MAJOR ARTICLE

# Safety and Efficacy of Corticosteroids for the Treatment of Septic Shock: A Systematic Review and Meta-Analysis

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***Background.*** Septic shock is common and results in significant morbidity and mortality. Adjunctive treatment with corticosteroids is common, but definitive data are lacking. We aimed to determine the efficacy and safety of corticosteroid therapy among patients with septic shock.

***Methods.*** Medline, Embase, Cochrane Library, Web of Science, and Google Scholar were searched for randomized trials and observational studies published from January 1993 through December 2008. Studies were selected if they included adults with septic shock, discussed treatment with intravenous corticosteroids, and reported at least 1 outcome of interest (e.g., mortality, shock reversal, or incidence of superinfection). Two reviewers independently agreed on eligibility, assessed methodologic quality, and abstracted data.

***Results.*** Pooled relative risks (RRs) and 95% confidence intervals (CIs) were estimated for 28-day all-cause mortality, shock reversal at 7 days, and incidence of superinfection with use of random-effects models. Analyses, stratified by adrenal responsiveness, were prespecified. Eight studies (6 randomized trials) involving a total of 1876 patients were selected. Overall, corticosteroid therapy did not result in a statistically significant difference in mortality (42.2% [369 of 875 patients] vs. 38.4% [384 of 1001]; RR, 1.00; 95% CI, 0.84–1.18). A statistically significant difference in the incidence of shock reversal at 7 days was observed between patients who received corticosteroids and those who did not (64.9% [314 of 484 patients] vs. 47.5% [228 of 480]; RR, 1.41; 95% CI, 1.22–1.64), with similar point estimates for both corticotropin stimulation test responders and nonresponders. No statistically significant difference was found in the incidence of superinfection between patients treated with corticosteroids and patients not treated with corticosteroids (25.3% [114 of 450 patients] vs. 22.7% [100 of 441]; RR, 1.11; 95% CI, 0.86–1.42).

***Conclusions.*** In patients with septic shock, corticosteroid therapy appears to be safe but does not reduce 28-day all-cause mortality rates. It does, however, significantly reduce the incidence of vasopressor-dependent shock, which may be a clinically worthwhile goal.

Septic shock is common, occurring in 2%-20% of hospitalized patients, and although overall mortality has decreased because of advancements in medical care, the incidence of septic shock is increasing, resulting in an increasing number of survivors with varying degrees of disability [1–4]. With an increasing population at risk (older persons, patients with multiple comorbidities, and immunosuppressed patients, such as those who have undergone transplantation), we can expect the incidence of septic shock to continue to increase during the next few decades. Optimizing our treatment strategy for septic shock is therefore imperative if we hope to improve outcomes.

Septic shock invariably results in intensive care unit admission and has a reported mortality rate of 36%-61% [5]. Nevertheless, other than early and appropriate administration of antimicrobial therapy [6–10], source control, organ support (including mechanical ventilation and renal replacement therapy), and perhaps, recombinant activated C in patients with Acute Physi-

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ology and Chronic Health Evaluation (APACHE) II scores ⩾25 [11], few adjunctive therapies exist that definitely improve outcomes for this devastating but common condition.

Adjunctive corticosteroid therapy is commonly prescribed to patients with septic shock, despite the fact that few randomized controlled trials have demonstrated a survival benefit [12, 13]. The most significant trial to date demonstrated a 10% reduction in 28-day mortality rates among patients with inadequate adrenal reserve who were treated with hydrocortisone and fludrocortisone (in which inadequate adrenal responsiveness was defined as a <9-$\mu$g/dL increase in serum cortisol level after the administration of 250 $\mu$g of intravenous corticotropin) [12]. A reduction in time to shock reversal was also observed. The results of this trial led to widespread corticosteroid use in patients with septic shock and inclusion of this adjunctive therapy in international practice guidelines [14].

In 2008, the large, well-conducted Corticosteroid Therapy of Septic Shock (CORTICUS) trial was unable to reproduce this reduction in mortality [15]. Consistent with other smaller trials [12, 13], the CORTICUS trial demonstrated a decrease in time to shock reversal (defined as maintenance of systolic blood pressure ⩾90 mm Hg without vasopressor support for ⩾24 h) among patients receiving corticosteroid therapy.

Although corticosteroids are generally thought to be safe, there are concerns related to immunosuppression and the potential for bacterial superinfection in patients who are already septic. Because of the uncertainty of benefit and potential for harm, we undertook a systematic review and meta-analysis to determine the safety (by incidence of superinfection) and efficacy (by 28-day all-cause mortality and incidence of shock reversal) of corticosteroid therapy among patients with septic shock.

