# Corticosteroids in the Treatment of Severe Sepsis and Septic Shock in Adults

## A Systematic Review

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**Context** The benefit of corticosteroids in severe sepsis and septic shock remains controversial.

**Objective** We examined the benefits and risks of corticosteroid treatment in severe sepsis and septic shock and the influence of dose and duration.

**Data Sources** We searched the CENTRAL, MEDLINE, EMBASE, and LILACS (through March 2009) databases as well as reference lists of articles and proceedings of major meetings, and we contacted trial authors.

**Study Selection** Randomized and quasi-randomized trials of corticosteroids vs placebo or supportive treatment in adult patients with severe sepsis/septic shock per the American College of Chest Physicians/Society of Critical Care Medicine consensus definition were included.

**Data Extraction** All reviewers agreed on trial eligibility. One reviewer extracted data, which were checked by the other reviewers and by the trials' authors whenever possible. Some unpublished data were obtained from the trials' authors. The primary outcome for this review was 28-day mortality.

**Results** We identified 17 randomized trials (n=2138) and 3 quasi-randomized trials (n=246) that had acceptable methodological quality to pool in a meta-analysis. Twenty-eight-day mortality for treated vs control patients was 388/1099 (35.3%) vs 400/1039 (38.5%) in randomized trials (risk ratio [RR], 0.84; 95% confidence interval [CI], 0.71-1.00; $P$=.05; $I^2$=53% by random-effects model) and 28/121 (23.1%) vs 24/125 (19.2%) in quasi-randomized trials (RR, 1.05, 95% CI, 0.69-1.58; $P$=.83). In 12 trials investigating prolonged low-dose corticosteroid treatment, 28-day mortality for treated vs control patients was 236/629 (37.5%) vs 264/599 (44%) (RR, 0.84; 95% CI, 0.72-0.97; $P$=.02). This treatment increased 28-day shock reversal (6 trials; 322/481 [66.9%] vs 276/471 [58.6%]; RR, 1.12; 95% CI, 1.02-1.23; $P$=.02; $I^2$=4%) and reduced intensive care unit length of stay by 4.49 days (8 trials; 95% CI, –7.04 to –1.94; $P<.001$; $I^2$=0%) without increasing the risk of gastroduodenal bleeding (13 trials; 65/800 [8.1%] vs 56/764 [7.3%]; $P$=.50; $I^2$=0%), superinfection (14 trials; 184/998 [18.4%] vs 170/950 [17.9%]; $P$=.92; $I^2$=8%), or neuromuscular weakness (3 trials; 4/407 [1%] vs 7/404 [1.7%]; $P$=.58; $I^2$=30%). Corticosteroids increased the risk of hyperglycemia (9 trials; 363/703 [51.6%] vs 308/670 [46%]; $P<.001$; $I^2$=0%) and hypernatremia (3 trials; 127/404 [31.4%] vs 77/401 [19.2%]; $P<.001$; $I^2$=0%).

**Conclusions** Corticosteroid therapy has been used in varied doses for sepsis and related syndromes for more than 50 years, with no clear benefit on mortality. Since 1998, studies have consistently used prolonged low-dose corticosteroid therapy, and analysis of this subgroup suggests a beneficial drug effect on short-term mortality.

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SEVERE SEPSIS PLACES A LARGE BURden on health care systems, with an incidence ranging from 50 to 300 cases per 100 000 population and a short-term mortality of 20% to 25%, reaching up to 50% when shock is present.[1] In sepsis, the hypothalamic-pituitary-adrenal axis affects inflammation through white blood cells, cytokines, and nitric oxide production.[2] In parallel, inflammatory cytokines may either suppress cortisol response to adrenocorticotropin,[3] resulting in insufficient adrenal output,[4] or compete with intracellular glucocorticoid receptor function, resulting in peripheral tissue glucocorticoid resistance.[5,6] Both high-dose (eg, 30 mg/kg of methylprednisolone[7]) and low-dose (eg, 0.1 mg/kg of dexamethasone[8,9]) corticosteroids prolong survival in septic animals. In healthy volunteers challenged with endotoxin, low-dose corticosteroids (eg, 10 mg of prednisolone) prevent release

**For editorial comment see p 2388.**

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of proinflammatory cytokines and activation of endothelial cells and neutrophils and inhibit the acute-phase response without altering the coagulation-fibrinolysis balance.[10] In patients with septic shock, a 3-day course of corticosteroids reduces symptoms of systemic inflammation and cessation of treatment amplifies the systemic inflammatory response.[11] Importantly, patients with sepsis have elevated circulating levels of proinflammatory cytokines for weeks after clinical resolution of infection.[12] Finally, a recent randomized controlled study of hydrocortisone, 200 mg/d, in 82 patients with septic shock found lower mortality in those treated for 7 days vs 3 days (24% vs 32%, respectively).[13] Thus, corticosteroids may be of benefit in septic shock and the duration of treatment could differentially affect patient response to treatment.

Initial trials investigating high-dose corticosteroids, usually given as a single bolus in an attempt to block any potential proinflammatory cytokine burst, found no evidence for a survival benefit.[14] Two recent systematic reviews including randomized controlled trials of lower doses (≤300 mg/d of hydrocortisone or equivalent) and longer durations (≥5 days) of treatment with corticosteroids[15-19] found that corticosteroids may improve survival in septic shock patients.[20,21] However, a recent negative multicenter trial result has cast doubt on their benefit-risk ratio.[22] Thereafter, recent international guidelines restricted the use of corticosteroids in septic shock to patients who are poorly responsive to fluid replacement and vasopressors.[23,24]

We performed a new systematic review of the effects of corticosteroids on 28-day mortality in patients with severe sepsis and septic shock, and we examined, as a secondary objective, whether the dose or duration of treatment with corticosteroids influenced patients' outcomes.

## METHODS

A longer version of this review will be published in the Cochrane Library.[25]

### Search Strategy

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

**Electronic Searches.** We searched the Cochrane Infectious Diseases Group's trials register for relevant trials up to August 2003 using the search terms *sepsis* and *septic shock*. Full details of the Cochrane Infectious Diseases Group's methods and the journals that were hand-searched are published in the Cochrane Library in the section on Collaborative Review Groups. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (Issue 1, 2009) using the search terms *sepsis*, *septic shock*, *steroids*, and *corticosteroids* (for detailed search strategy, see Appendix 1 of the supplemental methods published online). We also searched the following electronic databases using the topic search terms in combination with the search strategy for identifying trials developed by the Cochrane Collaboration[26]: (1) SilverPlatter MEDLINE (1966 to March 2009) using the search terms *sepsis*, *septic shock*, *steroids*, *corticosteroids*, *adrenal cortex hormones*, and *glucocorticoids*; (2) SilverPlatter EMBASE (1974 to March 2009) using the search terms *sepsis*, *septic shock*, *steroids*, and *corticosteroids*; (3) LILACS (http://www.bireme.br; accessed March 2009) using the search terms *sepsis*, *steroids*, and *corticosteroids*.

**Other Sources.** We checked the reference lists of all trials identified by the above methods and contacted authors to identify any additional published or unpublished data. We also searched the proceedings of the annual meetings of major critical care medicine symposia; ie, the Society of Critical Care Medicine, the American Thoracic Society, the International Symposium on Intensive Care and Emergency Medicine, the American College of Chest Physicians, and the European Society of Intensive Care Medicine for years 1998 to 2008 (inclusive).

Finally, we searched for ongoing randomized controlled trials in the metaRegister of Controlled Trials using the search terms *sepsis*, *septic shock*, *steroids*, *corticosteroids*, *adrenal cortex hormones*, and *glucocorticoids* (http://www.controlled-trials.com/mrct/active; accessed March 2009).

