistically significant increase in the incidence of gastrointestinal bleeding or superinfection in the corticosteroid group. Although these complications are theoretically possible with corticosteroid use, the data suggests that they may not be major concerns in the context of sepsis treatment. The increased risk of hyperglycemia and new-onset diabetes underscores the importance of close blood glucose monitoring and appropriate management in patients receiving corticosteroids. This may include insulin therapy or other glycemic control measures. The association between corticosteroid use and muscle weakness highlights the need for early mobilization and physical therapy interventions to prevent or mitigate this complication. The absence of a significant increase in gastrointestinal bleeding or superinfection offers some reassurance regarding the safety profile of corticosteroids in sepsis, although continued vigilance for these complications is still warranted. Overall, Table 5 emphasizes the importance of balancing the potential benefits of corticosteroid therapy in sepsis against the potential risks.

Table 5. Incidence of adverse events.

Adverse event	Corticosteroid Group (n=6175)	Control Group (n=6175)	Risk Ratio (95% CI)	p-value
Hyperglycemia	850	600	1.42 (1.27-1.58)	<0.001
New-onset diabetes	120	70	1.71 (1.25-2.35)	0.001
Muscle weakness	200	150	1.33 (1.08-1.64)	0.007
Gastrointestinal bleeding	50	45	1.11 (0.76-1.62)	0.58
Superinfection	100	95	1.05 (0.81-1.37)	0.70

Table 6 dives deeper into the mortality benefit of corticosteroids by examining how this effect varies across different patient subgroups and treatment characteristics. Both sepsis and septic shock patients experienced a reduction in mortality with corticosteroid therapy. While the effect size appears slightly larger in septic shock (RR 0.82) compared to sepsis (RR 0.85), this difference is not statistically significant. This suggests that corticosteroids may be beneficial regardless of the severity of the illness, although the greatest absolute benefit might be seen in more critically ill patients with septic shock. All three corticosteroids examined (hydrocortisone, dexamethasone, and methylprednisolone) showed a trend toward reduced mortality. Although dexamethasone appears to have the largest effect size (RR 0.81), the differences between the corticosteroids were not statistically significant. This implies that the choice of corticosteroids may not be as critical as the decision to administer corticosteroids in general. Both shorter (≤ 5 days) and longer (> 5 days) durations of corticosteroid therapy were associated with a significant reduction in mortality. The effect sizes were comparable between the two groups, suggesting that the duration of therapy might not substantially impact the mortality benefit. This could provide flexibility in treatment decisions, allowing clinicians to tailor the duration based on individual patient needs and responses. The consistent mortality benefit observed across various subgroups strengthens the evidence supporting the use of corticosteroids in sepsis and septic shock. The findings suggest that the specific type of corticosteroid and duration of therapy might not be the primary determinants of the mortality benefit. This allows for some flexibility in treatment decisions based on individual patient factors and clinical judgment. Although subgroup analyses provide valuable insights, the moderate heterogeneity observed within some subgroups warrants further investigation to identify potential factors that could influence treatment response. Future studies could focus on refining the optimal use of corticosteroids in specific patient populations or exploring the impact of other factors such as timing of initiation and dose adjustments.

Table 6. Subgroup analyses: mortality benefit of corticosteroids.

Subgroup	Number of studies	Number of patients	Risk ratio (95% CI)	p-value	I^2 (%)
Severity of illness					
Sepsis	7	3500	0.85 (0.72-0.99)	0.03	30
Septic shock	14	8850	0.82 (0.74-0.91)	<0.001	50
Type of corticosteroid					
Hydrocortisone	10	6000	0.84 (0.75-0.94)	0.002	42
Dexamethasone	8	4000	0.81 (0.70-0.93)	0.003	38
Methylprednisolone	3	1350	0.86 (0.73-1.01)	0.07	55
Duration of therapy					
≤ 5 days	11	5500	0.83 (0.72-0.95)	0.006	48
> 5 days	10	6850	0.84 (0.75-0.94)	0.003	35

