

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 ($I^2 = 0\%$; relative benefit, 1.23, [95% CI, 1.01 to 1.50]; $P = 0.036$) and shock reversal ($I^2 = 0\%$; 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 ($I^2 = 14\%$; 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.

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See editorial comment on pp 70-72.

Despite effective antibiotics, septic shock remains the most common cause of death in the intensive care unit, incurring a mortality rate of 30% to 50% (1, 2). Several therapies targeting the upregulated inflammatory pathways of sepsis have been studied to improve survival. However, few therapies have proven beneficial (3–10). In the 1960s, preclinical studies reported that high doses of glucocorticoids in models of *Escherichia coli* and endotoxic shock improved survival. These studies prompted the initiation of human sepsis trials (11–13). Subsequently, more than 50 human trials have examined the role of high-dose steroid therapy in sepsis. These trials administered doses of methylprednisolone as high as 30 to 120 mg/kg of body weight over 24 hours. Because the reported results of these trials were inconsistent, there was little consensus on the appropriate use of steroids in patients with septic shock.

To clarify the treatment effects of high-dose steroids, 3 meta-analyses performed in the 1990s examined the more rigorously conducted randomized, controlled clinical trials of sepsis (7, 14, 15). The meta-analysis by Lefering and colleagues (14) incorporated 10 trials and found no overall beneficial effect of glucocorticoid therapy on mortality in septic patients (absolute difference in mortality rates between treatment and control groups, -0.2 percentage point [95% CI, -9.2 percentage points to 8.8 percentage points]). A second meta-analysis by Cronin and colleagues (15) examined 9 trials with variable effects ($P = 0.02$) and

reported no evidence of a beneficial effect of high-dose steroids on mortality from sepsis (relative risk for death with treatment, 1.13 [CI, 0.99 to 1.29]). A third meta-analysis, performed by our group (7), examined the trials included in the previous meta-analyses. Nine trials, which were the same as those investigated by Cronin and colleagues (15), met inclusion criteria for that analysis (7). In this group of trials, we identified 1 study (16) as a statistical outlier that accounted for the variability reported by Cronin and colleagues. After exclusion of this outlier, our analysis revealed a homogenous group of 8 studies ($P > 0.2$) that demonstrated an overall increase in mortality associated with the use of high-dose steroids in septic patients (odds ratio of survival with treatment, 0.70 [CI, 0.55 to 0.91]; $P = 0.008$) (7). The increased mortality in these studies may have been due to the immunosuppressive effects of steroids, which led to more severe secondary infections (17–19). In response to these overall discouraging results, the use of high-dose glucocorticoids in septic patients decreased in the late 1980s and 1990s.

Recently, interest in examining the role of the adrenal axis in sepsis has been renewed. Briegel and colleagues (20) reported that septic patients have an attenuated response to corticotropin stimulation testing during their acute illness. Furthermore, Annane and colleagues (21) demonstrated that a high cortisol level and an attenuated response to corticotropin stimulation indicate relative adrenal insuffi-

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

ciency during sepsis that may increase mortality. On the basis of these findings, several clinical trials have been performed to determine whether administering glucocorticoids in dosages similar to the amount produced physio-

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).

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

Figure 1. Flow diagram of the published articles evaluated for inclusion in this meta-analysis.

