

The effects of steroids during sepsis depend on dose and severity of illness: an updated meta-analysis

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Abstract

A previous meta-analysis determined that the effects of steroids during sepsis were dose-dependent; since then, additional trials have been published. The current analysis updates our previous analysis examining the effects of steroids during sepsis. A literature search from 2004 to 2008 identified seven randomized controlled trials in adult patients; these were added to 14 previously identified trials. The effects of steroids on mortality were highly variable among the 21 trials ($p < 0.001$, $I^2 = 60\%$). In trials published before 1989, which involved short courses of high-dose steroids, steroids increased mortality ($n = 8$, $I^2 = 14\%$, OR of death 1.39 [95% CI 1.04–1.86], $p 0.03$). In trials published after 1997, which involved longer courses of lower-dose steroids, steroids consistently improved shock reversal ($n = 7$, $I^2 = 0\%$, OR of shock reversal 1.66 [95% CI 1.25–2.20], $p < 0.001$), but demonstrated a more heterogeneous beneficial effect on mortality ($n = 12$, $I^2 = 25\%$, OR of death 0.64 [95% CI 0.45–0.93], $p 0.02$). An inverse linear relationship between severity of illness and the effects of steroids on mortality was identified across all trials ($p 0.03$) and within the subgroup of trials published after 1997 ($p 0.03$); steroids were harmful in less severely ill patient populations and beneficial in more severely ill patient populations. There was no effect of response to adrenocorticotrophic hormone (ACTH) stimulation testing concerning the effects of steroids and no increase in steroid-associated adverse events. Low-dose steroids appear to improve mortality rates in patients with septic shock who are at high risk of death; however, additional trials in this subpopulation are necessary to definitively determine the role of low-dose steroids during sepsis.

Keywords: Corticosteroids, glucocorticoids, meta-analysis, review, sepsis, septic shock, steroids
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Introduction

Septic shock is one of the most common causes of death in the intensive-care unit. Despite effective therapies directed at the infecting agent (appropriate antibiotics, drainage procedures, etc.) and aggressive cardiovascular support (fluid resuscitation, vasopressors, etc.), mortality due to septic shock remains unacceptably high, at 30–60% [1–4]. Multiple adjunctive therapies for septic shock have been developed and studied in clinical trials, including agents directed against specific bacterial toxins, anti-inflammatory agents, and

antithrombotic agents. Despite promising preclinical results, few therapies have demonstrated improved survival in controlled clinical trials [5]. Moreover, these beneficial effects have not been consistent in confirmatory trials. The varying treatment effects of these agents can be explained, in part, by methodological differences among the clinical trials; specifically, when the trials have been compared, several factors that may alter the efficacy of these agents have been identified [5–7]. For example, a meta-analysis of clinical trials of mediator-specific anti-inflammatory agents in sepsis demonstrated a significant relationship between severity of illness and treatment effect, characterized by beneficial effects in

severely ill patient populations and no effect, or potentially harmful effects, in less severely ill patient populations [6]. Furthermore, a meta-analysis of trials of glucocorticoids in the treatment of sepsis demonstrated a significant relationship between steroid dose and treatment effect, with high doses having harmful effects and low doses having potentially beneficial effects [7]. In addition, others have reported that the beneficial effects of steroids in sepsis trials are dependent on a blunted response to a corticotropin stimulation test [8]. On the basis of these analyses, the influence of factors that might alter the efficacy of a therapy in clinical sepsis trials need to be evaluated when attempting to define the role of an adjunctive therapy in the treatment of sepsis.

Glucocorticoids have been studied extensively as adjunctive therapy in septic patients for over 40 years. Our previous meta-analysis examining the effects of steroid dose in sepsis demonstrated that early studies (published before 1989), which involved predominantly short courses of high-dose steroids, reported increased mortality and worsened secondary infections [7]. In contrast, more recent trials (published after 1997) involved longer courses of lower-dose steroids and demonstrated beneficial treatment effects, including improved shock reversal and survival [7]. Since the publication of this meta-analysis, multiple trials (including a large, multicentre, randomized controlled trial) have been performed. Therefore, with the current meta-analysis, we aimed to update our previous analysis and to determine whether severity of illness, drug dose, and response to corticotropin stimulation testing influence the treatment effects of steroids during sepsis [9].