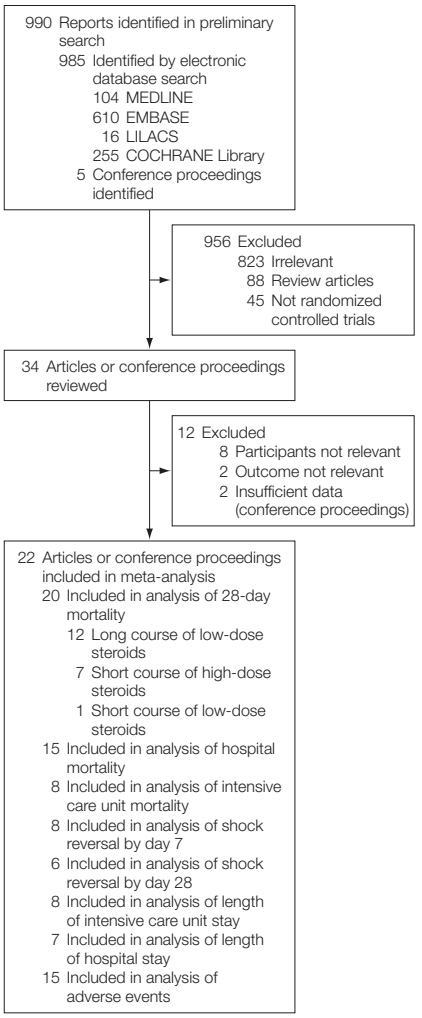
### Study Selection

Six authors (D.A., E.B., P.E.B., J.B., D.K., and Y.K.) checked the titles and abstracts identified with the search strategy and examined in full any trial that potentially met the inclusion criteria. Whenever possible, 1 author was blinded to the journal in which the article was published, the authors, the institution, and the magnitude and direction of the results. Five authors (D.A., P.E.B., J.B., D.K., and Y.K.) evaluated all trials. Any disagreement among the 5 authors was settled by discussion with the sixth author (E.B.) until a consensus was reached. Study authors' were contacted by 1 author (D.A.) for clarification when necessary. The authors decided which trials fit the inclusion criteria. We included randomized or quasi-randomized (ie, using systematic methods, such as alternation, assignment based on date of birth, case record number, and date of presentation) controlled trials with or without blinding, with a primary focus on adults with severe sepsis or septic shock.[27] We included data from trials on acute lung injury and acute respiratory distress syndrome (ARDS) if separate data were included for patients with sepsis or when contact with the authors resulted in provision of the data. We considered studies on intravenous treatment with any type of corticosteroid preparation (eg, cortisone, hydrocortisone, methylprednisolone, betamethasone, or dexamethasone). A low dose of corticosteroid treatment was defined as a total daily dose of 300 mg or less of hydrocortisone (or equivalent). Studies using treatments that exceeded this daily dosage were considered to be investigating high-dose corticosteroids. A prolonged course was defined as a full dose of treatment for at least 5 days; otherwise, treatment was considered a short course. The control intervention could include standard therapy (antibiotics, fluid replacement, inotropic or vasopressor therapy, mechanical ventilation, or renal replacement therapy) or placebo.

### Data Collection and Analysis

**Data Extraction.** One author (D.A.) designed a standard data extraction form, and 4 other authors (P.E.B., J.B., D.K., and Y.K.) amended and validated the design

**Figure 1.** Literature Search and Study Selection




of the form prior to abstraction of data. Then, 4 authors (D.A., P.E.B., J.B., and D.K.) independently extracted data. The authors of the trials were contacted (by D.A.) to provide missing data when possible. One author (D.A.) entered the data into the computer (administrative staff independently reentered all data to achieve a double entry), and 5 authors (E.B., P.E.B., J.B., D.K., and Y.K.) checked it.

**Assessment of Methodological Quality.** We documented the method of generation of allocation sequence and allocation concealment and we described, whenever possible, whom among patients, caregivers, data collectors, outcome assessors, and data analysts remained blinded.[28] We also documented whether the analysis respected the intention-to-treat principle and considered loss to follow-up as adequate (≥90% of randomized participants included in the analysis), unclear (not reported), or inadequate (<90% of randomized participants included in the analysis). Any disagreement among the 5 authors (D.A., P.E.B., J.B., D.K., and Y.K.) was settled by discussion with the sixth author (E.B.) until a consensus was reached. We contacted study authors for clarification when necessary.

**Data Analyses.** The primary outcome for this meta-analysis was 28-day all-cause mortality. Indeed, this was the primary outcome in most randomized controlled trials on sepsis conducted in the past 15 years.[29] Most studies performed before 1992 reported 14-day or hospital mortality rates. For these studies, we used 14-day or hospital mortality rates to compute the pooled analysis on 28-day mortality unless actual 28-day mortality rates could be obtained from study authors. Secondary outcomes were intensive care unit and hospital mortality rates and lengths of stay in survivors, the number of patients with shock reversal (as defined by stable hemodynamic status for ≥24 hours after withdrawal of vasopressor therapy) at day 7 and at day 28, and the number of patients with adverse events (ie, gastrointestinal bleeding, superinfection, hyperglycemia, hypernatremia, neuromuscular weakness).

For each outcome and for each study, we computed $2 \times 2$ tables summarizing the number of patients who experienced the event or outcome in each comparison group and the total number of patients in each group. All statistical calculations were performed using Review Manager version 5,[30] except meta-regression analyses that were computed using STATA/IC version 10.0 (Stata Corp, College Station, Texas). We calculated a weighted treatment effect across trials. The results were expressed as risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes, and weighted mean difference (95% CI) for continuous outcomes. We used the Mantel-Haenszel random-effects model for all analyses. All reported *P* values are 2-sided, and values of $P<.05$ were considered statistically significant.

To identify potential sources of heterogeneity (when the $I^2$ statistic was 20% or more), we a priori sought to conduct a subgroup analysis based on dose/duration characteristics; that is, a long course (≥5 days) of low-dose (≤300 mg/d of hydrocortisone or equivalent) corticosteroids. This subgroup analysis allowed the evaluation of a strategy based on new developments in the understanding of the role of corticosteroids in host response to sepsis that has been tested in trials performed after 1992.[20,21] Older trials used short courses (1-4 boluses within 24 hours) of high-dose corticosteroids (>300 mg of hydrocortisone or equivalent) as an anti-inflammatory approach, while the most recent trials used low-dose corticosteroids for longer periods of time as hormone replacement strategy. To further explore the putative interaction between steroid dose/duration and the magnitude of effect, we considered performing a meta-regression analysis using dosage and duration of corticosteroid treatment as predictors. We also a priori tested the interaction between baseline severity of illness and the magnitude of effect in a meta-regression analysis using mortality rates in control groups as predictors. We conducted sensitivity analyses for generation of allocation sequence, concealment of allocation, and blinding. We sought evidence of publication bias using the funnel plot method.

We assessed the validity of the subgroup analysis (dose/duration) on the basis of the following criteria: (1) subgroup comparisons within studies rather than between studies; (2) hypothesis preceded the analysis; (3) 1 of very few hypotheses; (4) large and consistent difference across studies; and (5) external evidence to support the results.[31] When subgroup analyses met these criteria and were found to be statistically significant, we applied Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria to evaluate the quality of evidence.[32]

## RESULTS

### Description of Studies

Our search results are detailed in FIGURE 1. The search strategy yielded 34 randomized controlled trials investigating