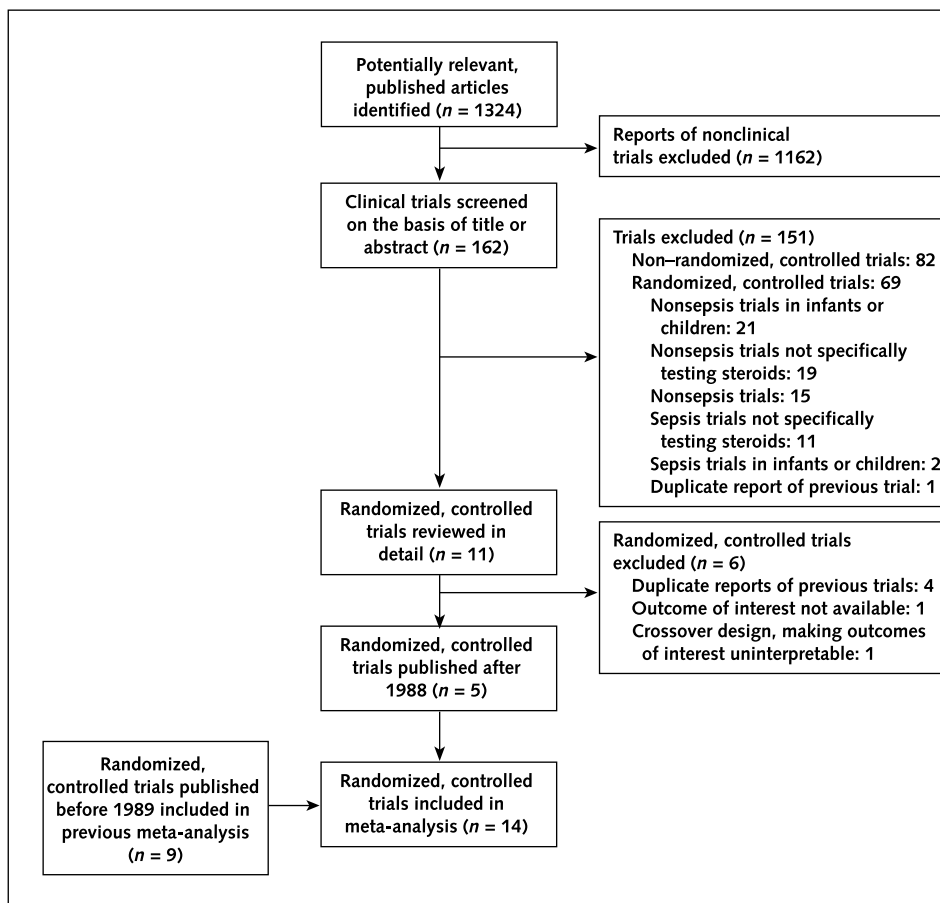


Table 1. Randomized, Controlled Trials of Steroids in Patients with Sepsis*

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

* ARDS = acute respiratory distress syndrome.

† For all patients enrolled, follow-up was complete for the end points listed.

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 ° C or < 36 ° C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min, and leukocyte count > 12 × 10⁹ 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 dura-

tion 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 I² value (26, 27). When statistically significant heterogene-

Table 2. Study Characteristics of Trials Published before 1989 vs. after 1997*

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

* 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.

§ Study enrollment criteria used unless actual average value to time of drug administration was reported in the trial.

|| 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.

ity of treatment effects was observed, studies were partitioned (for example, early vs. late studies) to decrease the heterogeneity of studies in a particular partition and increase the differences among the partitions, which can be seen when the I^2 value is substantially lower in each partition as compared with the overall I^2 value (28). One study increased the I^2 value substantially in the set of early studies and was removed from all subsequent analyses. Partitioning variables were determined by regressing study characteristics (for example, steroid dose in first 24 hours) on mortality, specifically the log relative survival benefit (29). Regression was performed by using an inverse-variance-weighted restricted maximum likelihood random-effects method. When the regression was performed by using log steroid dose in the first 24 hours as the independent variable, 1 study was observed to be both a statistical outlier and influential. An indicator variable for this study was included in the regression analysis. Similar estimates of the slope associated with the effect of log steroid dose in the first 24 hours were observed when the influential study was removed and for early and late studies separately. A regression analysis that included control group mortality rate as an additional independent variable did not change the relationship between steroid dose in the first 24 hours and relative survival benefit. All pooled relative survival benefits are reported with associated 95% CIs by using a fixed-effects model. Random-effects estimates of survival were also calculated and reported. Statistically significant differences in characteristics between early and late studies were assessed by using analysis of variance (ANOVA) (when a

weighted analysis was needed) or a 2-sample Wilcoxon test (when an unweighted analysis was performed). To analyze the different types of severity of illness scores used in the studies, we computed an effect size for each. This effect size was calculated by determining the difference between the mean steroid severity score and the mean control severity score, divided by the control standard deviation in each study.