## METHODS

***Literature search.*** We searched Medline, Embase, Cochrane Library, Web of Science, and Google Scholar for clinical trials and systematic reviews published from January 1993 through December 2008, restricting our search to English-language studies involving adults. Studies published before 1993 were excluded to limit heterogeneity caused by the considerable changes in patient population (e.g., increased age, comorbidity, and proportion of patients with immunosuppression) and time-related improvements in critical care. Early goal-directed therapy, lung-protective mechanical ventilation, routine stress ulcer and thromboembolism prophylaxis, continuous renal replacement therapy, and activated protein C have all become standard treatments during the past 15 years, resulting in a reduction in overall intensive care unit mortality.

We used the search terms "sepsis" or "septic shock" and "steroids." Multiple preliminary search strategies were explored, including the use of medical subject heading terms; however, keyword searching yielded the broadest search results. We reviewed references in previously published meta-analyses to find missing studies [16–23] and contacted content experts. We considered both randomized trials and high-quality observational studies.

***Study selection.*** Inclusion criteria were defined as adult clinical trials or rigorous observational studies of patients with septic shock, comparison of use of intravenous corticosteroids with use of placebo or control agents, and reporting of ⩾1 of the 3 outcomes of interest. Septic shock was defined by suspected or documented clinical evidence of infection, ⩾2 of 4 systemic inflammatory response syndrome criteria, organ hypoperfusion, and systolic blood pressure <90 mm Hg, despite fluid resuscitation or the need for vasopressors for at least 1 h.

Outcomes of interest were 28-day mortality, shock reversal at 7 days, and incidence of superinfection. Other adverse events (e.g., gastrointestinal bleeding, hyperglycemia, and hypernatremia) were not evaluated in our meta-analysis. One prespecified subgroup analysis was performed on the basis of adrenal responsiveness (corticotropin stimulation test responders vs. nonresponders).

The physiologic response to septic shock includes hypothalamic-pituitary-adrenal axis stimulation, which is thought to be an important protective survival response. Circulating proinflammatory mediators caused by sepsis may result in a state of relative corticosteroid insufficiency with reduced cortisol production and increased cortisol tissue resistance [24]. In addition, changes in corticotropin-binding globulin and free cortisol levels occur in patients with critical illness. The diagnosis of corticosteroid insufficiency in patients with septic shock is therefore complicated and should include measures of both adrenal function and peripheral cortisol resistance; however, such a test does not exist. Free cortisol level testing is rarely available, and to our knowledge, no commercially available measures of cortisol resistance exist. Therefore, the corticotropin stimulation test has historically been used as a measure of corticosteroid sufficiency based on adrenal responsiveness, even though interpretation of its results for a critically ill patient may be difficult.

Previous trials have defined patients with corticosteroid insufficiency as corticotropin stimulation test nonresponders (patients who have a <9-$\mu$g/dL increase in serum cortisol level after the administration of 250 $\mu$g of intravenous corticotropin). Responders are correspondingly defined as those who have a >9-$\mu$g/dL increase in serum cortisol level after corticotropin administration. According to biological rationale, nonresponders may benefit preferentially from corticosteroid replacement therapy, compared with responders.