Methods

The medical literature from January 2004 to December 2008 was searched using the following keywords in MEDLINE, EMBASE and the Cochrane library: 'steroids and sepsis', 'steroids and septic shock', 'glucocorticoids and sepsis', 'glucocorticoids and septic shock', 'corticosteroids and sepsis', and 'corticosteroids and septic shock'. In addition, abstracts from national and international critical-care conferences and published meta-analyses were reviewed to identify other potentially relevant studies and outcomes not previously identified. Consistent with our previous analysis, clinical trials were included if they fulfilled all of the following criteria: a prospective randomized controlled trial design comparing glucocorticoid treatment with a control group (with or without placebo treatment), enrolment of adult patients who met the criteria for sepsis or septic shock, and a primary endpoint including either shock reversal or sur-

vival. Within each study, criteria for sepsis or septic shock needed to be defined and consistent with the ACCP/SCCM consensus definitions for sepsis, severe sepsis, and septic shock [10]. In addition, similar treatments must have been administered to both the steroid and control groups, with the exception of the steroid treatment regimen being investigated.

Each included trial was independently reviewed by two investigators using a standardized protocol and data collection form, with discrepancies being resolved by a third party. Abstracted data on patient characteristics, study characteristics, treatment interventions and treatment outcomes were collected, including: the presence of sepsis, severe sepsis, or septic shock; type, dose and duration of steroid administered; incidence and severity of complications of therapy (including secondary infections, gastrointestinal bleeding, and neuropathy); response to corticotropin stimulation testing; proportion of patients with shock reversal; and mortality. Trial quality was assessed by evaluating the method of randomization, use of blinding, and withdrawal/dropout reporting, based on the methods of Jadad [11]. To account for the different steroid regimens used in the trials, all doses were converted to hydrocortisone equivalents [12].

Statistical analysis

The OR of death following treatment, as compared with control, was estimated using a random-effects model (Comprehensive Meta-Analysis; Biostat Inc., Englewood, NJ, USA). Heterogeneity across studies was assessed using a Mantel-Haenszel derived Cochran Q statistic, and reported with an I^2 -value. [13,14] As previously, trials were partitioned and excluded when significant heterogeneity or influence was present, to decrease the heterogeneity within a group of studies, and to maximize differences among groups of studies [7]. Variables previously evaluated to explain the heterogeneity in the treatment effects were again explored, using meta-regression techniques (Comprehensive Meta-analysis, SAS v 9.2; SAS Institute, Cary, NC, USA) [7]. Potential bias was assessed by creating a funnel plot, and formally tested using Egger's regression method [15]. In addition, a jack-knife sensitivity analysis of the late studies was performed by sequentially removing each study to detect the studies that contributed most to the remaining heterogeneity within this group of trials [16]. All pooled ORs of death are reported with associated 95% CIs, using random-effects models. Significant differences in characteristics between early and late studies were assessed using an ANOVA, when a weighted analysis was needed, or a two-sample Wilcoxon test, when an unweighted analysis was performed.

Results

Study flow and quality

The current literature search identified seven new prospective randomized controlled trials, published since 2003, which met our inclusion criteria and were included in the current analysis (Fig. 1) [17–23]. Characteristics of the 21 trials included in this analysis are depicted in Table 1 [8,17–36]. All included studies were prospective randomized trials that involved similar co-interventions in each study group, with the exception of the steroid regimen being investigated. Blinding, randomization schemes and patient follow-up were adequate in most trials, with all but two studies having a Jadad quality score of three or higher (Table 1) [23,31]. Among the 21 trials, three have been published only in abstract form [23,29,35].