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

Table 2. Continued

Total Steroid Dose Administered†	Duration of Therapy‡	Steroid Taper?	Indication for Therapy	Time to Initiation of Therapy after Shock or Indication for Enrollment§
mg			h	
1050	6 d	No	Severe infection	Immediate
7000	3 d	No	Severe infection	Immediate
42 000	24 h	No	Shock	9
11 200	48 h	No	Shock	Immediate
21 700	4 h	No	Shock	17.5
42 000	24 h	No	Severe sepsis	<2
26 250	9 h	No	Sepsis	2.8
42 000	24 h	No	Shock	Immediate
1500	5 d	Yes	Vasopressor-dependent shock	>48
1209	6 d	Yes	Vasopressor-dependent shock	23
900	3 d	Yes	Vasopressor-dependent shock	>72
300	10 d	No	Severe sepsis	>2
1400	7 d	No	Vasopressor-dependent shock	8
Median, 23 975	Median, 1 d	Ratio, 0/8	Median: Shock	Median, <2
Median, 1209	Media, 6 d	Ratio, 3/5	Median: Vasopressor-dependent shock	Median, 23

[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

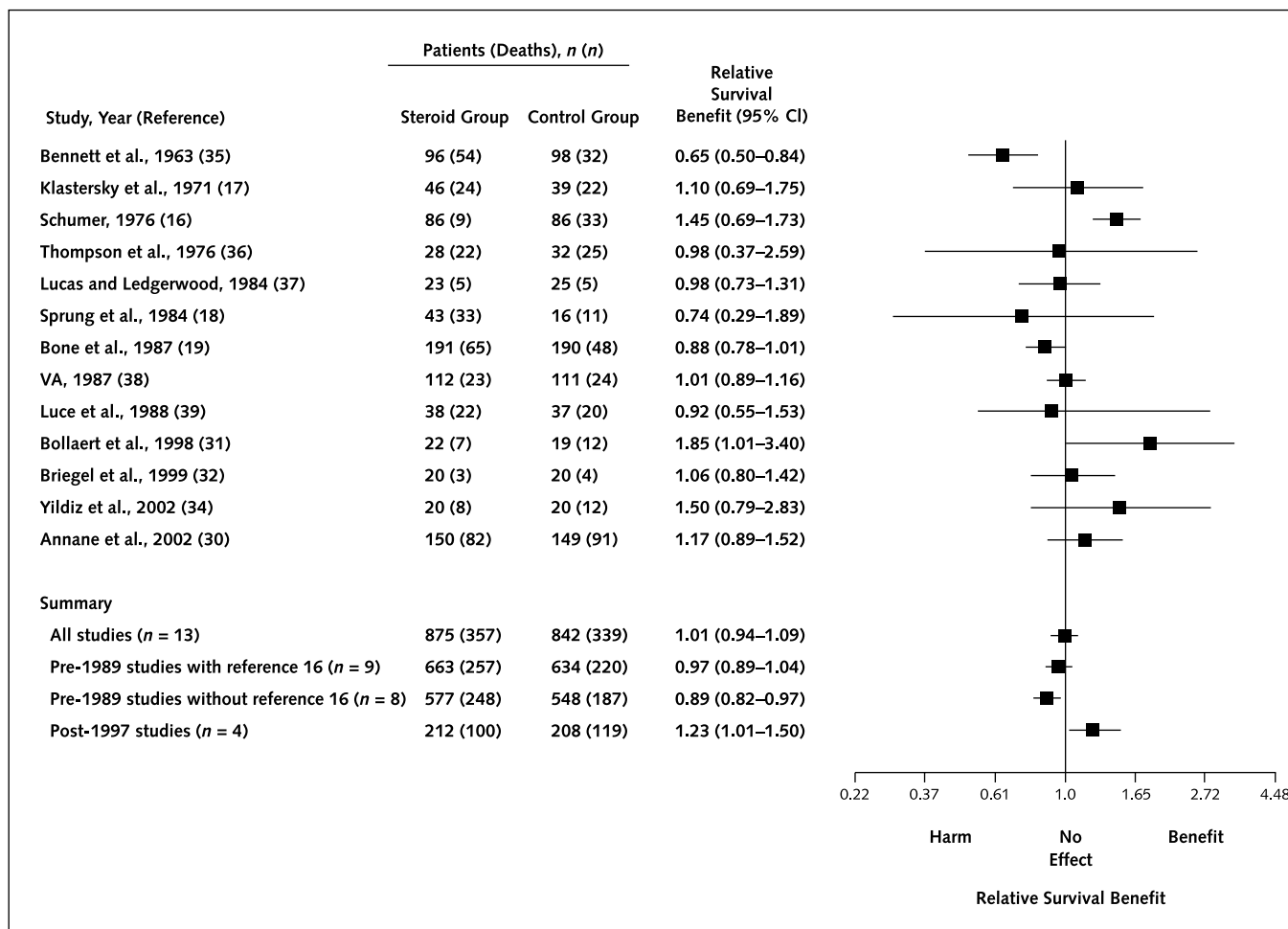
(8 years) than any other study and reported the lowest mortality rate with steroid treatment of any study (10%; next lowest mortality rate, 21%) (16). Furthermore, this study, which enrolled "septic shock patients consecutively admitted" at 1 institution over 8 years, reported the results of simultaneous 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-