**Table 1.** Characteristics of Included Studies

| Source | No. of Sites | Population | No. of Participants | Interventions | Primary Outcome | Secondary Outcomes |
|---|---|---|---|---|---|---|
| Wagner et al,[34] 1955 | 2 | Pneumococcal pneumonia; shock was present only in 3 patients | 113 | (1) hydrocortisone (orally, 80 mg on admission, then 60 mg every 8 h on day 1, 40 mg every 6 h on day 2, 20 mg every 6 h on day 3, 10 mg every 6 h on day 4, and 10 mg every 12 h on day 5); (2) standard therapy (first 85 patients); (3) placebo (last 28 patients) | Fever | Pleuritic pains, patient well-being |
| Klastersky et al,[37] 1971 | 1 | Advanced cancer and life-threatening infection | 85 | (1) Betamethasone (1 mg/kg/d in 2 intravenous doses for 3 consecutive days); (2) placebo | 30-d mortality | Safety |
| Schumer,[39] 1976 | 1 | Septic shock and positive blood cultures | 172 | (1) Dexamethasone (3 mg/kg as a single intravenous bolus); (2) methylprednisolone (30 mg/kg as a single intravenous bolus); (3) placebo<br>Treatment may have been repeated once after 4 h and had to be initiated at the time of diagnosis. | 28-d mortality | Safety |
| Sprung et al,[42] 1984 | 2 | Vasopressor-dependent septic shock | 59 | (1) Dexamethasone (6 mg/kg as a single intravenous 10- to 15-min infusion); (2) methylprednisolone (30 mg/kg as a single intravenous 10- to 15-min infusion); (3) no treatment; (4) placebo<br>Treatment may have been repeated once after 4 h if shock persisted and had to be initiated at the time of diagnosis. | Hospital mortality, shock reversal | Complications of septic shock, safety |
| Lucas and Ledgerwood,[41] 1984 | 1 | Septic shock | 48 | (1) Dexamethasone (2 mg/kg as a single intravenous bolus followed by a maintenance infusion of 2 mg/kg every 24 h for 2 d); (2) standard treatment | 14-d mortality (unclear) | Hemodynamic and pulmonary function, safety |
| Bone et al,[45] 1987 | 19 | Severe sepsis, septic shock | 382 (severe sepsis, n=234; septic shock, n=148) | (1) Methylprednisolone (30-mg/kg 20-min intravenous infusion every 6 h for 24 h); (2) placebo<br>Treatment had to be initiated by 2 h after time entry criteria were met. | 14-d development of shock for severe sepsis | Shock reversal; 14-d death and safety |
| VASSCSG,[46] 1987 | 10 | Severe sepsis, septic shock | 223 (severe sepsis, n=123; septic shock, n=100) | (1) Methylprednisolone (30 mg/kg as a single intravenous 10- to 15-min infusion followed by a constant infusion of 5 mg/kg/h for 9 h); (2) placebo<br>Treatment had to be initiated within 2 h | 14-d mortality | Safety |
| Luce et al,[47] 1988 | 1 | Septic shock | 75 | (1) Methylprednisolone (30-mg/kg 15-min intravenous infusion every 6 h for 24 h); (2) placebo | Prevention of ARDS | Hospital mortality |
| Bollaert et al,[15] 1998 | 2 | Vasopressor- and ventilator-dependent septic shock | 41 | (1) Hydrocortisone (100-mg intravenous bolus every 8 h for 5 d then weaned over 6 d); (2) placebo<br>Treatment had to be initiated ≥48 h after shock onset. | Shock reversal | 28-d mortality, hemodynamic function, safety |
| Briegel et al,[16] 1999 | 1 | Vasopressor- and ventilator-dependent septic shock | 40 | (1) Hydrocortisone (100-mg loading dose then 0.18 mg/kg/h continuous infusion until shock reversal, then weaning); (2) placebo<br>Treatment had to be initiated ≤72 h after shock onset. | Shock reversal | 28-d mortality. hemodynamic function, organ dysfunction, safety |
| Chawla et al,[17] 1999 | 1 | Vasopressor-dependent septic shock | 44 | (1) Hydrocortisone (100-mg intravenous bolus every 8 h for 3 d then weaning over 4 d); (2) placebo<br>Treatment had to be initiated ≥72 h after shock onset. | Shock reversal | 28-d mortality, hemodynamic function, safety |

*(continued)*

**Table 1.** Characteristics of Included Studies (continued)

| Source | No. of Sites | Population | No. of Participants | Interventions | Primary Outcome | Secondary Outcomes |
|---|---|---|---|---|---|---|
| Annane et al,[18] 2002 | 19 | Vasopressor- and ventilator-dependent septic shock | 300 | (1) Hydrocortisone (50-mg intravenous bolus every 6 h for 7 d plus fludrocortisone, 50 µg orally every 24 h for 7 d); (2) respective placebos<br>Treatment had to be initiated ≤8 h after shock onset. | 28-d mortality in non-responders | 28-d mortality in responders and in all patients, intensive care unit mortality, hospital mortality, 1-y mortality, shock reversal, organ failure–free days, safety |
| Yildiz et al,[19] 2002 | 1 | Sepsis, severe sepsis, septic shock | 40 (sepsis, n=14; severe sepsis, n=17; septic shock, n=9) | (1) Prednisolone (2 intravenous boluses, 5 mg at 6 AM and 2.5 mg at 6 PM for 10 d); (2) placebo | 28-d mortality | Safety |
| Keh et al,[11] 2003 | 1 | Vasopressor-dependent septic shock | 40 | (1) Hydrocortisone (100-mg 30-min intravenous infusion then 10 mg/h continuous infusion for 3 d); (2) placebo<br>All participants received hydrocortisone for 3 d preceded or followed by placebo for 3 d | Immune response | Hemodynamic function, organ function, safety |
| Confalonieri et al,[50] 2005 | 6 | Severe community-acquired pneumonia | 46 | (1) Hydrocortisone (200-mg intravenous loading bolus, then 10 mg/h continuous infusion for 7 d, then weaning over 4 d); (2) placebo | Improvement in $PaO_2$:$FiO_2$ and in MODS score by day 8 | Duration of mechanical ventilation, length of stay, hospital and 60-d survival, safety |
| Oppert et al,[51] 2005 | 1 | Vasopressor-dependent septic shock | 40 | (1) Hydrocortisone (50-mg intravenous bolus then 0.18 mg/kg/h continuous infusion up to vasopressor cessation >1 h, then weaned by steps of 0.02 mg/kg/h every d; (2) placebo | Time to vasopressor cessation | Cytokine response, 28-d survival, SOFA score |
| Tandan et al,[52] 2005 | 1 | Septic shock and adrenal insufficiency | 28 | (1) Hydrocortisone (stated low-dose but actual dose and duration not reported; (2) placebo | 28-d mortality or survival to hospital discharge | Shock reversal, APACHE II score, safety |
| Rinaldi et al,[53] 2006 | 1 | Severe sepsis and vaso-pressor-free | 40 | (1) Hydrocortisone (300 mg/d as a continuous infusion for 6 d, then tapered off); (2) standard therapy | Not explicitly stated | Microalbuminuria-creatinine ratio, serum levels of C-reactive protein and procalcitonin, duration of MV, SOFA score, length of stay |
| Cicarelli et al,[55] 2007 | 1 | Vasopressor-dependent septic shock | 29 | (1) Dexamethasone (0.2 mg/kg intravenously, 3 doses at intervals of 36 h); (2) placebo | Duration of vasopressor use | Duration of MV mortality |
| Meduri et al,[56] 2007 | 5 | Early ARDS (≤72 h after diagnosis of ARDS), severe sepsis or septic shock | 91 (early ARDS); 61 (severe sepsis or septic shock) | (1) Methylprednisolone (1-mg/kg loading dose, then continuous infusion of 1 mg/kg/d [d 1-14], 0.5 mg/kg/d [d15-21], 0.25 mg/kg/d [d 22-25], and 0.125 mg/kg/d [d 26-28]). If MV free before day 14, patient was advanced to day 15 of drug therapy.<br>Treatment was given intravenously until enteral intake was restored, then it was given as a single oral dose.<br>(2) Placebo | Improvement in Lung Injury Score at day 7 | MV free days, MODS score at day 7, survival, C-reactive protein levels at day 7, safety |
| Huh et al,[13] 2007 | 1 | Septic shock and adrenal insufficiency | 82 | (1) Hydrocortisone every 6 h as an intravenous 50-mg bolus for 3 d; (2) hydrocortisone every 6 h as an intravenous 50-mg bolus for 7 d | 28-d mortality | Shock reversal, duration of MV, length of stay, safety |
| Sprung et al,[22] 2008 | 52 | Septic shock | 499 | (1) Hydrocortisone (50 mg every 6 h for 5 d, then 50 mg every 12 h for 3 d, then 50 mg every 24 h for 3 d); (2) placebo | 28-d mortality in nonresponders | 28-d mortality in responders and in all patients, intensive care unit mortality, hospital mortality, 1-y mortality, shock reversal, organ failure–free days, safety |

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome; MV, mechanical ventilation; SOFA, Sequential Organ Failure scale; VASSCSG, Veterans Administration Systemic Sepsis Cooperative Study Group.

corticosteroid treatment in severe sepsis or septic shock.[11,13,15-19,22,33-58] Of these, we excluded 12 trials.* The reasons for excluding these trials are discussed herein (eTable 1, available at http://www.jama.com). We included the remaining 22 trials and have described them herein (TABLE 1). Ten additional randomized trials of prolonged treatment with low-dose corticosteroids are still ongoing (eTable 2).

**Source of Information.** For 13 trials, we extracted data from articles and obtained additional unpublished information from primary authors† (Appendix 2 of the supplemental methods published online). In 1 trial, contact with authors did not provide additional information.[47]

**Trial Centers.** Six trials were multicenter (ie, >2 centers)[18,22,45,46,50,56] and 1 trial was multinational.[22]

**Description of Participants.** Seven trials included patients both with severe sepsis and with septic shock.[19,34,37,41,45-47] However, only 1 study provided separate data for septic shock.[45] Two trials included patients with severe sepsis.[50,53] One trial included patients with early ARDS, and the primary author provided data for patients with severe sepsis or septic shock.[56] The remaining trials investigated exclusively patients with vasopressor-dependent septic shock. Two trials included only septic shock patients with adrenal insufficiency (defined by a postcorticotrophin stimulation cortisol change of <9 μg/dL).[13,52] Five trials administered a short corticotrophin test at study entry.[15,18,22,51,56]

**Control.** Two trials did not use a placebo, and the corticosteroid treatment was compared with a standard therapy.[41,53] In 1 trial, a placebo was used in only 1 center.[42] In another trial, a placebo was available only at the end of the study.[34] Thus, the corticosteroid therapy was compared with a standard therapy in the first 85 patients and with a placebo in the last 28 patients. In the remaining trials, corticosteroid therapy was compared with placebo.