Effects of steroids on mortality

The effects of steroids on mortality were highly variable among the 21 trials ($p < 0.001$, $I^2 = 60\%$), with an overall non-significant effect on mortality (Fig. 2). Consistent with our previous analysis, heterogeneity decreased when the 21 trials were partitioned into studies published before 1989 [24,25,27,30–35] and published after 1997 [8,17–23,26,28,29,36]. As the group of trials published before 1989 was identical to our previous analysis, they were analysed in a similar fashion, with subsequent exclusion of a single outlier study from subsequent analyses (Fig. 2) [33]. Similar to the findings of our previous meta-analysis, the treatment effects of steroids were significantly different in trials published before 1989 than in trials published after 1997 ($p < 0.001$). Steroids increased mortality in trials published before 1989

($n = 8$, $I^2 = 14\%$, OR of death 1.39, 95% CI 1.04–1.86, $p < 0.03$), and decreased mortality in trials published from 1997 through 2008 ($n = 12$, $I^2 = 25\%$, OR of death 0.64, 95% CI 0.45–0.93, $p < 0.02$).

Influence of steroid regimen and control mortality on the treatment effects of steroids

As compared with the trials published before 1989, trials published from 1997 through 2008 involved lower total doses of steroids over a longer duration, and were more likely to taper the steroids ($p < 0.007$, $p < 0.01$, and $p < 0.01$, respectively) (Table 2). Mean control mortality rates, indications for therapy, and percentage of enrolled patients with shock or patients receiving vasopressors were similar between the two groups of studies.

Meta-regression analysis of all of the trials revealed a significant direct linear relationship between steroid dose and the OR of death ($p < 0.03$), characterized by beneficial effects at lower doses and harmful effects at higher doses (Fig. 3). In addition, meta-regression analysis demonstrated a significant inverse linear relationship between severity of illness of the patient population (measured by control odds of death) and the OR of death ($p < 0.02$), indicating that, in less severely ill patients, steroids were harmful and, as severity of illness increased, steroids became beneficial (Fig. 3). As in our previous analysis, a single overly influential trial was identified and removed from the meta-regression analyses [25]. The results of the current meta-regression analyses remain essentially unchanged, whether the influential study is included or excluded.

A subgroup analysis of the trials published after 1997 using meta-regression analysis demonstrated a significant inverse linear relationship between severity of illness of the patient

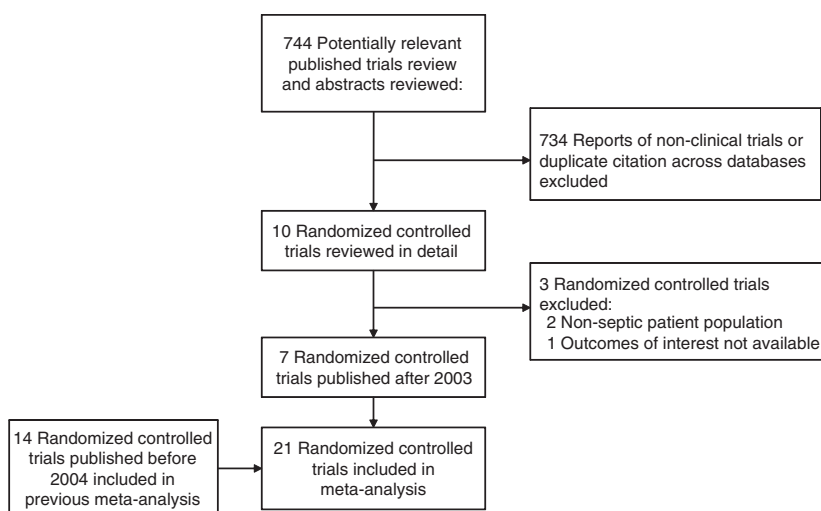


FIG. 1. Study selection flow diagram.

