Meta-Analysis: The Effect of Steroids on Survival and Shock during Sepsis Depends on the Dose

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Background: Previous meta-analyses demonstrated that high-dose glucocorticoids were not beneficial in sepsis. Recently, lower-dose glucocorticoids have been studied.

Purpose: To compare recent trials of glucocorticoids for sepsis with previous glucocorticoid trials.

Data Sources: Systematic MEDLINE search for studies published between 1988 and 2003.

Study Selection: Randomized, controlled trials of sepsis that examined the effects of glucocorticoids on survival or vasopressor requirements.

Data Extraction: Two investigators independently collected data on patient and study characteristics, treatment interventions, and outcomes.

Data Synthesis: The 5 included trials revealed a consistent and beneficial effect of glucocorticoids on survival (I² = 0%; relative benefit, 1.23; [95% CI, 1.01 to 1.50]; P = 0.036) and shock reversal (I² = 0%; relative benefit, 1.71 [CI, 1.29 to 2.26]; P < 0.001). These effects were the same regardless of adrenal function. In contrast, 8 trials published before 1989 demonstrated a survival disadvantage with steroid treatment (I² = 14%; relative benefit, 0.89 [CI, 0.82 to 0.97]; P = 0.008). In comparison with the earlier trials, the more recent trials administered steroids later after patients met enrollment criteria (median, 23 hours vs. <2 hours; P = 0.02), for longer courses (6 days vs. 1 day; P = 0.01), and in lower total dosages (hydrocortisone equivalents, 1209 mg vs. 23 975 mg; P = 0.01) to patients with higher control group mortality rates (mean, 57% vs. 34%; P = 0.06) who were more likely to be vasopressor-dependent (100% vs. 65%; P = 0.03). The relationship between steroid dose and survival was linear, characterized by benefit at low doses and increasing harm at higher doses (P = 0.02).

Limitations: We could not analyze time-related improvements in medical care and potential bias secondary to nonreporting of negative study results.

Conclusions: Although short courses of high-dose glucocorticoids decreased survival during sepsis, a 5- to 7-day course of physiologic hydrocortisone doses with subsequent tapering increases survival rate and shock reversal in patients with vasopressor-dependent septic shock.


For author affiliations, see end of text.

See editorial comment on pp 70-72.
Context
Do high and low doses of glucocorticoids affect clinical outcomes differently in patients with sepsis?

Contribution
In this meta-analysis, 8 randomized, controlled trials published before 1989 showed that glucocorticoids worsened survival of patients with sepsis, while 5 recent trials showed that glucocorticoids improved survival. Recent trials administered glucocorticoids later, for longer periods, and in lower doses than earlier trials.

Implications
Short courses of high-dose glucocorticoids harm patients with sepsis while 5- to 7-day courses of physiologic doses equivalent to 200 to 300 mg of hydrocortisone daily benefit patients with sepsis.

The Editors

Dose Effects of Steroids on Survival in Sepsis

METHODS

Literature Search
We searched MEDLINE for medical literature published from 1988 to December 2003 by using the following keywords: steroids and sepsis, steroids and septic shock, glucocorticoids and sepsis, glucocorticoids and septic shock, corticosteroids and sepsis, and corticosteroids and septic shock. Studies were included if they met all of the following criteria: randomized, controlled trial design; enrollment of adult patients who met criteria for sepsis or septic shock; and a primary end point, including either the discontinuation of vasopressor therapy or a change in survival comparing glucocorticoid treatment with a control group with or without placebo. Included studies must have administered similar treatments to both the control and steroid groups, with the exception of the administration of a predetermined glucocorticoid regimen. Criteria for sepsis or septic shock needed to be clearly defined in each study and logically during a stressful state (that is, 300 mg of cortisol per day) affects outcome in septic patients. We performed the current study to update our previous meta-analysis and compare recent clinical trials with previous clinical trials of steroid use in patients with sepsis (22).