Figure 2. Effects of steroids on survival in previous and recent sepsis trials.



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.

ative survival benefit, 1.23 [CI, 1.01 to 1.50]; $P = 0.036$) (Figure 2). The trials published before 1989 (16–19, 35–39) revealed a nonbeneficial treatment effect of steroids (relative survival benefit, 0.97 [CI, 0.89 to 1.04]; $P > 0.2$) that statistically differed from those of the trials published after 1997 ($P = 0.02$). Furthermore, as previously demonstrated, the effects of glucocorticoids on survival in the trials published before 1989 varied widely ($I^2 = 75\%$; $P = 0.001$). This was secondary to 1 study that was a statistical outlier with methodologic differences in comparison with the other 8 studies (16) (Figure 2). Excluding this study revealed a consistent effect of steroids with an overall decrease in survival ($I^2 = 14\%$; $P > 0.2$) (relative survival benefit, 0.89 [CI, 0.82 to 0.97]; $P = 0.008$) (Figure 2).

Study size did not affect the treatment effects of steroids ($P > 0.2$). Thus, the effects of steroids were opposite in the trials published before 1989 compared with those published after 1997.

Effects of Steroid Dose and Control Group Mortality Rate on the Treatment Effect of Steroids

The total dose of glucocorticoids used in the trials published before 1989 was greater than that of studies published after 1997 ($P = 0.01$) (Table 2). Furthermore, a regression analysis performed on all trials demonstrated that as the dose of steroids increased, the relative survival benefit decreased linearly ($P = 0.02$), indicating that steroids were beneficial at lower doses and became harmful as the dose increased (Figure 3). One trial that methodolog-

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 ($P > 0.2$).

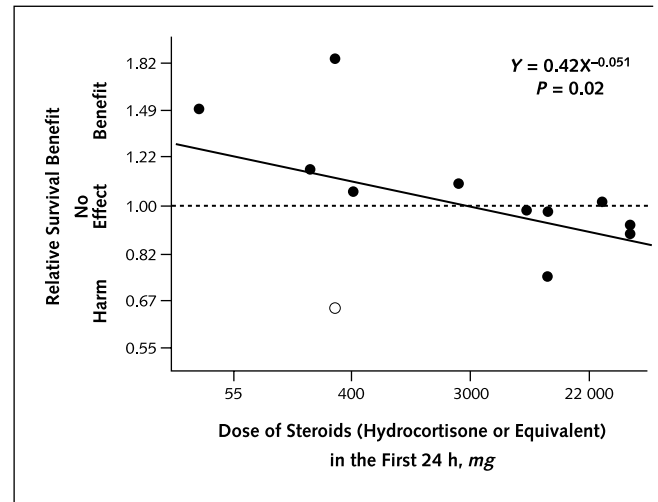
Effects of Steroids on Vasopressor Requirements

Trials performed after 1997 reported a consistent effect of glucocorticoids on shock reversal ($I^2 = 0\%$; $P > 0.2$) (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 $\mu\text{g}/\text{dL}$) from baseline. The third study (31) defined a nonresponder as having a change in cortisol level less than 165.53 nmol/L (6 $\mu\text{g}/\text{dL}$) 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

Figure 3. Effects of steroid dose on survival.