TABLE 1. Randomized controlled trials of steroids in sepsis

Author	Year published	Treatment	Baseline differences reported	Study design	Co-interventions reported	Endpoints available for meta-analysis ^a	Jadad score
Bennett et al. [25]	1963	Hydrocortisone 300 mg × 1, then decreased by 50 mg/day	Yes	Double-blind	Antibiotics, vasopressors	Hospital mortality, complications of treatment	4
Klastersky et al. [30]	1971	Betamethasone 1 mg/kg/day for 3 days	No	Double-blind	Antibiotics, vasopressors, fluids	20-day mortality, complications of treatment	4
Schumer [33]	1976	Dexamethasone 3 mg/kg or methylprednisolone 30 mg/kg; may be repeated × 1	No	Double-blind	Antibiotics	28-day mortality, complications of treatment	4
Thompson et al. [35]	1976	Methylprednisolone 30 mg/kg × 1, and then repeated up to three times within 24 h if in shock	No	Double-blind	Antibiotics	Hospital mortality, toxicities of treatment	3
Lucas et al. [31]	1984	Dexamethasone 2 mg/kg bolus followed by 2 mg/kg/24 h in first 48 h	No	Open-label	Antibiotics, digoxin, fluids, diuresis	14-day mortality, complications of treatment	1
Sprung et al. [34]	1984	Methylprednisolone 30 mg/kg or dexamethasone 6 mg/kg; repeat × 1 at 4 h if still in shock	No	Open-label	Antibiotics, vasopressors, fluids	Hospital mortality, shock reversal, complications of treatment	3
Bone et al. [27]	1987	Methylprednisolone 30 mg/kg × 4	Yes	Double-blind	Standard therapy	14-day mortality, shock reversal, complications of treatment	5
Veterans Administration [24]	1987	Methylprednisolone 30 mg/kg bolus followed by 5 mg/kg/h for 9 h	Yes	Double-blind	Antibiotics, fluids	14-day mortality, complications of treatment	5
Luce et al. [32]	1988	Methylprednisolone 30 mg/kg × 4 over 24 h	No	Double-blind	Antibiotics, standard care	Hospital mortality, ARDS, complications of treatment	5
Bollaert et al. [26]	1998	Hydrocortisone 100 mg every 8 h × 5 days, and then 6-day taper	No	Double-blind	Antibiotics, vasopressors, fluids	28-day mortality, shock reversal, complications of treatment	5
Briegel et al. [28]	1999	Hydrocortisone 100 mg × 1, and then 0.18 mg/kg/h until off pressors, and then 6-day taper	No	Double-blind	Antibiotics, vasopressors, fluids	30-day mortality, shock reversal, complications of treatment	5
Chawla et al. [29,37]	1999	Hydrocortisone 100 mg every 8 h × 3 days, and then tapered over 4 days	No	Double-blind	Not reported	Shock reversal; 28-day mortality, complications of treatment	3
Yildiz et al. [36]	2002	Prednisolone 5 mg every morning and 2.5 mg every afternoon × 10 days	No	Double-blind	Antibiotics, vasopressors, fluids	28-day mortality, complications of treatment	5
Annane et al. [8]	2002	Hydrocortisone 50 mg every 6h + fludrocortisone 50 µg every day × 7 days	No	Double-blind	Antibiotics, vasopressors, fluids	28-day mortality, shock reversal, complications of treatment	5
Confalonieri et al. [18]	2005	Hydrocortisone 200 mg × 1, and then 10 mg/h × 7 days	Yes	Double-blind	Antibiotics	Shock reversal, hospital and 60-day mortality, complications of treatment	5
Mussack et al. [19]	2005	Hydrocortisone 100 mg × 1, and then 0.18 mg/kg/h until off pressors, and then 6-day taper	No	Double-blind	Antibiotics, vasopressors, fluids	Shock reversal; 28-day mortality	4
Oppert et al. [20]	2005	Hydrocortisone 50 mg × 1, and then 0.18 mg/kg/h until off pressors, and then 3-day taper	No	Double-blind	Antibiotics, vasopressors, fluids	Shock reversal; 28-day mortality	5
Tandan et al. [23]	2005	Low-dose steroids (regimen not specified)	Not specified	Not specified	Not specified	Shock reversal; 28-day mortality	1
Rinaldi et al. [21]	2006	Hydrocortisone 12.5 mg/h × 6 days, and then tapered	No	Open-label	Antibiotics, fluids	Hospital mortality	3
Cicarelli et al. [17]	2007	Dexamethasone 0.2 mg/kg every 36 h × 3	Yes	Double-blind	Antibiotics, vasopressors, fluids	28-day mortality, complications of treatment	5
CORTICUS [22]	2008	Hydrocortisone 50 mg every 6 h × 5 days, and then tapered over 6 days	No	Double-blind	Antibiotics, vasopressors, fluids	Shock reversal; 28-day mortality, complications of treatment	5