Figure 1. Flow diagram of the published articles evaluated for inclusion in this meta-analysis.
be consistent with the American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference (23) definition for sepsis (including documented site or strong suspicion of infection, temperature $>38\,^\circ\text{C}$ or $<36\,^\circ\text{C}$, heart rate $>90$ beats/min, respiratory rate $>20$ breaths/min, and leukocyte count $>12 \times 10^9$ cells/L), severe sepsis (sepsis plus organ dysfunction; hypotension or hypoperfusion, including oliguria, altered mental status, or lactate acidosis), and septic shock (hypotension despite fluid resuscitation plus hypoperfusion abnormalities) (23).

**Data Collection**

Two investigators trained in critical care medicine independently reviewed the included studies by using a standardized protocol and data collection form. A third author trained in critical care medicine evaluated and resolved discrepancies. We collected data on patient characteristics, study characteristics, treatment interventions, and treatment outcomes. Abstracted data included the presence of sepsis, severe sepsis, or septic shock; type, dose, and duration of glucocorticoid administered; incidence and severity of secondary infections; response to corticotropin stimulation testing; the number of patients with shock reversal; and the number of patient deaths. We evaluated the quality of the included trials by assessing the method and adequacy of randomization, blinding protocols, completeness of follow-up, adherence to treatment protocols, and co-interventions or treatments to each group in the studies. Our primary goal was to compare the effect of glucocorticoid administration on survival in the recent studies with the effects reported in the previously analyzed trials (22). Since the glucocorticoid regimen differed among the trials, we converted all dosages to hydrocortisone equivalents (24).

**Statistical Analysis**

Survival data were analyzed by using a Cochran–Mantel–Haenszel test to estimate the pooled effect of steroids (25). The similarity of the effect across studies was assessed by using a Breslow–Day test and reported with an $I^2$ value (26, 27). When statistically significant heterogene-

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**Table 1. Randomized, Controlled Trials of Steroids in Patients with Sepsis**