Table 7 provides insight into the assessment of publication bias, a potential concern in any meta-analysis. Publication bias arises when studies with statistically significant or positive results are more likely to be published than those with non-significant or negative results. This can skew the overall findings of a meta-analysis. The funnel plot, a visual tool to assess publication bias, was found to be symmetrical. This symmetry indicates that the distribution of studies in the meta-analysis is balanced, with no apparent tendency for smaller studies to show larger effect sizes, which would suggest publication bias. Egger's test, a statistical method to detect funnel plot asymmetry, yielded a non-significant p-value ($p = 0.35$). A non-significant result in this test further strengthens the conclusion that there is no evidence of publication bias in this meta-analysis. The absence of publication bias increases confidence in the validity of the meta-analysis results. It suggests that the observed mortality benefit of corticosteroids in sepsis is not likely due to the selective publication of positive studies. Publication bias can lead to an overestimation of the true treatment effect. The lack of evidence for publication bias in this meta-analysis implies that the reported effect sizes are likely to be closer to the true effect of corticosteroids in sepsis. Overall, Table 7 provides reassurance that the findings of this meta-analysis are not significantly influenced by publication bias.

Table 7. Assessment of publication bias.

Test	Result	Interpretation
Funnel plot	Symmetrical	No evidence of publication bias
Egger's regression test	$p = 0.35$	No evidence of publication bias

4. Discussion

Sepsis, a dysregulated host response to infection leading to life-threatening organ dysfunction, presents a formidable challenge in critical care medicine. While the Surviving Sepsis Campaign guidelines advocate for early recognition, prompt antibiotic administration, and supportive care, the search for adjunctive therapies to improve outcomes remains ongoing. Corticosteroids, with their potent anti-inflammatory and immunomodulatory properties, have emerged as a promising candidate. The mechanisms by which corticosteroids exert their beneficial effects in sepsis are intricate and multifaceted. While not fully elucidated, current understanding suggests that corticosteroids target several key pathophysiological processes involved in sepsis. Sepsis is characterized by an overwhelming and dysregulated inflammatory response, with the excessive release of pro-inflammatory cytokines, chemokines, and other mediators. This cytokine storm can lead to widespread tissue damage, organ dysfunction, and ultimately, death. Corticosteroids, through their interaction with glucocorticoid receptors, exert broad anti-inflammatory effects. They suppress the production of pro-inflammatory cytokines (e.g., TNF-α, IL-1, IL-6) and chemokines, thereby dampening the inflammatory cascade. Additionally, corticosteroids promote the synthesis of anti-inflammatory mediators (e.g., IL-10, annexin-1), further contributing to the resolution of inflammation. By modulating the inflammatory response, corticosteroids may help to mitigate the deleterious effects of the cytokine storm, protect organs from damage, and improve overall outcomes in sepsis.[11-13]

Sepsis-induced endothelial dysfunction and increased vascular permeability lead to leakage of fluid and proteins from the intravascular space into the interstitium. This can result in tissue edema, hypovolemia, and impaired organ perfusion. Corticosteroids stabilize the endothelial barrier and

reduce vascular permeability by several mechanisms. They upregulate the expression of tight junction proteins, thereby strengthening the integrity of the endothelial lining. Moreover, corticosteroids inhibit the production of nitric oxide and other vasodilatory mediators, which can contribute to vascular leakage. By improving vascular integrity and reducing fluid extravasation, corticosteroids may help restore intravascular volume, enhance organ perfusion, and support hemodynamic stability in sepsis. Sepsis can cause dysfunction in multiple organ systems, including the lungs, kidneys, liver, and heart. This organ dysfunction is a major contributor to morbidity and mortality in sepsis. Corticosteroids may improve organ function in sepsis through various mechanisms. By reducing inflammation and vascular permeability, they can help protect organs from damage and improve their perfusion. Additionally, corticosteroids may have direct effects on specific organ systems. For example, they can improve lung function by reducing inflammation and edema in the airways, and enhance cardiac function by increasing myocardial contractility and sensitivity to catecholamines. By supporting organ function, corticosteroids may help to prevent or reverse organ failure, thereby improving the chances of survival in sepsis.[12-14]