***Validity assessment.*** Study quality was assessed indepen-

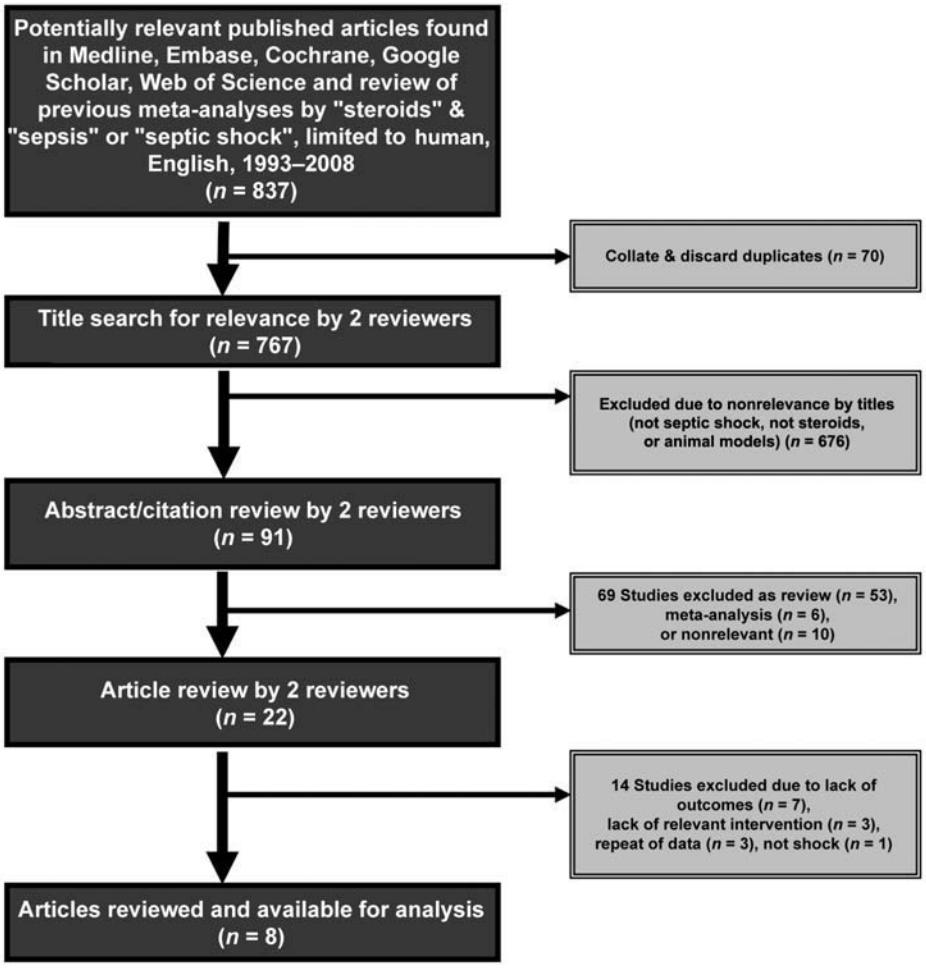


**Figure 1.** Search strategy and filtering used to obtain studies included in our review and meta-analysis.

dently by 2 authors with use of the Cronin method [16]. The Cronin score is a previously published septic shock–specific quality score, with a maximum of 14.5 indicating the highest quality.

***Data extraction.*** Data extraction was performed using a standardized form. Two independent investigators extracted data from each article. A third investigator resolved discrepancies. For articles that presented graphical displays of Kaplan-Meier curves for outcomes desired but that did not have a results table, values were extracted graphically and were cross-referenced with all available data. Multiple attempts were made to contact the primary authors of studies in which data necessary for our purposes were not presented.

***Sources of heterogeneity.*** Potential sources of heterogeneity were identified a priori. These sources included differences in corticosteroid therapy (i.e., type, dose, duration, and time from shock onset to first dose), study quality (i.e., study design, power, and completeness of follow-up), dates of publication (i.e., reflecting changes in standard of care in the treatment of septic shock over time), and proportion of corticotropin stimulation test responders and nonresponders in each study.

***Statistical analysis.*** Crude data were analyzed using L'Abbe plots in Excel (Microsoft) [25]. When appropriate, we pooled data across studies with use of random-effects models. Heterogeneity was assessed using $\chi^2$and $I^2$ statistics; $\tau^2$was used to assess interstudy variability. Review Manager, version 5.0 (Cochrane Collaboration), was used to perform statistical analyses.

## RESULTS

***Description of studies.*** The results of our search strategy are illustrated in figure 1. Quality of studies and abstracted data are summarized in tables 1 and 2, respectively. A total of 837 studies were retrieved. A total of 829 were excluded because they were duplicates (70 [8.4%]), were not relevant on the basis

**Table 1. Indicators of quality in the studies included in our review and meta-analysis.**

| Study (year) | Randomization | Concealed allocation | Explicit definition of septic shock | Losses to follow-up explained | Intention-to-treat analysis |
|---|---|---|---|---|---|
| Bollaert et al. [13] (1998) | Yes | Yes | Yes | Yes | Yes |
| Briegel et al. [26] (1999) | Yes | Yes | Yes | Yes | Yes |
| Chawla et al. [27] (1999) | Yes | Yes | Yes | No | Yes |
| Annane et al. [12] (2002) | Yes | Yes | Yes | Yes | Yes |
| Oppert et al. [29] (2005) | Yes | Yes | Yes | Yes | Yes |
| Levy et al. [28] (2005) | No[a] | NA | Yes | NA | NA |
| Raurich et al. [30] (2007) | No[b] | NA | Yes | NA | NA |
| Sprung et al. [15] (2008) | Yes | Yes | Yes | Yes | Yes |

**NOTE.** NA, not applicable.

[a] Retrospective cohort study that was randomized with respect to treatment with recombinant human activated protein C but not corticosteroid therapy.

[b] Case-control study.

of the title (676 [80.8%]) or abstract (10 [1.2%]), or lacked outcomes or interventions of interest (14 [1.7%]). Overall, we included 8 studies [12, 13, 15, 26–30] (6 of which were randomized trials) comprising 875 patients allocated to receive corticosteroids and 1001 control subjects.