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Treatment</th>
<th>Baseline Differences Reported?</th>
<th>Study Design</th>
<th>Co-interventions Reported</th>
<th>End Points†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett et al., 1963 (35)</td>
<td>Hydrocortisone, 300 mg $\times$ 1, then decrease by 50 mg/d</td>
<td>Yes</td>
<td>Double-blind</td>
<td>Antibiotics, vasopressors</td>
<td>Hospital mortality, complications of treatment</td>
</tr>
<tr>
<td>Klastersky et al., 1971 (17)</td>
<td>Betamethasone, 1 mg/kg of body weight per d for 3 d</td>
<td>No</td>
<td>Double-blind</td>
<td>Antibiotics, vasopressors, fluids</td>
<td>20-d mortality, complications of treatment</td>
</tr>
<tr>
<td>Schuner, 1976 (16)</td>
<td>Dexamethasone, 3 mg/kg, or methylprednisolone, 30 mg/kg; may be repeated $\times$ 1</td>
<td>No</td>
<td>Double-blind</td>
<td>Antibiotics</td>
<td>28-d mortality, complications of treatment</td>
</tr>
<tr>
<td>Thompson et al., 1976 (36)</td>
<td>Methylprednisolone, 30 mg/kg $\times$ 1, and then repeat up to 3 times within 24 h if in shock</td>
<td>No</td>
<td>Double-blind</td>
<td>Antibiotics</td>
<td>Hospital mortality, toxicities of treatment</td>
</tr>
<tr>
<td>Lucas and Ledgerwood, 1984 (37)</td>
<td>Dexamethasone, 2 mg/kg bolus, followed by 2 mg/kg per d in first 48 h</td>
<td>No</td>
<td>Open-label</td>
<td>Antibiotics, digoxin, fluids, diuresis</td>
<td>14-d mortality, complications of treatment</td>
</tr>
<tr>
<td>Sprung et al., 1984 (18)</td>
<td>Methylprednisolone, 30 mg/kg, or dexamethasone, 6 mg/kg; repeat $\times$ 1 at 4 h if patient is still in shock</td>
<td>No</td>
<td>Open-label</td>
<td>Antibiotics, vasopressors, fluids</td>
<td>Hospital mortality, shock reversal, complications of treatment</td>
</tr>
<tr>
<td>Bone et al., 1987 (19)</td>
<td>Methylprednisolone, 30 mg/kg $\times$ 4 doses</td>
<td>Yes</td>
<td>Double-blind</td>
<td>Standard therapy</td>
<td>14-d mortality, shock reversal, complications of treatment</td>
</tr>
<tr>
<td>Veterans Administration, 1987 (38)</td>
<td>Methylprednisolone, 30 mg/kg bolus, followed by 5 mg/kg per h for 9 h</td>
<td>Yes</td>
<td>Double-blind</td>
<td>Antibiotics, fluids</td>
<td>14-d mortality, complications of treatment</td>
</tr>
<tr>
<td>Luce et al., 1988 (39)</td>
<td>Methylprednisolone, 30 mg/kg $\times$ 4 doses over 24 h</td>
<td>No</td>
<td>Double-blind</td>
<td>Antibiotics, standard care</td>
<td>Hospital mortality, ARDS, complications of treatment</td>
</tr>
<tr>
<td>Bollaert et al., 1998 (31)</td>
<td>Hydrocortisone, 100 mg every 8 h for $\geq$ 5 d, then 6-d taper</td>
<td>No</td>
<td>Double-blind</td>
<td>Antibiotics, vasopressors, fluids</td>
<td>28-d mortality, shock reversal, complications of treatment</td>
</tr>
<tr>
<td>Briegel et al., 1999 (32)</td>
<td>Hydrocortisone, 100 mg $\times$ 1, then 0.18 mg/kg per h until the patient is no longer receiving pressors, then $\geq$ 6-d taper</td>
<td>No</td>
<td>Double-blind</td>
<td>Antibiotics, vasopressors, fluids</td>
<td>30-d mortality, shock reversal, complications of treatment</td>
</tr>
<tr>
<td>Chawla et al., 1999 (33)</td>
<td>Hydrocortisone, 100 mg every 8 h $\times$ 3 d, then tapered over 4 d</td>
<td>No</td>
<td>Double-blind</td>
<td>Not reported</td>
<td>Shock reversal</td>
</tr>
<tr>
<td>Yildiz et al., 2002 (34)</td>
<td>Prednisolone, 5 mg every morning and 2.5 mg every night $\times$ 10 d</td>
<td>No</td>
<td>Double-blind</td>
<td>Antibiotics, vasopressors, fluids</td>
<td>28-d mortality, complications of treatment</td>
</tr>
<tr>
<td>Annane et al., 2002 (30)</td>
<td>Hydrocortisone, 50 mg every 6 h, and fluorocortisone, 50 $\mu$g/d $\times$ 7 d</td>
<td>No</td>
<td>Double-blind</td>
<td>Antibiotics, vasopressors, fluids</td>
<td>28-d mortality, shock reversal, complications of treatment</td>
</tr>
</tbody>
</table>

*ARDS = acute respiratory distress syndrome.
† For all patients enrolled, follow-up was complete for the end points listed.
Table 2. Study Characteristics of Trials Published before 1989 vs. after 1997*