**Corticosteroid Dose and Duration.** Nine trials investigated a prolonged course of low-dose intravenous hydrocortisone.[13,15-17,22,50-53] Five trials investigated a prolonged course of low-dose intravenous hydrocortisone and oral fludrocortisone,[18] oral hydrocortisone,[34] intravenous prednisolone,[19] intravenous dexamethasone,[55] and intravenous methylprednisolone.[56] In 7 trials,[13,15,18,22,51,52,56] the effects of corticosteroids were analyzed in patients with adrenal insufficiency. In 1 trial,[13] the authors compared hydrocortisone, 50 mg intravenously every 6 hours, given for 3 days vs 7 days. Finally, 7 trials investigated a short course of high-dose methylprednisolone,[39,41,42,45-47] dexamethasone,[39,41,42] or betamethasone.[37]

**Outcomes.** Twenty-eight-day mortality rates were reported in 12 trials[13,15-19,22,37,50-52,55] and were obtained from the primary authors for 3 additional trials.[42,53,56] Three trials reported 14-day mortality rates.[41,45,46] Three trials reported hospital mortality rates,[34,39,47] with 1 trial reporting only 2 deaths among 113 patients during hospital stay.[34] One trial did not report mortality rates.[11] Among the 21 trials for which outcome data were obtained, we excluded the trial comparing 3 days vs 7 days of treatment.[13] Thus, data from 20 trials were pooled for this outcome measure.

Intensive care unit mortality rates were reported in 6 trials[15,16,18,22,50,56] and were obtained from the primary authors for 2 additional trials.[17,53] Hospital mortality rates were available for 15 trials.‡ The rates of shock reversal were reported at day 7 for 8 trials[15-18,22,42,45,51] and at day 28 for 6 trials.[15-18,22,52] The length of intensive care unit stay in survivors was obtained from primary authors of 8 trials,[15-18,22,50,53,56] and the length of hospital stay in survivors was available for 7 trials.[15,17-19,22,50,56]

## Risk of Bias in Included Studies

The detailed methodological quality of individual trials is shown in TABLE 2.

**Randomization.** In 2 trials, randomization (method of generation of allocation sequence) was judged inappropriate to minimize selection bias because it was based on hospital numbers.[34,41] The method appeared unclear in 1 trial.[13] Contact with the primary author allowed clarification that the randomization list was generated by computer and was judged adequate.[52] Randomization was judged adequate in the remaining trials. We judged the method for allocation concealment to be adequate in all but 5 trials. In 2 trials, assignment of treatment was based on hospital numbers[34,41] and in 1 trial on unsealed envelopes.[39] In 1 trial, the investigators at 1 of the 2 participating centers enrolling patients could have foreseen upcoming assignment because the local ethical committee refused the blinded allocation.[42] In another trial, the method for allocation concealment was not reported.[13]

**Blinding.** In 4 trials, blinding was uncertain (unblinded/unable to ascertain blinding).[34,39,41,42] In 1 trial,[34] blinding of treatment administration and of outcome assessment was used only at the end of the study (for the last 28 among 113 patients). In 1 trial, the method used to blind treatment administration and outcome assessment was not provided.[39] In 1 trial,[41] the authors stated that "steroids were administered in a nonblinded manner, because a previous unpublished double-blind study of steroid therapy for patients caused uniform defervescence in the steroid-treated patients, thereby permitting an accurate prediction of steroid supplementation by the nursing personnel." In the last trial,[42] the local ethical committee of 1 of the 2 centers did not permit double-blind allocation and administration of treatment. Then, for 40 of the 59 patients included in the trial, blinding was not possible. The remaining trials were deemed as appropriately double-blinded.

**Withdrawal.** Ten trials§ explicitly provided the number of and reasons for withdrawal or loss to follow-up.

*References 33, 35, 36, 38, 40, 43, 44, 48, 49, 54, 57, 58.
†References 11, 15-18, 22, 42, 50-53, 55, 56.
‡References 15-19, 22, 34, 37, 39, 41, 42, 47, 50, 53, 56.
§References 11, 15, 16, 18, 22, 41, 46, 51, 53, 56.

**Table 2.** Risk of Bias in Studies

| Source | Sequence Generation | Allocation Concealment | Blinding[a] | Incomplete Outcome Data Addressed |
|---|---|---|---|---|
| Wagner et al,[34] 1955 | Hospital No. | Inadequate, based on hospital numbers | No | Loss to follow-up not stated |
| Klastersky et al,[37] 1971 | Unclear (not stated) | Unclear (not stated) | Yes: patients, caregivers<br>Unclear: data collectors, outcome assessors, data analysts | No loss to follow-up |
| Schumer,[39] 1976 | Randomized card system | Unsealed envelopes | Yes: patients<br>No: caregivers, data collectors, outcome assessors, data analysts | No loss to follow-up |
| Lucas and Ledgerwood,[41] 1984 | Hospital No. | Inadequate, based on hospital No. | No | No loss to follow-up |
| Sprung et al,[42] 1984 | Computer-generated randomization list | Inadequate | Yes in 1 center<br>No in 1 center | No loss to follow-up |
| Bone et al,[45] 1987 | Computer-generated randomization list | Randomization was centralized | Yes | Lost to follow-up: 1 patient |
| VASSCSG,[46] 1987 | Computer-generated randomization list | Randomization was centralized | Yes | No loss to follow-up |
| Luce et al,[47] 1988 | Computer-generated randomization list | The trial infusion was prepared at a separate site, then taken to the bedside nurse every 24 h | Yes | 12/87 patients not analyzed and their follow-up not explained |
| Bollaert et al,[15] 1998 | Computer-generated randomization list | The trial infusion was prepared at a separate site, then taken to the bedside nurse every 24 h | Yes | No loss to follow-up |
| Briegel et al,[16] 1999 | Computer-generated randomization list | The trial infusion was prepared at a separate site, then taken to the bedside nurse every 24 h | Yes | No loss to follow-up |
| Chawla et al,[17] 1999 | Computer-generated randomization list | The trial infusion was prepared at a separate site, then taken to the bedside nurse every 24 h | Yes | No loss to follow-up |
| Annane et al,[18] 2002 | Computer-generated randomization list | Randomization was centralized | Yes | Lost to follow-up: 1 patient (withdrew consent) |
| Yildiz et al,[19] 2002 | Computer-generated randomization list | Combined coded numbers with drug allocation | Yes | No loss to follow-up |
| Keh et al,[11] 2003 | Computer-generated randomization list | The trial infusion was prepared at a separate site, then taken to the bedside nurse every 24 h | Yes | No loss to follow-up |
| Oppert et al,[51] 2005 | Computer-generated randomization list | The trial infusion was prepared at a separate site, then taken to the bedside nurse every 24 h | Yes | 7/48 patients not analyzed, 5 in steroid group and 2 in placebo group[b] |
| Confalonieri et al,[50] 2005 | Computer-generated randomization list | Randomization was centralized | Yes | Lost to follow-up: 2 at 60 d after randomization, all in placebo group |
| Tandan et al,[51] 2005 | Computer-generated randomization list | The trial infusion was prepared at a separate site, then taken to the bedside nurse every 24 h | Yes | Loss to follow-up not stated |
| Rinaldi et al,[53] 2006 | Computer-generated randomization list | Sealed envelopes | No | 12/52 patients dropped out, 6 in control group and 6 in steroid group[b] |
| Huh et al,[13] 2006 | Unclear (not stated) | Unclear (not stated) | Yes | No loss to follow-up |
| Cicarelli et al,[55] 2007 | Computer-generated randomization list | The trial infusion was prepared at a separate site, then taken to the bedside nurse every 24 h | Yes | No loss to follow-up; 3 patients were withdrawn after next of kin refused consent |
| Meduri et al,[56] 2007 | Computer-generated randomization list | Randomization was centralized | Yes | No loss to follow-up |
| Sprung et al,[22] 2008 | Computer-generated randomization list | Randomization was centralized | Yes | Lost to follow-up: 1 patient (withdrew consent) |

Abbreviation: VASSCSG indicates Veterans Administration Systemic Sepsis Cooperative Study Group.
[a] "Yes" indicates that patients, caregivers, data collectors, outcome assessors, and data analysts were all blinded; "no" indicates that patients, caregivers, data collectors, outcome assessors, and data analysts were not blinded.
[b] Information obtained from primary author.