ARDS, adult respiratory distress syndrome.

population and the OR of death (p 0.03), similar to the relationship demonstrated among all of the trials combined (Fig. 3). As expected, because the doses of steroids adminis-

tered in the trial published after 1997 were similar (range in hydrocortisone equivalents: 30–420 mg over first 24 h after enrolment), there was no relationship between steroid dose

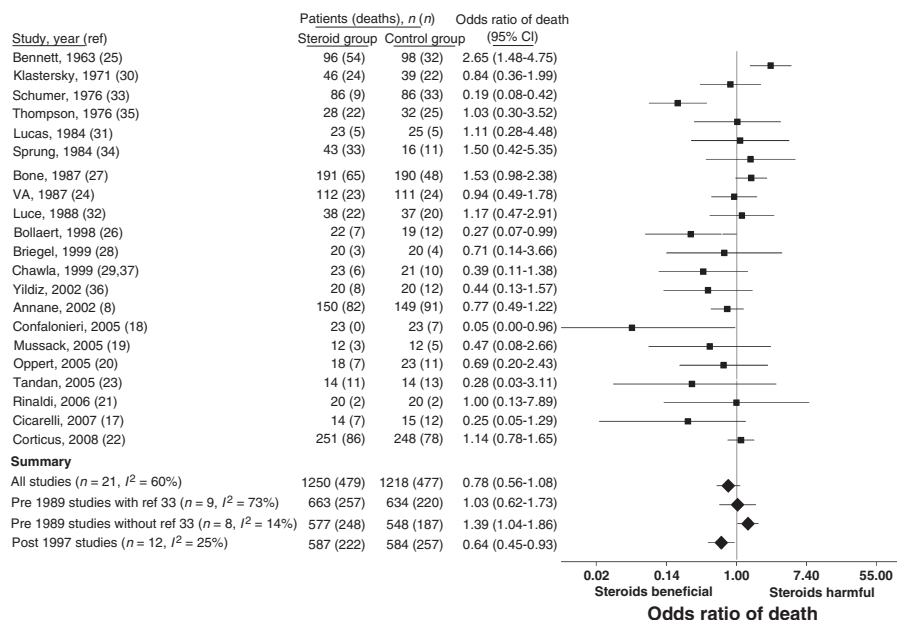


FIG. 2. Effects of steroids on mortality in randomized controlled sepsis trials. The OR of death and 95% CI with steroid therapy is shown. Analysis of all 21 trials demonstrated variability in the effects of steroids on mortality ($I^2 = 60\%$, $p < 0.001$). As previously, studies were partitioned into those published before 1989 and after 1997 to decrease heterogeneity. In the 12 trials published after 1997, there remained a moderate amount of heterogeneity in the effects of steroids on mortality ($I^2 = 25\%$, $p 0.20$), with an overall decrease in the OR of death with steroid therapy ($p 0.02$). Significant heterogeneity remained in the treatment effects of steroids in the nine trials published before 1989 ($I^2 = 73\%$, $p < 0.001$). Removal of a single trial that was a significant outlier [33] decreased the heterogeneity in these trials ($I^2 = 14\%$, $p 0.33$). In the remaining eight trials published before 1989, steroids significantly increased the OR of mortality ($p 0.03$).

and the OR of death within the group of trials published after 1997 (p not significant; data not shown).