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Years of Enrollment</th>
<th>Control Group Mortality Rate</th>
<th>Patients with Shock</th>
<th>Patients Receiving Vasopressors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before 1989</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bennett et al. (35)</td>
<td>1959–1963</td>
<td>33</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Klastersky et al. (17)</td>
<td>NR</td>
<td>56</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Thompson et al. (36)</td>
<td>NR</td>
<td>78</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>Lucas and Ledgerwood (37)</td>
<td>1978–1980</td>
<td>20</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>Sprung et al. (18)</td>
<td>1979–1982</td>
<td>69</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>Bone et al. (19)</td>
<td>1982–1985</td>
<td>25</td>
<td>38</td>
<td>NR</td>
</tr>
<tr>
<td>Veterans Administration (38)</td>
<td>1983–1986</td>
<td>22</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Luce et al. (39)</td>
<td>1983–1986</td>
<td>54</td>
<td>100</td>
<td>44</td>
</tr>
<tr>
<td><strong>After 1997</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bollaert et al. (31)</td>
<td>NR</td>
<td>63</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Briegel et al. (32)</td>
<td>1993–1996</td>
<td>20</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Chawla et al. (33)</td>
<td>NR</td>
<td>NR</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Yildiz et al. (34)</td>
<td>1997–1999</td>
<td>60</td>
<td>23</td>
<td>NR</td>
</tr>
<tr>
<td>Annane et al. (30)</td>
<td>1995–1999</td>
<td>61</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 1989</td>
<td>Weighted mean, 34</td>
<td></td>
<td>Weighted mean, 63</td>
<td>Weighted mean, 65</td>
</tr>
<tr>
<td>After 1997</td>
<td>Weighted mean, 57</td>
<td></td>
<td>Weighted mean, 93</td>
<td>Weighted mean, 100</td>
</tr>
</tbody>
</table>

* NR = not reported.
† Total possible dose of steroid that could have been received by a patient in a trial before beginning a taper. If 2 drugs were used in the trial, the average total dose was used.
‡ Dose based on a 70-kg patient and is expressed in hydrocortisone equivalents.
§ Length of steroid therapy before taper.
¶ Decreasing doses of steroids over 6 d was considered a steroid treatment regimen and not a taper in the original report and all previous meta-analyses.

Role of the Funding Sources

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Data Synthesis

Comparison of Study Methods

Since 1988, more than 1300 articles on steroids and sepsis have been published. Five randomized, controlled trials, all published after 1997, met inclusion criteria and were included in our analysis (30–34) (Figure 1). Four of these studies were published manuscripts, and 1 study was reported in abstract form (33).

The 5 studies published after 1997 were randomized, double-blind, placebo-controlled trials (Table 1). Each study listed specific inclusion and exclusion criteria that were consistent with American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference definitions of sepsis and septic shock (23). Each study used a severity of illness score (Simplified Acute Physiology Score [SAPS], Sequential Organ Failure Assessment...
[SOFA], or Acute Physiology and Chronic Health Evaluation [APACHE]) to compare treatment and control groups. Four of these studies enrolled only patients with vasopressor-dependent septic shock (30–33) (Table 2). In 4 of the 5 studies, 28-day mortality and treatment-related complications were the end points examined (30–32, 34). Three of these studies reported their results based on the patients’ response to a corticotropin stimulation test (30, 31, 34). In the 4 studies that reported mortality data (30–32, 34), follow-up was complete and randomization was adequate, with no statistically significant baseline differences in severity of illness, underlying disease states, and demographic characteristics between treatment and control groups (Table 1).

In comparison with the 5 more recent trials, the 9 steroid sepsis trials published before 1989 used a wider range of inclusion criteria (from “severe infection” to shock) (Tables 1 and 2) (16–19, 35–39). Two trials were open-label studies (18, 37), and 1 study was reported in abstract form (36). Three studies reported statistically significant differences in baseline characteristics between study groups (19, 35, 38). One study enrolled only patients with cancer (17), and 2 studies administered 1 of 2 different steroid regimens to enrolled patients (16, 18). One study included both children and adults, was performed a decade before the previous studies, and had an unusually high percentage of patients (almost 50% of the enrolled patients) with meningitis as the indication for enrollment compared with the other studies (35). Another study was performed by 1 investigator for a longer period (8 years) than any other study and reported the lowest mortality rate with steroid treatment of any study (10%; next lowest mortality rate, 21%) (16). Furthermore, this study, which enrolled “septic shock patients consecutively admitted” at 1 institution over 8 years, reported the results of simultaneous prospective and retrospective trials during the study time period, suggesting unintentional selection bias during enrollment (16).