The most common corticosteroid used was hydrocortisone (200–300 mg per day in divided doses), which was used in 7 studies. Differences in timing ranged from <8 h to several days from the time of diagnosis to treatment, and the duration of therapy ranged from 5 to 11 days. Two studies used corticosteroid infusions [26, 29], whereas the remainder administered bolus doses. Corticosteroid therapy was tapered in 4 studies [13, 26, 27, 29] and abruptly discontinued in 3 [12, 15, 30] (data were not available from 1 study [28]). Only 2 studies administered concomitant mineralocorticoid therapy (fludrocortisones [50 $\mu$g per day] in both) [12, 30]. Study quality varied; not unexpectedly, the 2 observational studies [28, 30] were identified as being of lower quality, compared with the randomized trials (table 1). The median Cronin quality score ranged from 11.0 to 13.0 for randomized trials.

Direct comparison of disease severity across the included studies was difficult, because multiple disease severity and/or organ dysfunction classification systems were used (Simplified Acute Physiology Score II, Sequential Organ Failure Assessment, and APACHE II score). In general, lower median disease severity scores and placebo-group mortality (28-day mortality rates, 31.5% vs. 61.1%) were observed in the CORTICUS trial [15], compared with the previous landmark trial by Annane et al. [12].

***All-cause mortality.*** Overall, corticosteroid therapy did not result in a statistically significant difference in all-cause mortality (42.2% [369 of 875 patients] in the corticosteroid group vs. 38.4% [384 of 1001] in the control group; RR, 1.00; 95% CI, 0.84–1.18) (figure 2). Data on 28-day mortality were available for all but 1 study [30], in which only in-hospital mortality was reported. When studies were arranged in chronological order, a survival benefit was observed with corticosteroid therapy in the smaller, earlier studies; however, more-recent, larger studies were not able to show a statistically significant effect.

In a predefined subgroup analysis of 4 studies, we examined the role of adrenal responsiveness, as previously defined. No statistically significant effect on mortality was seen in responders (36.0% [64 of 178 patients] in the corticosteroid group vs. 36.3% [69 of 190] in the control group; RR, 0.95; 95% CI, 0.70–1.28) or in nonresponders (45.1% [115 of 255] in the corticosteroid group vs. 50.2% [123 of 245] in the control group; RR, 0.90; 95% CI, 0.75–1.07).

***Shock reversal.*** Six studies that reported appropriate data were pooled, and we observed a statistically significant difference in the incidence of shock reversal at 7 days between the group that received corticosteroids and the control group (64.9% [314 of 484 patients] vs. 47.5% [228 of 480]; RR, 1.41; 95% CI, 1.22–1.64) (figure 3). Subgroup analysis of 4 studies examining shock reversal by adrenal responsiveness showed statistically significant effects in both responders (129 [72.5%] of 178 in the corticosteroid group vs. 103 [54.2%] of 190 in the control group; RR, 1.38; 95% CI, 1.06–1.79) and nonresponders (152 [59.6%] of 255 in the corticosteroid group vs. 104 [42.4%] of 245 in the control group; RR, 1.38; 95% CI, 1.17–1.62).

***Safety related to superinfection.*** The incidence of superinfection (data available from 5 studies) among all patients treated with corticosteroids was not statistically different from that among control subjects (25.3% [114 of 450 patients] vs. 100 [22.7%] of 441; RR, 1.11; 95% CI, 0.86–1.42) (figure 4).

***Sensitivity analyses, assessment of publication bias, and tests of heterogeneity.*** Sensitivity analyses were performed to examine cumulative and 1-study–removed meta-analyses. Sub-