**Intention-to-Treat Analysis and Adherence to Protocol.** Twelve trials explicitly reported the use of an intention-to-treat analysis (as the primary analysis) and the number of and reasons for nonadherence to protocol.‖ One trial reported only the use of intention-to-treat analysis.[47] The remaining trials provided no information about these criteria. With the exception of 5 trials, the number of analyzed participants matched the number of randomized participants. In 1 trial, 191 participants were randomized in the placebo group and 190 were analyzed for mortality outcome.[45] In 2 trials,[18,22] 1 patient withdrew consent and 299 of 300 and 499 of 500 randomized patients were analyzed, respectively. In 2 other trials, not all randomized patients were analyzed.[51,53] For these 2 trials, contact with primary authors provided accurate outcome information for patients not included in the analysis. In 1 trial, only 500 of the 800 expected patients were recruited, mainly because of low recruitment rate.[22]

## Explicit Definitions of Severe Sepsis and Septic Shock

Eleven trials provided explicit definitions of severe sepsis or septic shock (as defined above).¶ Eight trials provided definitions of severe sepsis and septic shock without referring to the need for vasopressor agents.[19,37,39,41,45-47,53] The definition of severe sepsis or septic shock was not explicitly given in 1 trial.[34] One trial included community-acquired pneumonia.[50] We obtained individual data from the primary author to verify that patients met criteria for severe sepsis, as defined in this systematic review. In 1 trial of early ARDS, contact with the primary author confirmed that definitions of severe sepsis and septic shock were similar to that used in this review.[56]

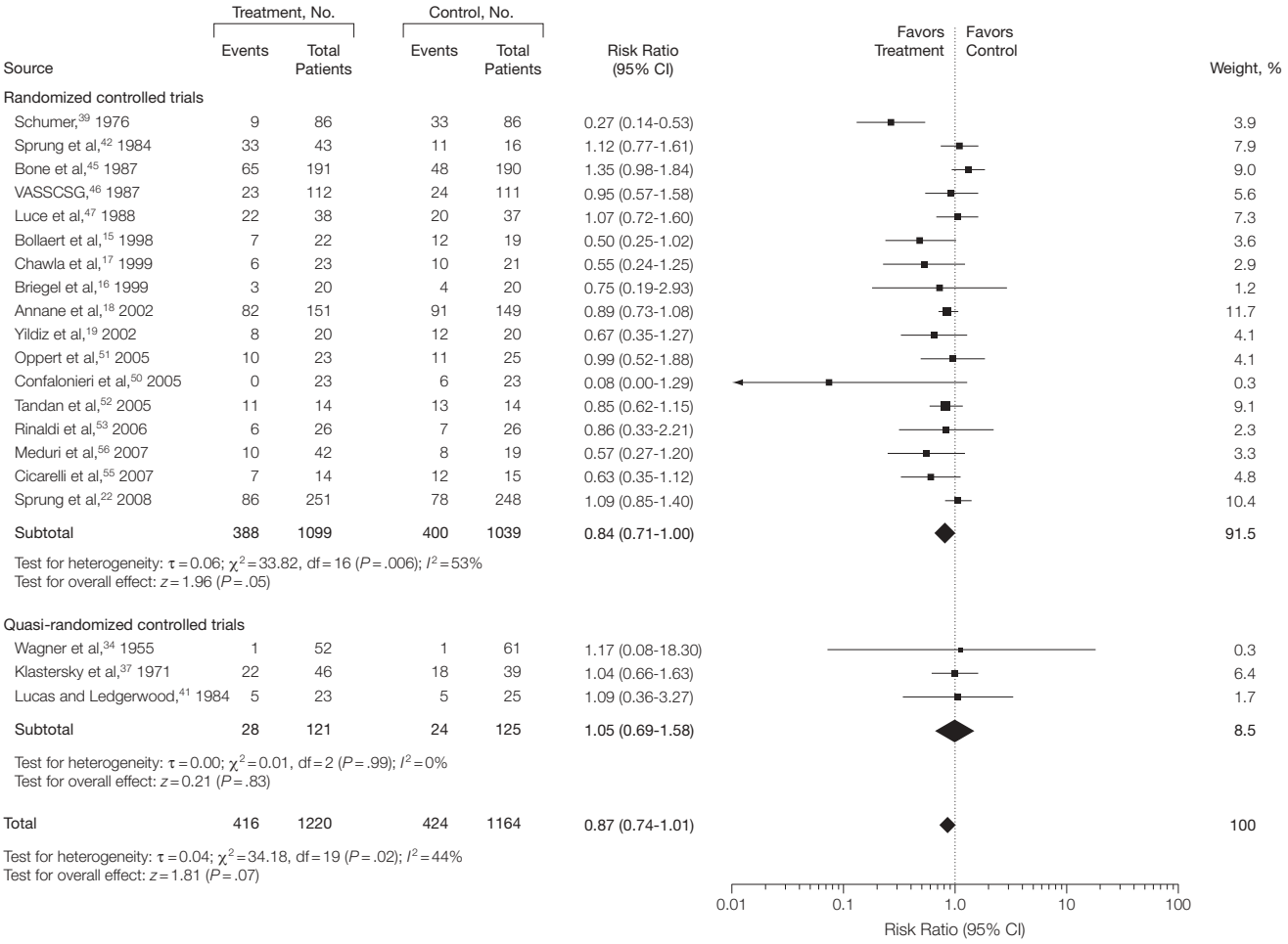
## Effects of Interventions

**Primary Outcome: 28-Day All-Cause Mortality.** We computed data from 17 randomized trials (n=2138) and 3 quasi-

‖References 11, 15-18, 22, 45, 46, 50, 51, 53, 56.

¶References 11, 13, 15-18, 22, 42, 51, 52, 55.

**Figure 2.** Twenty-Eight-Day Mortality in Randomized and Quasi-randomized Controlled Trials




CI indicates confidence interval; VASSCSG, Veterans Administration Systemic Sepsis Cooperative Study Group. Size of the data markers indicates weight of the study.

randomized trials (n=246). Twenty-eight-day mortality for treated vs control patients was 388 of 1099 (35.3%) vs 400 of 1039 (38.5%) in randomized trials (RR, 0.84; 95% CI, 0.71-1.00; $P=.05$; $I^2=53\%$ by random-effects model) and 28 of 121 (23.1%) vs 24 of 125 (19.2%) in quasi-randomized trials (RR, 1.05; 95% CI, 0.69-1.58; $P=.83$) (FIGURE 2). Subgroup analysis of the 12 randomized trials (n=1228) investigating prolonged low-dose corticosteroid treatment published between 1998 and 2009 showed little heterogeneity across studies ($\chi^2=12.89$; $P=.30$; $I^2=15\%$). In these trials, 28-day mortality for treated vs control patients was 236 of 629 (37.5%) vs 264 of 599 (44.1%) (RR, 0.84; 95% CI, 0.72-0.97; $P=.02$) (FIGURE 3). Removing the only study on community-acquired pneumonia[50] resulted in a consistent reduction in the risk of death (RR, 0.87; 95% CI, 0.77-0.98; $P=.02$), with no evidence for heterogeneity across the studies ($\chi^2=10.09$; $P=.43$; $I^2=1\%$).

Subgroup analyses of 7 trials (n=1043) investigating a short course of high-dose corticosteroids published between 1955 and 1988 showed substantial heterogeneity across studies ($\chi^2=18.63$; $P=.005$; $I^2=68\%$). In these short-course treatment trials, 28-day mortality for treated vs control patients was 179 of 539 (33.2%) vs 159 of 504 (31.5%) (RR, 0.94; 95% CI, 0.69-1.30) (Figure 3).