Influence of response to adrenocorticotrophic hormone (ACTH) stimulation testing on the treatment effects of steroids

Five of the trials published after 1997 report mortality results based on patient response to a 250- μg ACTH stimulation test (Fig. 4) [8,20,22,26,36]. Four of the studies defined a non-responder according to a change in cortisol level of $< 9 \mu\text{g/dL}$ from baseline [8,20,22,36]; the fifth study defined a non-responder according to a change in cortisol level of $< 6 \mu\text{g/dL}$ from baseline [26]. The treatment effects of steroids on mortality, based on response to ACTH stimulation testing, were similar ($p 0.86$), and consistent within each subgroup and overall (non-responder, $I^2 = 0\%$; responder, $I^2 = 14\%$; combined, $I^2 = 0\%$). Steroid therapy led to similar non-significant decreases in mortality in both non-responders (OR of death 0.84, 95% CI 0.59–1.12, $p 0.33$) and responders (OR of death 0.83, 95% CI 0.50–1.39, $p 0.49$). It is of note that there was no difference in the control mortality rate based on response to ACTH stimulation testing ($p 0.26$; non-responder control mortality 50%, 95% CI 31–69%; responder control mortality 38%, 95% CI 19–57%).

Effects of steroids on shock reversal

Seven trials published after 1997 reported a consistent effect of steroids on 28-day shock reversal ($p 0.70$, $I^2 = 0\%$), with an overall significant increase in shock reversal in patients treated with steroids as compared with controls (OR of shock reversal 1.66, 95% CI 1.25–2.20, $p < 0.001$) (Fig. 4) [8,19,22,23,26,28,29]. Severity of illness did not influence the effects of steroids on shock reversal across these trials (data not shown, $p 0.43$). Two trials published before 1989 reported opposite effects of high-dose steroids on shock reversal (data not shown, p not significant within each trial) [27,34].

Incidence of treatment-related complications in trials published after 1997

Several trials published after 1997 reported the incidence of treatment-related complications. As compared with controls, there was no increase in the incidence of secondary infections ($n = 8$, $I^2 = 19\%$, OR of secondary infection 0.96, 95% CI 0.63–1.45, $p 0.84$) [8,17,18,22,26,28,29,36,37], gastrointestinal bleeding ($n = 8$, $I^2 = 0\%$, OR of gastrointestinal bleeding 1.10, 95% CI 0.65–1.88, $p 0.72$) [8,17,18,22,26,28,29,36,37] or neuropathy ($n = 2$, $I^2 = 0\%$, OR of neuropathy 0.35, 95% CI 0.08–1.55, $p 0.17$) with steroid therapy [18,22].

TABLE 2. Characteristics of trials published before 1989 vs. after 1997

Author	Years in which patients were enrolled	Control mortality rate (%)	Patients with shock (%)	Patients receiving vasopressors (%)	Total steroid dose (mg of hydrocortisone equivalents) ^{a,b}	Length of therapy ^c	Steroid taper	Indication for therapy
Bennett et al. [25]	1959–1963	33	NR	NR	1050	6 days	No ^d	Severe infection
Klastersky et al. [30]	NR	56	NR	NR	7000	3 days	No	Severe infection
Thompson et al. [35]	NR	78	100	NR	42 000	24 h	No	Shock
Lucas et al. [31]	1978–1980	20	100	NR	11 200	48 h	No	Shock
Sprung et al. [34]	1979–1982	69	100	93	21 700	4 h	No	Shock
Bone et al. [27]	1982–1985	25	38	NR	42 000	24 h	No	Severe sepsis
Veterans Administration [24]	1983–1986	22	NR	NR	26 250	9 h	No	Sepsis
Luce et al. [32]	1983–1986	54	100	44	42 000	24 h	No	Shock
Bollaert et al. [26]	NR	63	100	100	1500	5 days	Yes	Vasopressor-dependent shock
Briegel et al. [28]	1993–1996	20	100	100	1209	6 days	Yes	Vasopressor-dependent shock
Chawla et al. [29,37]	NR	48	100	100	900	3 days	Yes	Vasopressor-dependent shock
Yildiz et al. [36]	1997–1999	60	23	NR	300	10 days	No	Severe sepsis
Annane et al. [8]	1995–1999	61	100	100	1400	7 days	No	Vasopressor-dependent shock
Confalonieri et al. [18]	2000–2003	30	7	7	1880	7 days	No	Pneumonia
Mussack et al. [19]	NR	42	100	100	1209	6 days	Yes	Vasopressor-dependent shock
Oppert et al. [20]	NR	48	100	100	453	2 days	Yes	Vasopressor-dependent shock
Tandan et al. [23]	NR	93	100	NR	NR	NR	NR	Septic shock
Rinaldi et al. [21]	NR	10	0	0	1800	6 days	Yes	Severe sepsis
Cicarelli et al. [17]	2004–2005	80	100	100	1119	3 days	No	Vasopressor-dependent shock
CORTICUS [22]	2002–2005	31	100	99	1000	5 days	Yes	Vasopressor-dependent shock
Summary	Value	Weighted mean (%)	Weighted mean (%)	Weighted mean (%)	Median	Median (days)	Rate	Median
	Before 1989	35	63	65	23 975	1	0/8	Shock
	After 1997	44	90	89	1209	6	7/11	Vasopressor-dependent shock