**Table 2. Characteristics of the studies included on our review and meta-analysis.**

| Study (year) | Location | No. of patients | Design | Intervention | Time to intervention | Baseline differences among groups | Corticotropin stimulation test | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Bollaert et al. [13] (1998) | France | 41 | RCT, double-blind, placebo-controlled | Hydrocortisone (100 mg IV every 8 h for ⩾5 days; then, 6-day taper) | >48 h after shock onset | No | Yes | Shock reversal, 28-day mortality, improvement in hemodynamics, and adverse events |
| Briegel et al. [26] (1999) | Germany | 40 | RCT, double-blind, placebo-controlled | Hydrocortisone (100 mg IV load; then, 0.18 mg/kg hourly infusion, until shock reversal; then, ⩾6-day taper) | <72 h after shock onset | No | No | Shock reversal, 28-day mortality, improvement in hemodynamics, organ system failure, and adverse events |
| Chawla et al. [27] (1999) | United States | 44 | RCT, double-blind, placebo-controlled | Hydrocortisone (100 mg IV every 8 h for 3 days, followed by 4-day taper) | >72 h after shock onset | No | No | Shock reversal, 28-day mortality, improvement in hemodynamics, and adverse events |
| Annane et al. [12] (2002) | France | 300 | RCT, double-blind, placebo-controlled | Hydrocortisone (50 mg IV every 6 h) and fludrocortisone (50 $\mu$g daily for 7 days) | <8 h after shock onset | No | Yes | 28-day, ICU, hospital, and 1-year mortality; shock reversal; and adverse events |
| Oppert et al. [29] (2005) | Germany | 41 | RCT, double-blind, placebo-controlled | Hydrocortisone (50 mg IV load; then, 0.18 mg/kg hourly until shock reversal; then, 3-day taper) | <24 h after shock onset | Yes; patients older in steroid group, lower platelet counts in placebo group | Yes | Shock reversal, 28-day mortality, cytokine response, and organ system failure |
| Levy et al. [28] (2005) | Multicenter | 1690 | Retrospective cohort study | Steroid type, dose, and duration unspecified | Not reported | No | No | 28-day mortality |
| Raurich et al. [30] (2007) | Spain | 203 | Case-control study | Hydrocortisone (50 mg every 6 h) and fludrocortisone (50 $\mu$g daily for 7 days) | <72 h after shock onset | Yes; higher severity of disease in steroid group | Yes; but results not stratified based on adrenal responsiveness | Shock reversal and in-hospital mortality |
| Sprung et al. [15] (2008) | Multicenter | 499 | RCT, double-blind, placebo-controlled | Hydrocortisone (50 mg IV every 6 h for 5 days, 50 mg every 12 h for 3 days, or 50 mg every 24 h for 3 days) | <72 h after shock onset | No | Yes | 28-day mortality, shock reversal, hospital and ICU length of stay, and adverse events |

**NOTE.** ICU, intensive care unit; IV, intravenous; RCT, randomized, controlled trial.

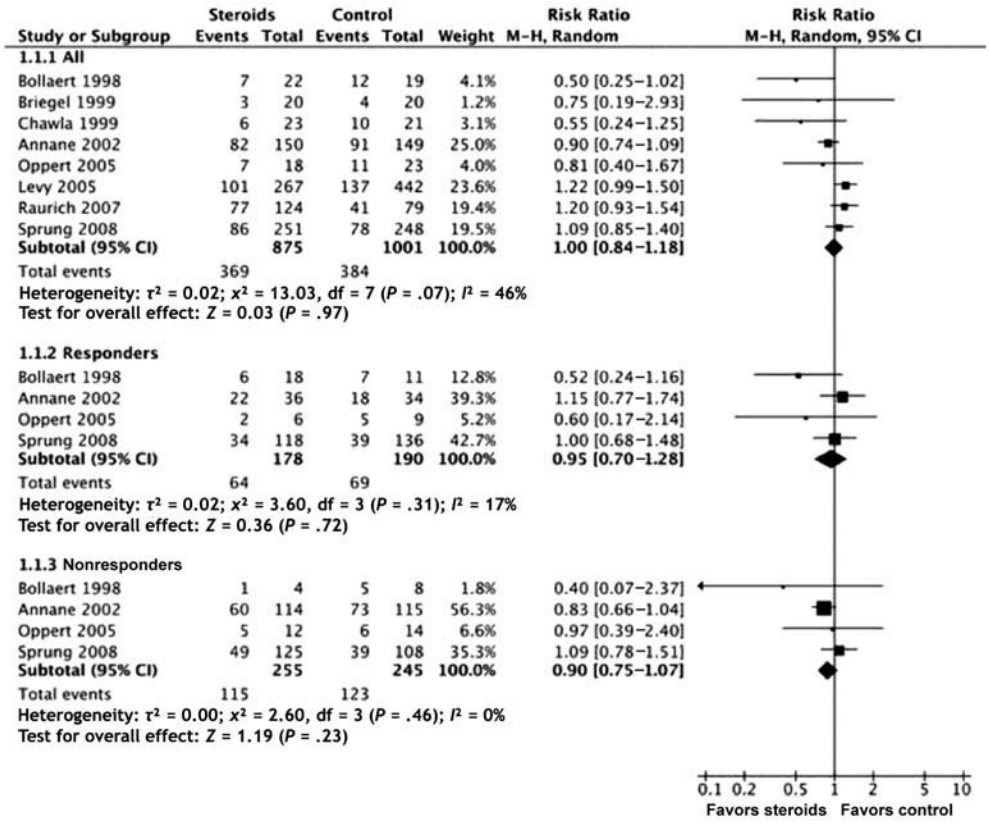


**Figure 2.** Effect of corticosteroids on 28-day all-cause mortality among patients with septic shock. Results are shown for all patients and for corticotropin stimulation test responders and nonresponders in subgroup analyses. In-hospital mortality was substituted for 28-day mortality in the study by Raurich et al. [30]. CI, confidence interval; df, degree of freedom. M-H, Mantel-Haenszel.

group analyses based on study quality (only randomized trials) and use of hydrocortisone were also performed. None of the analyses significantly altered our main results (data not shown). Degrees of heterogeneity that would preclude pooling of data were not present in any of our analyses; specific $\chi^2$, $I^2$, $\tau^2$, and $P$ values are provided in figures 2–4.