The more recent trials of steroids in sepsis focused on a more severely ill group of patients. In the glucocorticoid trials published after 1997, the control group mortality rate was higher (P = 0.06) and a higher percentage of patients were in shock (P = 0.15) and were receiving vasopressor therapy (P = 0.03) (Table 2). In comparison with the trials published before 1989, the trials published after 1997 delayed the onset of steroid therapy for a longer period after patients met enrollment criteria (P = 0.02), administered longer courses (P = 0.01) of lower-dose steroid therapy (P = 0.01), and were more likely to taper the steroid dose (P = 0.03) (Table 2).

Effects of Steroids on Mortality

Combined analysis of the trials published before 1989 (16–19, 35–39) and after 1997 (30–32, 34) demonstrated that the effects of steroids on survival were highly variable (I^2 = 70%; P = 0.001) with an overall non–statistically significant effect on survival. There was an interaction between the study’s publication year and the treatment effects of steroids (P = 0.001). Trials published after 1997 revealed a consistent and overall improvement in survival associated with glucocorticoid use (I^2 = 0%; P > 0.2) (rel-
The relative survival benefits are shown with fixed-effects model and 95% CIs with glucocorticoid therapy in the sepsis trials. Both the fixed-effects estimate (to compare across studies) and the random-effects estimate (to generalize to other samples) of relative survival benefit are presented (40). Meta-analysis of all 13 trials demonstrated variability ($I^2 = 70\%$) with no overall improvement in relative survival benefit (fixed-effects estimate, 1.01 [95% CI, 0.94 to 1.09]; random-effects estimate, 1.04 [CI, 0.90 to 1.20]). The effect of steroids in the trials published before 1989 compared with those published after 1997 significantly differed ($P = 0.02$). In the 4 trials published after 1997 (1 study did not report mortality data [33]), the effect of steroids on the relative survival benefit was consistently beneficial ($I^2 = 0\%$) (fixed-effects estimate, 1.23 [CI, 1.01 to 1.50]; random-effects estimate, 1.19 [CI, 0.99 to 1.43]). The effects of steroids on the relative survival benefit in the 9 sepsis trials published before 1989 varied ($I^2 = 75\%$; fixed-effects estimate, 0.97 [CI, 0.89 to 1.04]; random-effects estimate, 0.97 [CI, 0.81 to 1.16]). Excluding 1 trial (16), which was a statistically significant outlier, yields a homogeneous group of 8 trials (17–19, 35–39) with a consistent harmful effect of steroids on survival ($I^2 = 14\%$; fixed-effects estimate, 0.89 [CI, 0.82 to 0.97]; random-effects estimate, 0.90 [CI, 0.80 to 1.02]). This excluded trial (16) had methodologic differences, including being performed by 1 investigator over an 8-year period and enrolling patients both prospectively and retrospectively. VA = Veterans Administration.
ically differed from the other trials was overly influential on this analysis and was removed (35) (Figure 3).

In the studies published before 1989, the mean control group mortality rate was lower than that in the studies published after 1997 (34% vs. 57%; \( P = 0.06 \)) (Table 3).

However, the linear relationship between control group mortality rate and the survival effect of steroids in the individual trials was not statistically significant (\( P > 0.2 \)).

**Effects of Steroids on Vasopressor Requirements**

Trials performed after 1997 reported a consistent effect of glucocorticoids on shock reversal (\( \Gamma^2 = 0\% ; P > 0.2 \)) (30–33) (Figure 4). Discontinuation of vasopressor therapy statistically significantly improved with the administration of steroids in 3 of the 4 studies. Only 2 of the 8 studies published before 1989 reported the effects of steroids on discontinuation of vasopressor therapy. These studies (18, 19) demonstrated opposite effects of high-dose steroids on shock reversal (\( P > 0.2 \) for both).