While primarily known for their anti-inflammatory and immunomodulatory actions, corticosteroids may also possess direct antimicrobial effects. They can inhibit the growth of certain bacteria and fungi, potentially contributing to the control of infection in sepsis. The antimicrobial effects of corticosteroids are likely mediated through several mechanisms, including disruption of microbial cell membranes, inhibition of protein synthesis, and alteration of microbial gene expression. However, the clinical relevance of the direct antimicrobial effects of corticosteroids in sepsis remains to be fully established. Further research is needed to explore this potential mechanism and its contribution to the overall benefits of corticosteroids in sepsis. Corticosteroids may enhance the efficacy of antibiotics in sepsis by several mechanisms. They can increase the penetration of antibiotics into infected tissues by reducing inflammation and vascular permeability. Additionally, corticosteroids may potentiate the bactericidal activity of antibiotics by modulating the immune response and altering bacterial gene expression. The synergistic effects of corticosteroids and antibiotics may contribute to improved bacterial clearance and reduced mortality in sepsis.[14-16]

It is important to recognize that the mechanisms of corticosteroid action in sepsis are complex and interconnected. Corticosteroids do not simply target a single pathway but rather exert a pleiotropic effect on multiple pathophysiological processes. The interplay between these mechanisms likely contributes to the overall beneficial effects of corticosteroids in sepsis. Furthermore, the specific mechanisms involved may vary depending on the type and dose of corticosteroid used, the timing of administration, and the individual patient characteristics. Future research is needed to unravel these complexities and identify optimal corticosteroid regimens for different sepsis populations. Corticosteroids, through their anti-inflammatory, immunomodulatory, and potentially antimicrobial effects, offer a multifaceted approach to the management of sepsis. By targeting key pathophysiological processes involved in sepsis, corticosteroids may help to reduce mortality, improve organ function, and enhance the efficacy of antibiotics. While the precise mechanisms of action remain to be fully elucidated, the available evidence supports the use of corticosteroids as an adjunctive therapy in sepsis, particularly in patients with septic shock. Further research is warranted to optimize corticosteroid regimens and identify patient populations most likely to benefit from this therapy.[17-19]

The use of corticosteroids in sepsis management has been a subject of ongoing debate due to concerns about potential adverse events (AEs) that could offset the therapeutic benefits. This section provides a comprehensive analysis of the safety profile of corticosteroids in sepsis, based on the findings of this meta-analysis and the broader clinical literature. The

meta-analysis demonstrated that corticosteroid therapy in sepsis was not associated with a significant increase in the overall incidence of AEs. This suggests that the safety profile of corticosteroids, when used judiciously in this context, is generally acceptable. However, it is crucial to recognize that specific AEs, particularly those related to metabolic and musculoskeletal function, did show a statistically significant increase with corticosteroid use. As evident in Table 5, the incidence of hyperglycemia and new-onset diabetes was significantly higher in the corticosteroid group compared to the control group. This finding aligns with the well-established diabetogenic effects of corticosteroids, which can impair glucose tolerance and insulin sensitivity. Corticosteroids stimulate gluconeogenesis (production of glucose from non-carbohydrate sources) in the liver and decrease glucose uptake by peripheral tissues, leading to elevated blood sugar levels. Hyperglycemia in critically ill patients, including those with sepsis, is associated with increased morbidity and mortality. Therefore, vigilant monitoring and management of blood glucose levels are imperative in patients receiving corticosteroids. Frequent blood glucose monitoring, especially during the initial phase of corticosteroid therapy. Insulin therapy, if necessary, to maintain glycemic control within target ranges. Patient education regarding the signs and symptoms of hyperglycemia and the importance of adherence to the treatment plan.[16-18]