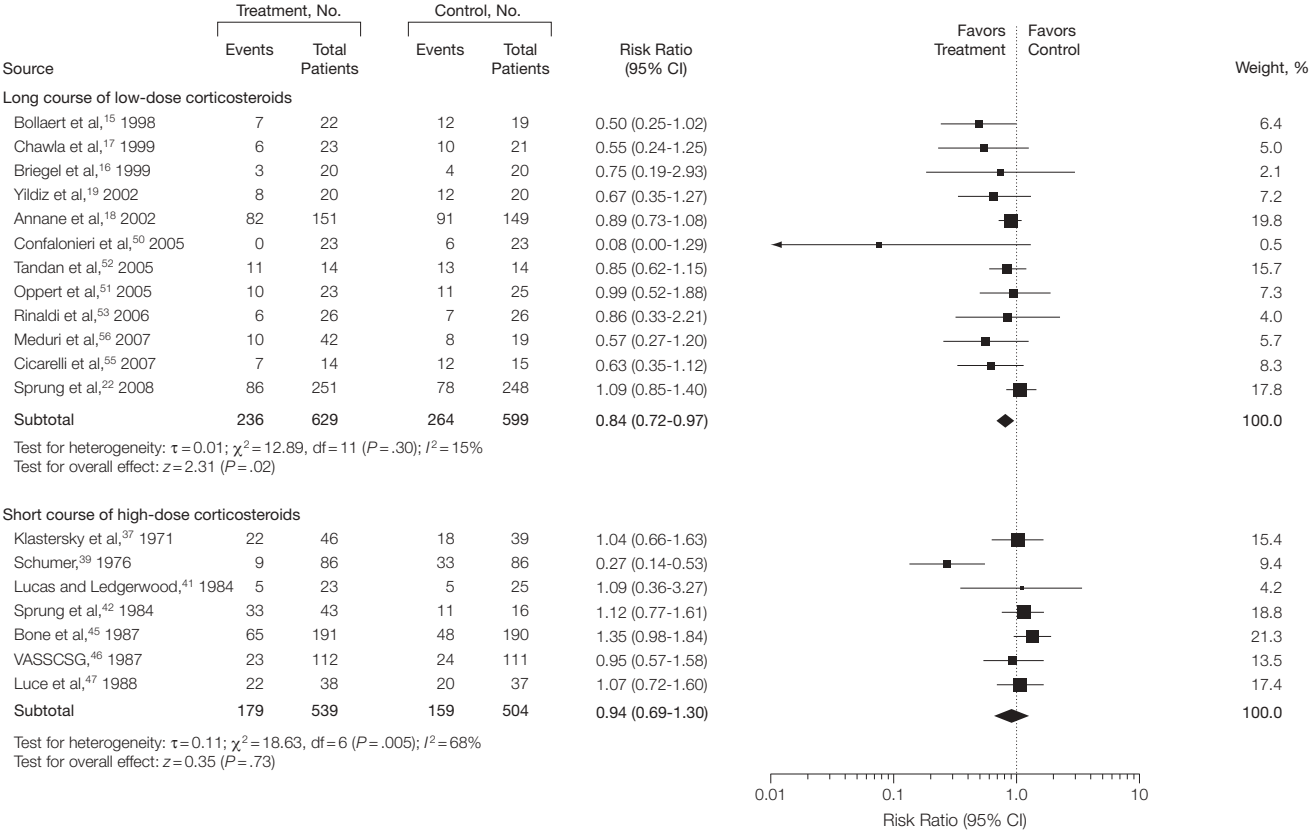
Meta-regression analysis confirmed the positive interaction between dose/duration of corticosteroid treatment and survival with a lower RR of dying with prolonged duration of treatment at low dose ($P=.01$), with lower daily doses ($P=.02$), and with lower cumulative doses ($P=.02$) (FIGURE 4). Meta-regression showed less interaction of mortality rate in the control group with corticosteroid effects ($P=.06$).

Subgroup analyses based on an adequate method for generation of allocation sequence, on adequate allocation concealment, or on blinding did not alter the overall treatment effects (data not shown). The funnel plot did not suggest evidence for publication bias (data not shown).

**Secondary Outcomes**. *Intensive Care Unit Mortality*. Eight trials investigating prolonged low-dose corticosteroid treatment reported intensive care unit mortality and showed a moderate degree of heterogeneity across studies ($\chi^2=12.86$; $P=.08$; $I^2=46\%$). Intensive care unit mortality for treated vs control patients was 226 of 558 (40.5%) vs 239 of 524 (45.6%) (RR, 0.81; 95% CI, 0.63-1.04; $P=.10$).

*Hospital Mortality*. Fifteen trials (n=1672) reported hospital mortality

**Figure 3.** Twenty-Eight-Day Mortality by Subgroup Based on Dose/Duration of Corticosteroid Therapy




CI indicates confidence interval. Size of the data markers indicates weight of the study.

and showed substantial heterogeneity across studies ($\chi^2$=27.95; $P$=.01; $I^2$=50%). Hospital mortality for treated vs control patients was 344 of 866 (39.7%) vs 355 of 806 (44.0%) (RR, 0.83; 95% CI, 0.68-1.00; $P$=.05). Subgroup analysis of 10 trials investigating prolonged low-dose corticosteroid treatment showed less heterogeneity across studies ($\chi^2$=12.55; $P$=.18; $I^2$=28%). Hospital mortality for treated vs control patients was 263 of 592 (44.4%) vs 280 of 556 (50.4%) (RR, 0.85; 95% CI, 0.72-1.00; $P$=.05). Subgroup analysis on 5 trials investigating a short course of high-dose corticosteroids showed substantial heterogeneity across trials ($\chi^2$=16.98; $P$=.002; $I^2$=76%). Hospital mortality for treated vs control patients was 91 of 236 (38.6%) vs 87 of 203 (42.9%) (RR, 0.84; 95% CI, 0.52-1.36; $P$=.47).

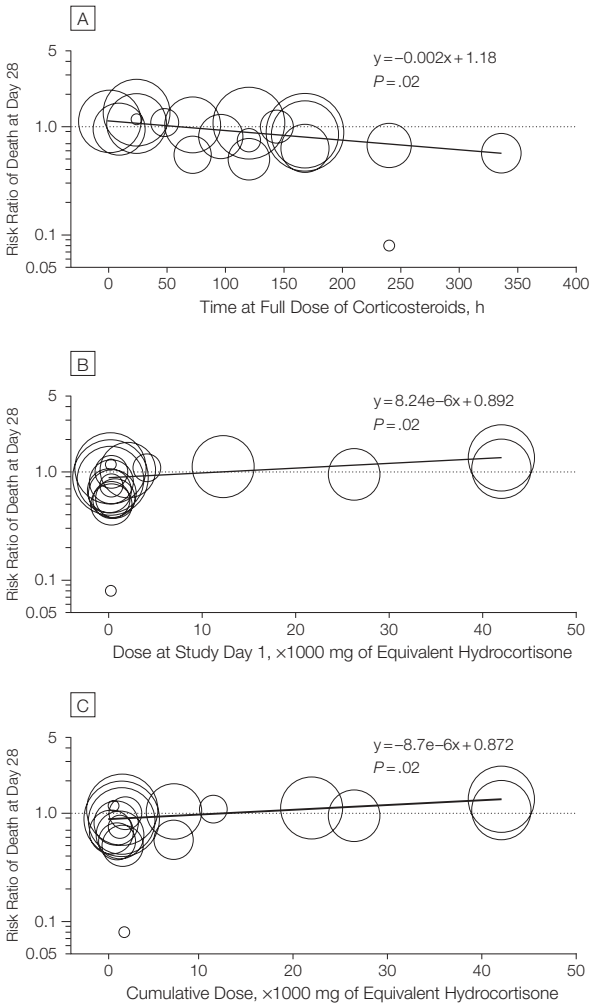
*Shock Reversal*. Eight trials (n=1268) reported shock reversal by day 7 and showed substantial heterogeneity across studies ($\chi^2$=21.48; $P$=.003; $I^2$=67%). Shock reversal by day 7 for treated vs control patients was 418 of 658 (63.5%) vs 315 of 610 (51.6%) (RR, 1.29; 95% CI, 1.06-1.58; $P$=.01). Subgroup analysis of 6 trials (n=965) investigating prolonged low-dose corticosteroid treatment showed much less heterogeneity across studies ($\chi^2$=6.32; $P$=.28; $I^2$=21%). Shock reversal by day 7 for treated vs control patients was 308 of 485 (63.5%) vs 226 of 480 (47.1%) (RR, 1.35; 95% CI, 1.16-1.57; $P$<.001) (FIGURE 5).