NR, not reported.

^aTotal possible dose of steroid that could have been received by a patient in a trial before beginning a taper; if two drugs were used in the trial, the average total dose was used.

^bDose based on a 70-kg patient.

^cLength of steroid therapy before taper was begun.

^dDecreasing doses of steroids over 6 days were considered to constitute a steroid treatment regimen and not a taper in the original report and all previous meta-analyses.

Publication bias and sensitivity analysis in trials published after 1997

Visual examination of a funnel plot of the trials published after 1997 suggests potential publication bias, with a disproportionately high number of the published small trials demonstrating beneficial treatment effects of steroids (Fig. 5). Formal testing for publication bias, using Egger's regression method, statistically supports the presence of publication bias in the studies published after 1997 (p 0.002). A jack-knife sensitivity analysis revealed that eight studies increased heterogeneity (I^2 increased) and four studies decreased heterogeneity (I^2 decreased) when the individual study was removed (Fig. 5). It is of note that the two studies with largest effect on the heterogeneity among these 12 trials ($I^2 = 25\%$) were the largest randomized controlled trial ($I^2 = 0\%$ if removed) [22] and the small trial with the largest beneficial treatment effect of steroids ($I^2 = 11\%$ if removed) [18].

Discussion

Since 2003, seven prospective randomized controlled trials have reported the effects of low-dose steroids on either shock reversal or mortality during sepsis. Previously, we iden-

tified five trials (published from 1997 to 2003) reporting the effects of low-dose steroids on either shock reversal or mortality during sepsis; these five trials demonstrated a consistent beneficial effect of low-dose steroids on both shock reversal and mortality [8,26,28,29,36,37]. Combined analysis of all 12 low-dose steroid trials published after 1997 demonstrated beneficial effects of low-dose steroids during sepsis. Similar to the findings of our previous analysis, low-dose steroids demonstrated a consistent improvement in shock reversal across the trials reporting this outcome. In contrast, heterogeneity in the effects of low-dose steroids on mortality increased to moderate levels in the current analysis. The differing effects of steroids on mortality across the 12 low-dose steroid trials may be explained, in part, by the influence of severity of illness on the treatment effects of steroids. An inverse linear relationship between severity of illness of the studied patient population and the effects of steroids on mortality was identified; low-dose steroids appear to increase mortality or have no effect in less severely ill patient populations, and to decrease mortality in more severely ill patient populations. Our current meta-analysis suggests that low-dose steroid therapy may reverse shock in most patients with septic shock, but may decrease mortality only in patients with more severe septic shock who are at high risk of death.