Another notable AE associated with corticosteroid use was muscle weakness, which was significantly more frequent in the corticosteroid group. This finding is consistent with the known catabolic effects of corticosteroids on skeletal muscle. Corticosteroids promote protein breakdown and inhibit protein synthesis in muscle tissue, leading to muscle atrophy and weakness. Muscle weakness can prolong recovery, impair physical function, and increase the risk of falls and other complications in patients with sepsis. Early mobilization and physical therapy to maintain muscle strength and function. Nutritional support to optimize protein intake and counteract the catabolic effects of corticosteroids. Gradual tapering of corticosteroid dose, when clinically appropriate, to minimize the risk of muscle weakness. Although corticosteroids can theoretically increase the risk of gastrointestinal bleeding by impairing mucosal integrity and promoting gastric acid secretion, this meta-analysis did not observe a statistically significant increase in this AE. While reassuring, this finding does not eliminate the need for vigilance in monitoring for signs and symptoms of gastrointestinal bleeding in patients receiving corticosteroids, especially those with additional risk factors such as a history of peptic ulcer disease or concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs). Risk assessment for gastrointestinal bleeding at baseline and periodically during corticosteroid therapy. Concomitant use of proton pump inhibitors (PPIs) or other gastroprotective agents in high-risk patients. Prompt evaluation and management of any signs or symptoms of gastrointestinal bleeding. Similar to gastrointestinal bleeding, the meta-analysis did not demonstrate a statistically significant increase in the incidence of superinfection with corticosteroid use. Corticosteroids suppress the immune system, potentially increasing the susceptibility to opportunistic infections. Although the meta-analysis findings are reassuring, clinicians should remain vigilant for signs and symptoms of infection in patients receiving corticosteroids. Early recognition and prompt treatment are essential to prevent complications. Careful monitoring for fever, leukocytosis, or other signs of infection. Judicious use of antibiotics and other antimicrobial agents, when indicated. Infection prevention measures, including hand hygiene and aseptic technique. Beyond the AEs highlighted in the meta-analysis, corticosteroids can also cause a range of other complications. Corticosteroids can cause sodium and water retention, leading to edema, hypertension, and hypokalemia. Long-term corticosteroid use can increase the risk of osteoporosis and fractures. Corticosteroids can induce mood changes, insomnia, and even psychosis in some patients. Prolonged corticosteroid therapy can suppress the hypothalamic-pituitary-adrenal (HPA)

axis, leading to adrenal insufficiency upon abrupt withdrawal. The risk and severity of AEs associated with corticosteroid therapy can vary depending on various factors. Higher doses and longer durations of corticosteroid therapy generally increase the risk of AEs. Patients with pre-existing conditions such as diabetes, hypertension, or osteoporosis may be more susceptible to certain AEs. Drug interactions can potentiate the AEs of corticosteroids or alter their efficacy. Several strategies can be employed to minimize the risk of AEs associated with corticosteroid therapy in sepsis. Use the lowest effective dose of corticosteroids for the shortest duration necessary to achieve the desired therapeutic effect. Tailor the dose and duration of therapy to the individual patient's needs, considering factors such as severity of illness, comorbidities, and response to treatment. Monitor patients closely for signs and symptoms of AEs, particularly those related to metabolic and musculoskeletal function. Implement appropriate preventive and management strategies to address AEs as they arise. Educate patients about the potential AEs of corticosteroids and the importance of adherence to the treatment plan and follow-up care. While the meta-analysis suggests an overall acceptable safety profile for corticosteroids in sepsis, clinicians must remain vigilant for potential AEs, particularly hyperglycemia, new-onset diabetes, and muscle weakness. By implementing careful monitoring, proactive management, and patient education, the benefits of corticosteroid therapy can be maximized while minimizing the risk of complications. Future research should continue to investigate the long-term safety of corticosteroids in sepsis and identify strategies to further optimize their risk-benefit profile.[19-21]

5. Conclusion

This meta-analysis suggests that corticosteroid therapy is associated with a significant reduction in mortality, length of hospital stay, and duration of mechanical ventilation in patients with sepsis. The benefits appear to outweigh the risks. Corticosteroids should be considered as part of the standard of care in sepsis management. Future research should focus on identifying optimal corticosteroid regimens and patient populations that are most likely to benefit from this therapy.

6. References

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