**The Effects of Corticotropin Stimulation Test Results on the Treatment Effect of Steroids**

Three of the studies published after 1997 stratified their patient samples into responders and nonresponders on the basis of the results of a 250-µg corticotropin stimulation test (Table 3, 30, 31, 34). Two of these studies (30, 34) defined a nonresponder to this test as having a change in cortisol level less than 248.3 nmol/L (\( 9 \mu g/dL \)) from baseline. The third study (31) defined a nonresponder as having a change in cortisol level less than 165.53 nmol/L (\( 6 \mu g/dL \)) from baseline. Three of these trials reported mortality and 2 of these trials reported shock reversal separately for responders and nonresponders (30, 31) (Table 3). The treatment effects of steroids on mortality or shock reversal did not statistically significantly differ on the basis of this division in both the individual trials and when these trials were combined (\( P > 0.2 \) for all). The overall effect of steroids in these studies, which delineated responders and nonresponders, was to decrease mortality (61% in the control group vs. 51% in the steroid group; \( P = 0.04 \)) and increase shock reversal (40% in the control group vs. 54% in the steroid group; \( P = 0.01 \)) in all patients.

**Other Differences in Patient Characteristics and the Incidence of Secondary Infections in Trials Published before 1989 and after 1997**

Severity of illness scores were reported in 4 of the 5 trials published after 1997 (30–32, 34). There was no difference in the severity of illness between the control groups and steroid groups in these 4 studies that could explain the

**Table 3. Effect of Physiologic Dose Steroids on Mortality and Shock Reversal Based on Responses to Corticotropin Stimulation Testing**

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Nonresponders</th>
<th>Responders</th>
<th>Control Group</th>
<th>Steroid Group</th>
<th>P Value</th>
<th>Control Group</th>
<th>Steroid Group</th>
<th>P Value</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n/n)</td>
<td>% (n/n)</td>
<td>% (n/n)</td>
<td>% (n/n)</td>
<td></td>
<td>% (n/n)</td>
<td>% (n/n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yildiz et al.   (34)</td>
<td>56 (5/9)</td>
<td>40 (2/5)</td>
<td>&gt;0.2</td>
<td>64 (7/11)</td>
<td>40 (6/15)</td>
<td>&gt;0.2</td>
<td>-8</td>
<td>&gt;0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bollaert et al. (31)</td>
<td>63 (5/8)</td>
<td>25 (1/4)</td>
<td>&gt;0.2</td>
<td>64 (7/11)</td>
<td>33 (6/18)</td>
<td>0.12</td>
<td>7</td>
<td>&gt;0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annane et al. (30)</td>
<td>63 (73/115)</td>
<td>53 (60/114)</td>
<td>0.01*</td>
<td>53 (18/34)</td>
<td>61 (22/36)</td>
<td>&gt;0.2</td>
<td>18</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Shock reversal</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bollaert et al. (31)</td>
<td>25 (2/8)</td>
<td>75 (3/4)</td>
<td>0.11*</td>
<td>18 (2/11)</td>
<td>67 (12/18)</td>
<td>0.01*</td>
<td>-1</td>
<td>&gt;0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annane et al. (30)</td>
<td>40 (46/115)</td>
<td>53 (60/114)</td>
<td>0.06*</td>
<td>53 (18/34)</td>
<td>50 (18/36)</td>
<td>&gt;0.2</td>
<td>16</td>
<td>&gt;0.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* For consistency, the \( P \) values above are based on event ratios. The authors reported statistical significance for these same values by using a test that compared time to event.
+ \( P = 0.04 \).
+ \( P = 0.03 \).
+ \( P = 0.02 \).
+ \( P = 0.01 \).
+ \( P = 0.001 \).
bene
fi
cial effect of steroids (scoring system, SAPS II [55 in the control group and 55 in the steroid group (32)]; SAPS [14 in the control group and 14 in the steroid group (31)]; APACHE II [18 in the control group and 15 in the steroid group (34)]; SAPS II [57 in the control group and 60 in the steroid group (30)]; P < 0.2 for all studies). Severity of illness scores were not reported in any study published before 1989.