The relationship between the dose of steroids administered in the first 24 hours after enrollment in a sepsis trial and relative survival benefit (black circles) is presented. There is a linear relationship (that is, the relative survival benefit decreases with high-dose steroids but increases with lower doses) ($P = 0.02$). One study (white circle) was overly influential in our regression analysis, was a statistical outlier ($P = 0.001$) compared with the other trials, and was therefore excluded (35). This study was performed before all of the other trials, included children, and had a high percentage of patients with meningitis.

(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

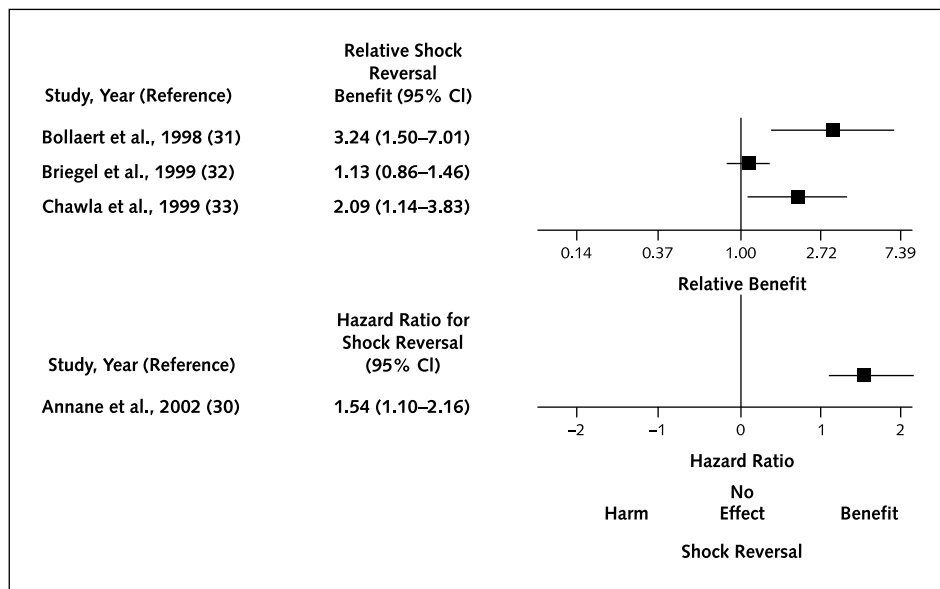
Severity of illness scores were reported in 4 of the 5 trials published after 1997 (30–32, 34). There was no difference in the severity of illness between the control groups and steroid groups in these 4 studies that could explain the

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

Study (Reference)	Nonresponders			Responders			Nonresponders vs. Responders	
	Control Group	Steroid Group	P Value	Control Group	Steroid Group	P Value	Difference	P Value
	% (n/n)			% (n/n)			%	
Mortality								
Yildiz et al. (34)	56 (5/9)	40 (2/5)	>0.2	64 (7/11)	40 (6/15)	>0.2	-8	>0.2
Bollaert et al. (31)	63 (5/8)	25 (1/4)	>0.2	64 (7/11)	33 (6/18)	0.12	7	>0.2
Annane et al. (30)	63 (73/115)	53 (60/114)	0.10*†	53 (18/34)	61 (22/36)	>0.2	18	0.16
Shock reversal								
Bollaert et al. (31)	25 (2/8)	75 (3/4)	0.11*‡	18 (2/11)	67 (12/18)	0.01*§	-1	>0.2
Annane et al. (30)	40 (46/115)	53 (60/114)	0.06*	53 (18/34)	50 (18/36)	>0.2	-16	>0.2

* 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.
 † $P = 0.04$.
 ‡ $P = 0.03$.
 § $P = 0.03$.
 || $P = 0.001$.

Figure 4. Effects of steroids on shock reversal.



The relative benefit (95% CI) and the hazard ratio (with 95% CI) of shock reversal for the sepsis trials published after 1997 are presented. Of note, in 3 of the 4 studies, the discontinuation of vasopressor therapy with steroid treatment statistically significantly improved. In the fourth trial, the effect of steroid therapy on vasopressor discontinuation was similar to the effect in the other trials ($I^2 = 0\%$; $P > 0.2$).

beneficial 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 subsamples (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 vasopressors. 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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