## DISCUSSION

In this meta-analysis, corticosteroid therapy had no effect on 28-day all-cause mortality among patients with septic shock, regardless of adrenal responsiveness. However, the incidence of shock reversal at 7 days was significantly higher among patients who received corticosteroids than among control subjects and was similar among corticotropin stimulation test responders and nonresponders. Although we could not demonstrate improved survival, our analyses clearly demonstrate that corticosteroid therapy improves time to shock reversal in patients with septic shock and appears to be safe in these patients, with no evidence of a statistically significant difference in the incidence of superinfection.

Severity and duration of shock are considered to be important surrogate markers of mortality [31–34], although reversal of shock and improved survival were not associated in this meta-analysis. Reversal of shock, however, implies that vasopressor support is no longer required, which may facilitate transfer out of the critical care setting; this has implications for both patients (because of reduced risk of iatrogenic adverse events) and the health care system (because of decreased costs and better allocation of scarce resources). Reversal of shock, therefore, is a clinically relevant end point to consider and may be a worthwhile goal. The lack of harm, in that there was no statistically significant difference in mortality or incidence of superinfection between the corticosteroid and control groups, is similarly reassuring.

Despite synthesization of all the available data from the past 15 years, a conclusive answer regarding the use of corticosteroids for treatment of septic shock and its effect on mortality remains elusive. Previous studies have been limited by small sample sizes and lower than expected placebo event rates, resulting in inadequate power to detect a difference in mortality. Meta-analyses performed in the 1990s were unable to show a survival benefit with corticosteroid use for patients with sepsis [16, 17, 35]. Three more recent meta-analyses subsequently demonstrated a survival advantage with the use of low-dose

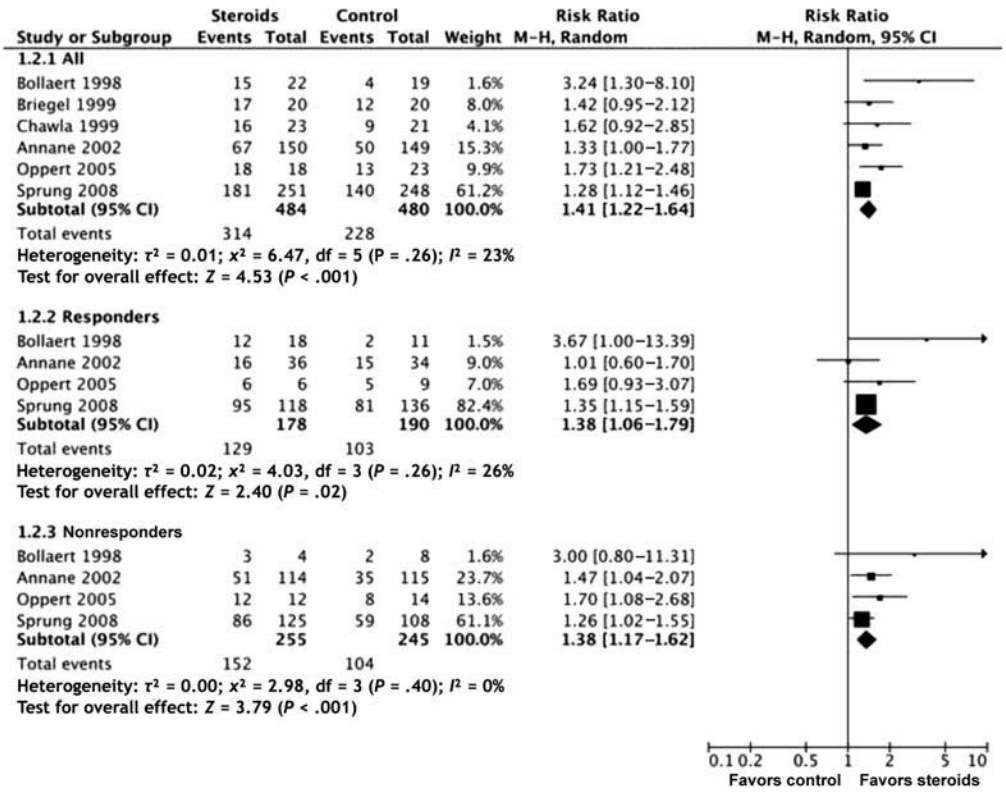


**Figure 3.** Effect of corticosteroids on the incidence of 7-day shock reversal in patients with septic shock. Results are shown for all patients and for corticotropin stimulation test responders and nonresponders in subgroup analyses. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

corticosteroid therapy in patients with sepsis and septic shock, but statistically significant results were largely borne out in subgroup analyses [18, 21, 22].