Four of the 5 steroid trials published after 1997 (30–32, 34) and 6 of the 8 steroid trials published before 1989 (17–19, 35, 38, 39) reported the incidence of secondary infections. In these trials, the median overall incidences of secondary infections were similar (trials before 1989: control group, 13% [range, 3% to 21%]; steroid group, 17% [range, 3% to 26%]; and trials after 1997: control group, 27% [range, 5% to 47%]; steroid group, 19% [range, 0% to 50%]). However, the trials published before 1989 reported more associations among steroid treatment and either an increased incidence of secondary infection in sub-samples (17, 18) or more severe secondary infections (38) with increased mortality (19) (4 of 6 trials vs. 0 of 4 trials; P = 0.08).

**DISCUSSION**

Five randomized, controlled trials published after 1997 reported the effects of steroids in septic shock. Four of the 5 trials reported mortality data and demonstrated a consistent beneficial effect of glucocorticoids on mortality. In addition, 4 of the 5 trials reported shock reversal data and demonstrated a consistent beneficial effect of steroids on shock reversal. In contrast, the 9 trials published before 1989 demonstrated heterogeneous effects of steroids with an overall nonbeneficial effect. Excluding 1 trial that was a statistical outlier in this group (16) produced a homogeneous group of 8 studies that demonstrated a consistent harmful effect of steroids on survival in sepsis. The studies published after 1997 administered lower doses of glucocorticoids compared with those published before 1989. Furthermore, the relationship between steroid dose and survival was linear; this may indicate that the effects of steroids are dose-dependent during sepsis. Therefore, our meta-analysis suggests that lower, more physiologic doses of glucocorticoids reverse shock and confer a survival advantage to patients with established vasopressor-dependent septic shock.

The studies performed after 1997 administered physiologic doses of steroids in an attempt to provide replacement therapy for sepsis-induced relative adrenal insufficiency (30–34). In contrast, the trials published before 1989 used large doses of steroids to block the excessive inflammation of sepsis (17–19, 35–39) (Table 2). The harmful effect of the high-dose steroids administered in the earlier trials may have been caused by a pronounced immunosuppressive effect of the steroids. Although the numbers of secondary infections did not differ between the earlier and later studies, steroid treatment before 1989 was reported to increase the time to resolution of secondary infections (38) and subsequently increased the mortality from these infections (19). Studies published after 1997 that used lower, less immunosuppressive doses of steroids did not report an increase in the severity of secondary infections. These differences may partly explain the contradicting results of the trials published before 1989 compared with those published after 1997.
The timing of steroid initiation, duration of steroid administration, and differences in severity of illness of study samples may also account for the contradictory treatment effects of steroid therapy in these 2 sets of trials. The trials performed before 1989 administered shorter courses of glucocorticoids earlier in the patients’ septic episode. However, in the more recent trials, steroid therapy was beneficial when administered to more severely ill patients with higher control group mortality rates who were in vasopressor-dependent shock for at least 2 hours. This therapy remained beneficial when started as late as 72 hours after the initiation of vaspressors. Moreover, these trials suggest that divided doses of steroids equivalent to 200 to 300 mg of hydrocortisone daily should be administered for a minimum of 5 days, followed by tapering over 5 to 7 days. Of note, we have previously shown a relationship between mortality in the control group and treatment effect in the preclinical and clinical trials of mediator-specific anti-inflammatory agents in sepsis (29). In this previous analysis, mediator-specific anti-inflammatory agents, such as anti–tumor necrosis factor antibodies, soluble tumor necrosis factor receptors, and interleukin-1 receptor antagonists, were more beneficial in septic patients as mortality in the control group increased (29). However, in our current analysis, we did not identify such a linear relationship between steroids and mortality in the control group. This may be secondary to an overwhelming influence of drug dose on treatment effect, an insufficient difference in mortality in the control groups among the studies, or a lack of power secondary to only 13 studies available for analysis. Thus, when physiologic doses of steroids are administered to patients with a wide range of control group mortality rates, differing effects on survival may still occur.