Six trials (n=952) reported shock reversal by day 28 and showed little heterogeneity across studies ($\chi^2$=5.19; $P$=.39; $I^2$=4%). Shock reversal by day 28 for treated vs control patients was 322 of 481 (66.9%) vs 276 of 471 (58.6%) (RR, 1.12; 95% CI, 1.02-1.23; $P$=.02) (Figure 5).

*Length of Stay*. Eight trials (n=622) reported length of intensive care unit stay in survivors and showed no heterogeneity across studies ($\chi^2$=2.78; $P$=.90; $I^2$=0%). The weighted mean difference in the length of stay was –4.49 days (95% CI, –7.04 to –1.94; $P$<.001) in favor of the corticosteroid-treated group. Seven trials (n=552) reported length of hospital stay in survivors and showed no difference between groups (data not shown).

*Serious Adverse Events*. Data for adverse events for treated vs control patients, respectively, are as follows. Gastroduodenal bleeding (data available in 1594 patients) was observed in 65 of 827 (7.9%) vs 56 of 767 (7.3%) (RR, 1.12; 95% CI, 0.81-1.53; $P$=.50), with no heterogeneity across the studies ($I^2$=0%). Superinfections (data available for 1917 patients) were observed in 184 of 983 (18.7%) vs 170 of 934 (18.2%) (RR, 1.01; 95% CI, 0.82-1.25; $P$=.92), with no heterogeneity across the studies ($I^2$=8%). Neuromuscular weakness (data available for 811 patients) was observed in 4 of 407 (1%) vs 7 of 404 (1.7%) (RR, 0.63; 95% CI, 0.12-3.35; $P$=.58), with some heterogeneity across studies ($I^2$=30%). In contrast, hyperglycemia (data available for 1434 patients) was observed in 385 of 745 (51.7%) vs 314 of 689 (45.6%) (RR, 1.16; 95% CI, 1.07-1.25; $P$<.001), with no heterogeneity across the studies ($I^2$=0%). Hypernatremia (data avail-

**Figure 4.** Interaction Between Dose/Duration and Survival Benefit With Corticosteroids




Meta-regression analysis confirmed the positive interaction between dose/duration and survival benefit with corticosteroids, with lower risk ratios of death with (A) longer duration of treatment at a full dose ($P$=.01), (B) lower daily doses ($P$=.02), and (C) lower cumulative doses ($P$=.02). One study[39] was excluded because it increased the $I^2$ value substantially in the set of early studies. Size of the data markers indicates weight of the study.

able for 805 patients) was observed in 127 of 404 (31.4%) vs 77 of 401 (19.2%) (RR, 1.61; 95% CI, 1.26-2.06; $P<.001$), with no heterogeneity across the studies ($I^2=0\%$).

## COMMENT

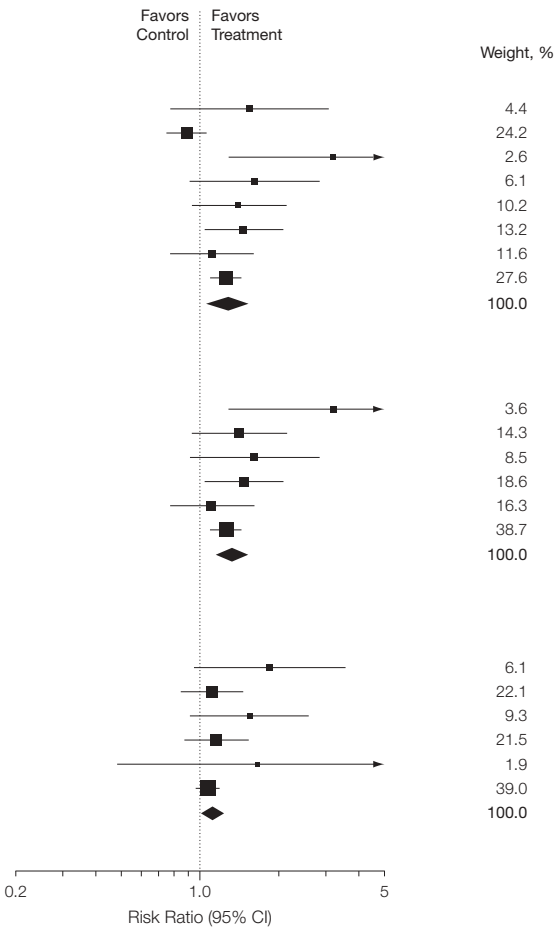
For this review, we performed a comprehensive literature search with no restriction for language or publication status, assuming a very limited risk of missing important trials. We included only trials that compared corticosteroid treatment with standard therapy alone or with placebo and we excluded trials in children.

Overall, this review showed no significant effect of corticosteroid treatment on 28-day mortality, intensive care unit mortality, or hospital mortality in severe sepsis or septic shock. However, the nominal *P* values for these outcomes were very close to .05 and there was strong heterogeneity in the results. Sensitivity analyses based on methodological quality of trials failed to show benefit from corticosteroid treatment and also failed to solve the heterogeneity. However, analyses of the trials investigating prolonged course (≥5 days) of low-dose corticosteroid treatment (≤300 mg of hydrocortisone or equivalent) demonstrated a significant reduction in 28-day all-cause mortality ($P=.02$) and hospital mortality ($P=.05$).

Although this subgroup analysis is a between-study and not a within-study hypothesis, we thought its validity was acceptable according to recently proposed criteria.[31] First, the hypothesis for an interaction between dose/duration and corticosteroid effects on mortality was a priori defined. Second, we conducted only 3 subgroup analyses (based on methodological quality of studies, dose/duration, and baseline risk of death). Third, treatment effect was large, about a 6.6% absolute difference in mortality, and rather consistent between 28-day and hospital mortality (RRs of 0.84 and 0.85, respectively). Meta-regression analysis further confirmed the interaction of the dose/duration on corticosteroids effects on mortality. Fourth, there is strong external evidence supporting these results. Experimental and human studies have shown that a dose

**Figure 5.** Shock Reversal by Day 7 and by Day 28

| Source | Treatment, No. Events | Treatment, No. Total Patients | Control, No. Events | Control, No. Total Patients | Risk Ratio (95% CI) | Weight, % |
|---|---|---|---|---|---|---|
| **Shock reversal at day 7** | | | | | | |
| Sprung et al,[42] 1984 | 25 | 43 | 6 | 16 | 1.55 (0.78-3.06) | 4.4 |
| Bone et al,[45] 1987 | 85 | 130 | 83 | 114 | 0.90 (0.76-1.06) | 24.2 |
| Bollaert et al,[15] 1998 | 15 | 22 | 4 | 19 | 3.24 (1.30-8.10) | 2.6 |
| Chawla et al,[17] 1999 | 16 | 23 | 9 | 21 | 1.62 (0.92-2.85) | 6.1 |
| Briegel et al,[16] 1999 | 17 | 20 | 12 | 20 | 1.42 (0.95-2.12) | 10.2 |
| Annane et al,[18] 2002 | 60 | 151 | 40 | 149 | 1.48 (1.06-2.06) | 13.2 |
| Oppert et al,[51] 2005 | 14 | 18 | 16 | 23 | 1.12 (0.78-1.61) | 11.6 |
| Sprung et al,[22] 2008 | 186 | 251 | 145 | 248 | 1.27 (1.12-1.44) | 27.6 |
| **Subtotal** | **418** | **658** | **315** | **610** | **1.29 (1.06-1.58)** | **100.0** |
| Test for heterogeneity: $\tau=0.04$; $\chi^2=21.48$, df=7 ($P=.003$); $I^2=67\%$<br>Test for overall effect: $z=2.51$ ($P=.01$) | | | | | | |
| **Shock reversal at day 7 in trials of long course of low-dose corticosteroids** | | | | | | |
| Bollaert et al,[15] 1998 | 15 | 22 | 4 | 19 | 3.24 (1.30-8.10) | 3.6 |
| Briegel et al,[16] 1999 | 17 | 20 | 12 | 20 | 1.42 (0.95-2.12) | 14.3 |
| Chawla et al,[17] 1999 | 16 | 23 | 9 | 21 | 1.62 (0.92-2.85) | 8.5 |
| Annane et al,[18] 2002 | 60 | 151 | 40 | 49 | 1.48 (1.06-2.06) | 18.6 |
| Oppert et al,[51] 2005 | 14 | 18 | 16 | 23 | 1.12 (0.78-1.61) | 16.3 |
| Sprung et al,[22] 2008 | 186 | 251 | 145 | 248 | 1.27 (1.12-1.44) | 38.7 |
| **Subtotal** | **308** | **485** | **226** | **480** | **1.35 (1.16-1.57)** | **100.0** |
| Test for heterogeneity: $\tau=0.01$; $\chi^2=6.32$, df=5 ($P=.28$); $I^2=21\%$<br>Test for overall effect: $z=3.89$ ($P<.001$) | | | | | | |
| **Shock reversal at day 28** | | | | | | |
| Bollaert et al,[15] 1998 | 15 | 22 | 7 | 19 | 1.85 (0.96-3.56) | 6.1 |
| Briegel et al,[16] 1999 | 18 | 20 | 16 | 20 | 1.13 (0.86-1.46) | 22.1 |
| Chawla et al,[17] 1999 | 17 | 23 | 10 | 21 | 1.55 (0.93-2.58) | 9.3 |
| Annane et al,[18] 2002 | 67 | 151 | 57 | 149 | 1.16 (0.88-1.52) | 21.5 |
| Tandan et al,[52] 2005 | 5 | 14 | 3 | 14 | 1.67 (0.49-5.67) | 1.9 |
| Sprung et al,[22] 2008 | 200 | 251 | 183 | 248 | 1.08 (0.98-1.19) | 39.0 |
| **Subtotal** | **322** | **481** | **276** | **471** | **1.12 (1.02-1.23)** | **100.0** |
| Test for heterogeneity: $\tau=0.00$; $\chi^2=5.19$, df=5 ($P=.39$); $I^2=4\%$<br>Test for overall effect: $z=2.41$ ($P=.02$) | | | | | | |