A meta-analysis by Minneci et al. [18] from 2004 was able to show a mortality benefit in 5 studies published from 1997 through 2002; 4 of these studies were included in our analysis [12, 13, 26, 27]. The fifth study, by Yildiz et al. [36], was not included in our analysis, because it was not limited to patients with septic shock; patients with sepsis, severe sepsis, or septic shock were similarly enrolled, and specific mortality rates for each of these subpopulations were not reported.

In a meta-analysis by Annane et al. [21], 16 randomized controlled trials met their inclusion criteria, although a survival benefit was only demonstrated in a subgroup of 4 trials of long courses of low-dose corticosteroid therapy. All 4 of these trials were included in our analysis [12, 13, 26, 27].

Boyer et al. [22] were similarly able to demonstrate a reduction in 28-day mortality rates (RR, 0.88; 95% CI, 0.78–1.00; $P = .04$) among patients with severe sepsis and septic shock and among those treated with long courses of low-dose corticosteroids (RR, 0.76; 95% CI, 0.64–0.90; $P = .002$). However, this analysis was not restricted to only patients with septic shock.

We can only conclude, therefore, that our analysis resulted in far different conclusions, because we (1) restricted our analysis only to patients with septic shock and (2) included additional recent large trials, such as the CORTICUS trial. To definitively answer this important clinical question, an additional multicenter trial is required. Perhaps an individual patient data meta-analysis might similarly shed further light on this question.

Heterogeneity, as in any meta-analysis, affects the validity and generalizability of results. Potential sources of heterogeneity that we anticipated included differences in corticosteroid therapy (including type of corticosteroid, dose, timing of administration, duration of therapy, whether discontinuation of therapy was abrupt or tapered, and whether concomitant mineralocorticoid therapy was used [in some studies]), study quality, date of publication, differences in patient populations by adrenal responsiveness, and varying severity of disease at the time of presentation. We were unable to explore all of these potential sources of heterogeneity because of the limited number of studies.

We restricted our analysis to randomized controlled trials (thus excluding the 2 observational studies) and to trials in which hydrocortisone was the only corticosteroid used. This

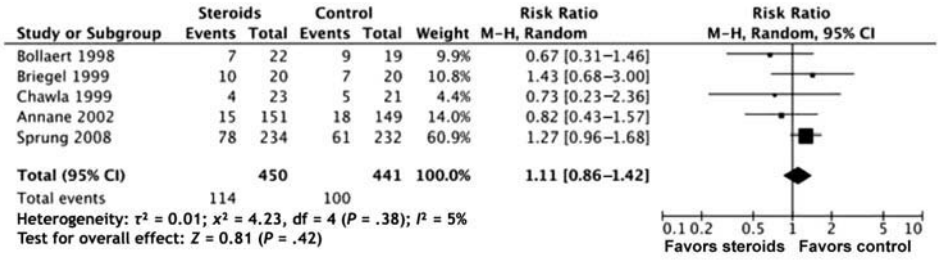


**Figure 4.** Effect of corticosteroids on the incidence of superinfection among patients with septic shock. CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel.

restriction did not alter our results (data not shown). We also performed cumulative and 1-study–removed meta-analyses, which similarly did not alter our results.

Differences in disease severity at the time of presentation resulted in heterogeneity in our analysis, which we were unable to account for. Direct comparisons of disease severity among the included studies were difficult, because multiple disease severity and/or organ dysfunction classification systems were used. Lower median disease severity scores and placebo-group mortality, however, were observed in the CORTICUS trial, which was one of the larger trials included in our analysis. Perhaps the overall lower disease severity contributed to the lack of survival benefit in this trial and in our meta-analysis.

Lastly, but perhaps most importantly, a stratified analysis of corticotropin stimulation test responders, compared with nonresponders, was defined a priori. The stratified analysis demonstrated a statistically significant increase in shock reversal at 7 days in responders and nonresponders. The complexity of the hypothalamic-pituitary-adrenal axis response in critical illness remains poorly understood, and diagnostic methods to assess its function remain inadequate. The corticotropin stimulation test, despite its widespread implementation, remains a poor indicator of hypothalamic-pituitary-adrenal function in patients with critical illness [37]. Changes in corticotropin-binding globulin, free cortisol, and tissue resistance that occur in critical illness are not assessed by the corticotropin stimulation test. For this reason and given the results of this meta-analysis, if clinicians want to reduce time to shock reversal with corticosteroid therapy in patients with septic shock, it should be done regardless of corticotropin stimulation test responsiveness.