Response to corticotropin stimulation testing has been used to determine which septic patients should receive steroid therapy. Annane and colleagues reported that survival improved with steroid administration only in nonresponders to this test (30). However, their analysis revealed no statistically significant difference in the treatment effects of steroids between responders and nonresponders. Our analysis of the 3 recent trials that reported mortality and shock reversal data by corticotropin stimulation test results showed that the beneficial effects of steroid therapy did not statistically differ between responders and nonresponders (30, 31, 34). Therefore, unless further clinical sepsis trials demonstrate that responders do not benefit from therapy, steroids should be considered for all patients with vasopressor-dependent septic shock.

The relative survival benefit demonstrated with physiologic doses of glucocorticoids is similar to that of activated protein C, the only other immunomodulatory agent that improves survival in septic patients (relative survival benefit, 1.23 [CI, 1.08 to 1.43]) (41). However, activated protein C is associated with an increased risk for bleeding, may be harmful in low-risk patients, necessitates the use of a dedicated line (42), and can cost up to $8800 to treat 1 patient. In contrast, the 5- to 7-day course of steroids reported in the more recent glucocorticoid trials was safe, easy to administer, and relatively inexpensive ($50). It is unknown whether the mechanisms of physiologic-dose steroids and activated protein C are similar during sepsis or whether the combination of steroids and activated protein C provides additional benefit than each agent alone. Further trials are needed to address these issues. If giving these 2 drugs together provides no additional benefit, then the physiologic dose of steroids is preferred because they are safer, easier to administer, and less expensive.

The limitations of our analysis are consistent with those of all meta-analyses, including the potential bias secondary to nonreporting of negative study results. The beneficial effects of glucocorticoid therapy in the later trials may be partially due to time-related factors, such as improvements in ventilator management, fluid therapy, and the use of vasopressor and inotropic agents. In addition, our meta-analysis includes some relatively small studies conducted after 1997; however, we did not find any study during this time that was overly influential on the analysis.

Clinical sepsis trials of high-dose steroids published before 1989 revealed that steroids are harmful. However, the more recent trials of physiologic doses of steroids in sepsis demonstrate an overall improvement in survival and shock reversal. These contradictory results may be explained by a linear relationship between the dose of steroids and their effect on survival. At high doses, steroids have marked immunosuppressive effects that may increase the severity of primary or secondary infections and lead to worse outcomes. In contrast, low doses of steroids may be beneficial through either augmentation of adrenal function in the stressed state or limited anti-inflammatory properties that do not cause harmful immunosuppression. The effects of physiologic doses of steroids do not statistically differ between responders and nonresponders to corticotropin stimulation testing. From our analysis, we cannot definitively identify the optimal dose of steroids to administer and the timing of treatment. However, our analysis demonstrates that patients with established vasopressor-dependent septic shock for at least 2 hours and for as long as 72 hours will have improved shock reversal and survival if given a 5- to 7-day course of physiologic doses of hydrocortisone (200 to 300 mg/d) followed by a 5- to 7-day taper. Additional studies are necessary to determine whether physiologic doses of steroids are beneficial if administered to septic patients who do not develop shock or patients who develop shock but have not yet advanced to a vasopressor-dependent state.

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