CI indicates confidence interval. Size of the data markers indicates weight of the study.

of 300 mg or less of hydrocortisone or equivalent can reverse the systemic inflammatory response, endothelial activation, and coagulation disorders secondary to an infection,[59] thus arguing against the use of higher doses. Moreover, at these low doses, corticosteroids have been shown to improve rather than to suppress innate immunity in patients with septic shock.[58] It is now established that severe sepsis results in a sustained proinflammatory state, arguing against a short course of treatment.[12] Similarly, 1 randomized controlled trial has compared a short course of treatment (3 days) with a longer course (7 days).[13] This study suggested both reduction in shock duration and mortality in favor of the 7-day strategy.

However, we judged the quality of evidence as moderate rather than high because 1 of the 2 largest trials on long course of low-dose corticosteroids did not find a survival benefit.[22] In addition, there were some differences between trials investigating prolonged low-dose corticosteroid treatment. First, populations varied, with trials including either patients with both severe sepsis and septic shock[19] or with only severe sepsis[53] and focusing on community-acquired pneumonia[50] or on septic shock and adrenal insufficiency.[13,52] Some trials included only early septic shock[13,18,52] while other trials included late septic shock[15,17,55] or both early and late septic shock.[11,16,22] One trial has combined fludrocortisone to hydrocortisone and found survival benefit.[18] Whether addition of fludrocortisone to hydrocortisone partly influenced outcome in septic shock is currently investigated in 2 randomized controlled trials. Finally, there was no standardization on concomitant therapy. For example, in some trials, patients may have received antithrombin III supplementation or intravenous polyclonal immunoglobulins.[16,22]

The beneficial effects observed on mortality with prolonged low-dose corticosteroid treatment may be related to the favorable effect of the treatment on shock resolution. Indeed, this review showed that prolonged corticosteroid treatment resulted in a substantial reduction of shock duration, with fewer patients remaining on vasopressor therapy by day 7 and by day 28. Similarly, this study showed that prolonged low-dose corticosteroid treatment substantially shortened intensive care unit stay. Moreover, prolonged corticosteroid treatment improves innate immunity[58] and attenuates the severity of inflammation[11,50,51,53] and the intensity and duration of organ system failure.[11,16,50,51]

Finally, this review also showed no evidence that corticosteroid treatment is associated with increased risk of gastroduodenal bleeding, superinfection, or acquired neuromuscular weakness. Of note, none of the studies included a prospective screening of neuromuscular complications. Thus, this adverse event was likely underreported. In contrast, corticosteroids were associated with an increased risk of developing hyperglycemia and hypernatremia. One randomized controlled trial suggested that continuous hydrocortisone infusion, compared with bolus administration, might result in fewer episodes of hyperglycemia.[60]

The recent update of the Surviving Sepsis Campaign suggested that intravenous hydrocortisone should be given only to adult septic shock patients after blood pressure is identified to be poorly responsive to fluid resuscitation and vasopressor therapy (grade 2C).[23] This systematic review confirms that no recommendation can be made for children, as only 2 studies of low methodological quality[35,48] have investigated the benefit-risk ratio of corticosteroids in children with severe sepsis or septic shock. It also confirms that the quality of evidence for the effects of prolonged low-dose corticosteroid treatment is moderate. The meta-regression analysis may suggest some interaction between baseline risk of death and corticosteroids effects ($P = .06$). Interestingly, removing the study by Annane et al[18] had little impact on the point estimates for 28-day mortality (RR, 0.79; 95% CI, 0.65-0.97). The current meta-analysis showed a major effect of prolonged corticosteroid treatment on shock reversal which may partly account for the observed survival benefit. This finding might suggest that prolonged corticosteroid treatment should be given only to patients with vasopressor-dependent septic shock. The Surviving Sepsis Campaign guidelines also suggest that physicians should wean the patient from corticosteroids when vasopressors are no longer required (grade 2D). In this systematic review, the RR for 28-day mortality was not different in studies with or without a weaning strategy (0.77 vs 0.84) and, therefore, our findings are insufficient to support either a gradual or an abrupt interruption of treatment. The meta-regression suggested that corticosteroids should be given for at least 100 hours before tapering to be beneficial. This finding may argue against giving corticosteroids only during vasopressor therapy.

## CONCLUSIONS

### Implications for Practice

Overall, corticosteroids did not affect 28-day all-cause mortality in severe sepsis and septic shock. Meta-analysis of a subgroup of 12 trials investigating prolonged low-dose corticosteroid treatment suggests a favorable effect on all-cause mortality. According to these findings, corticosteroids should be considered at a daily dose of 200 to 300 mg of hydrocortisone (or equivalent) as intravenous bolus or continuous infusion. Although evidence is not particularly robust, we suggest that treatment should be given at full dose for at least 100 hours and only in adults with vasopressor-dependent septic shock. There is insufficient evidence from this meta-analysis to support either a gradual or an abrupt interruption of treatment. The evidence accumulated from 7 trials uniformly does not support the use of a short course of high-dose corticosteroids in severe sepsis or septic shock.

### Implications for Research

Ongoing trials should clarify (1) the survival benefit from prolonged low-dose corticosteroid treatment in adult septic shock and a potential interaction with activated protein C; (2) the

role of a prolonged low-dose corticosteroid treatment for treating septic shock in children; (3) the role of a prolonged low-dose corticosteroid treatment in severe sepsis, particularly in patients with community-acquired infections; and (4) the additional role of mineralocorticoid replacement.

Additional studies are needed to explore the role of prolonged low-dose corticosteroid treatment for septic shock in developing countries to extend generalizability and the optimal timing to start treatment, the optimal dose of hydrocortisone (or equivalent), and the duration and mode of withdrawal of treatment.

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**Author Contributions:** Dr Annane had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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*Acquisition of data:* Annane, Bollaert, Briegel, Confalonieri, De Gaudio, Keh, Kupfer, Oppert, Meduri.
*Analysis and interpretation of data:* Annane, Bellissant, Bollaert, Briegel, Confalonieri, De Gaudio,Keh, Kupfer.
*Drafting of the manuscript:* Annane, Bellissant.
*Critical revision of the manuscript for important intellectual content:* Annane, Bellissant, Bollaert, Briegel, Confalonieri, De Gaudio, Keh, Kupfer, Oppert, Meduri.
*Statistical analysis:* Annane, Bellissant, Kupfer.
*Obtained funding:* Annane, Kupfer.
*Administrative, technical, or material support:* Annane, Bollaert, Briegel, Keh, Kupfer, Oppert.
*Study supervision:* Annane, Bellissant, Briegel, Confalonieri.
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**Role of the Sponsors:** None of the institutions/sponsors of individual studies had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.
**Additional Information:** Appendixes 1 and 2 (supplemental methods) and eTables 1 and 2 are available at http://www.jama.com.
**Additional Contributions:** We thank Charles L. Sprung, MD, Hadassah Hebrew University Medical Center, Jerusalem, Israel, for providing unpublished data.

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