Corticosteroid therapy appears to be safe for patients with septic shock; to date, no statistically significant difference in mortality or incidence of superinfection has been observed between patients who have received corticosteroid therapy and those who have not. Although corticosteroid therapy does not reduce mortality rates, it appears to consistently reduce time to shock reversal. Until more definitive trials are completed, corticosteroid therapy remains a reasonable and safe therapy for patients with septic shock.

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## References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med **2001**; 29:1303–10.
2. Matot I, Sprung CL. Definition of sepsis. Intensive Care Med **2001**; 27(Suppl 1):S3–9.
3. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med **2003**; 348:1546–54.
4. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Facing the challenge: decreasing case fatality rates in severe sepsis despite increasing hospitalizations. Crit Care Med **2005**; 33:2555–62.
5. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS): a prospective study. JAMA **1995**; 273:117–23.
6. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med **2006**; 34:1589–96.
7. Schramm GE, Johnson JA, Doherty JA, Micek ST, Kollef MH. Methicillin-resistant *Staphylococcus aureus* sterile-site infection: the importance of appropriate initial antimicrobial treatment. Crit Care Med **2006**; 34:2069–74.
8. Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. Am J Med **2003**; 115:529–35.
9. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest **2000**; 118:146–55.
10. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med **2003**; 31:2742–51.
11. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of re-

combinant human activated protein C for severe sepsis. N Engl J Med **2001**; 344:699–709.
12. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA **2002**; 288:862–71.
13. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med **1998**; 26:645–50.
14. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med **2008**; 36:296–327.
15. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med **2008**; 358:111–24.
16. Cronin L, Cook DJ, Carlet J, et al. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. Crit Care Med **1995**; 23:1430–9.
17. Lefering R, Neugebauer EA. Steroid controversy in sepsis and septic shock: a meta-analysis. Crit Care Med **1995**; 23:1294–303.
18. Minneci PC, Deans KJ, Banks SM, Eichacker PQ, Natanson C. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. Ann Intern Med **2004**; 141:47–56.
19. Sevransky JE, Nour S, Susla GM, Needham DM, Hollenberg S, Pronovost P. Hemodynamic goals in randomized clinical trials in patients with sepsis: a systematic review of the literature. Crit Care **2007**; 11: R67.
20. Annane D. Corticosteroids for septic shock. Crit Care Med **2001**; 29(Suppl):S117–20.
21. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. BMJ **2004**; 329:480.
22. Boyer A, Chadda K, Salah A, Annane D. Glucocorticoid treatment in patients with septic shock: effects on vasopressor use and mortality. Int J Clin Pharmacol Ther **2006**; 44:309–18.
23. Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med **2008**; 36:1937–49.
24. Meduri GU, Yates CR. Systemic inflammation-associated glucocorticoid resistance and outcome of ARDS. Ann N Y Acad Sci **2004**; 1024: 24–53.
25. L'Abbe KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. Ann Intern Med **1987**; 107:224–33.
26. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. Crit Care Med **1999**; 27:723–32.
27. Chawla K, Kupfer Y, Goldman I, Tessler S. Hydrocortisone reverses refractory septic shock. Crit Care Med **1999**; 27(Suppl):A33.
28. Levy H, Laterre PF, Bates B, Qualy RL. Steroid use in PROWESS severe sepsis patients treated with drotrecogin alfa (activated). Crit Care **2005**; 9:R502–7.
29. Oppert M, Schindler R, Husung C, et al. Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. Crit Care Med **2005**; 33:2457–64.
30. Raurich JM, Llompart-Pou JA, Ibanez J, et al. Low-dose steroid therapy does not affect hemodynamic response in septic shock patients. J Crit Care **2007**; 22:324–9.
31. Benchekroune S, Karpati PC, Berton C, et al. Diastolic arterial blood pressure: a reliable early predictor of survival in human septic shock. J Trauma **2008**; 64:1188–95.
32. Lundberg JS, Perl TM, Wiblin T, et al. Septic shock: an analysis of outcomes for patients with onset on hospital wards versus intensive care units. Crit Care Med **1998**; 26:1020–4.
33. Roman-Marchant O, Orellana-Jimenez CE, De Backer D, Melot C, Vincent JL. Septic shock of early or late onset: does it matter? Chest **2004**; 126:173–8.
34. Jones AE, Aborn LS, Kline JA. Severity of emergency department hypotension predicts adverse hospital outcome. Shock **2004**; 22:410–4.
35. Zeni F, Freeman B, Natanson C. Anti-inflammatory therapies to treat sepsis and septic shock: a reassessment. Crit Care Med **1997**; 25: 1095–100.
36. Yildiz O, Doganay M, Aygen B, Guven M, Kelestimur F, Tutuu A. Physiological-dose steroid therapy in sepsis [ISRCTN36253388]. Crit Care **2002**; 6:251–9.
37. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. J Clin Endocrinol Metab **2006**; 91:3725–45.