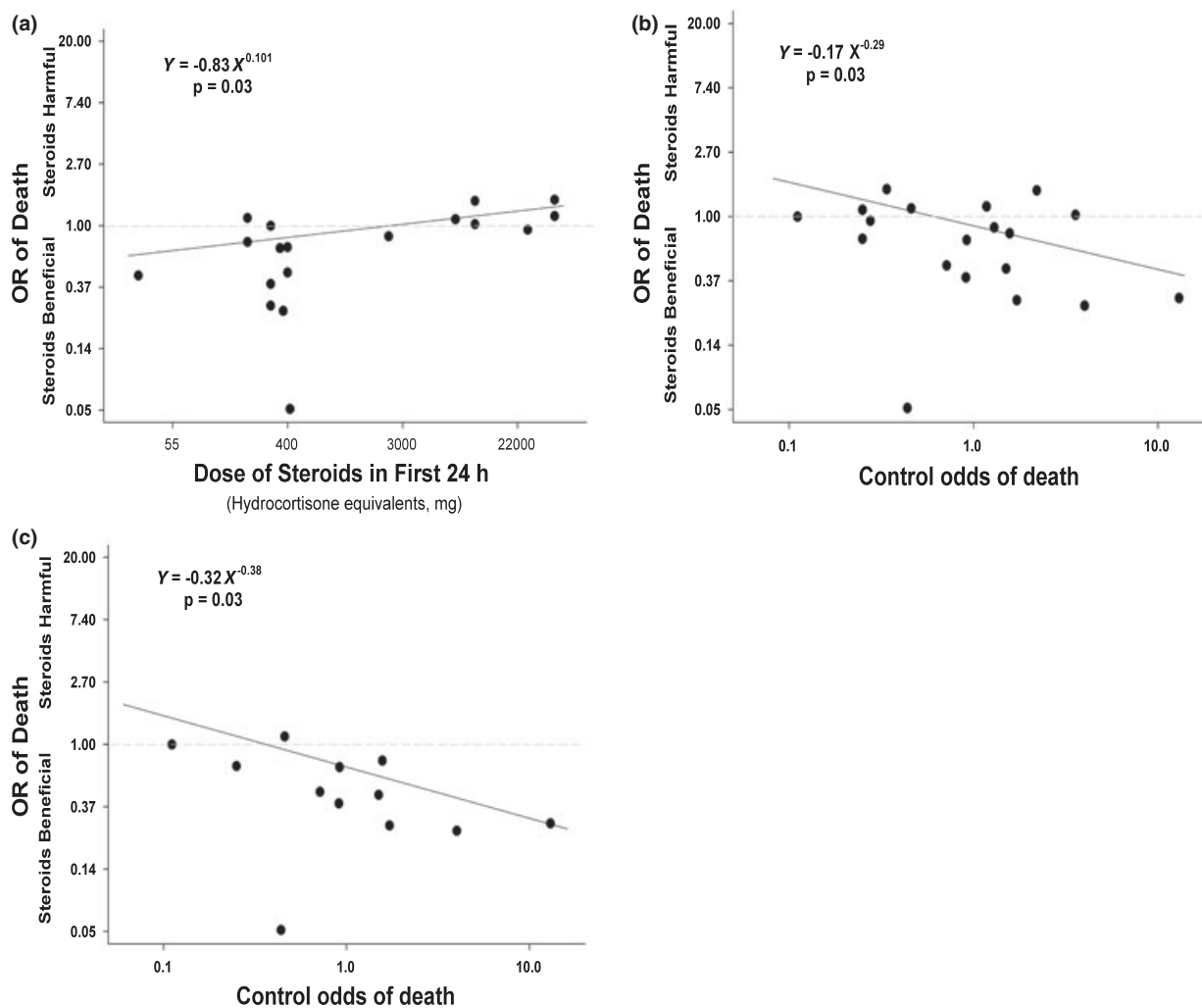


FIG. 3. Influence of steroid dose and severity of illness on the effects of steroids on mortality. (a) There is a significant linear relationship between the dose of steroids administered in the first 24 h after study enrolment and the OR of death across the steroid sepsis trials (p 0.03); steroids decreased mortality at lower doses, and increased mortality as steroid dose increased. (b) A significant inverse linear relationship between the control odds of death (a measure of severity of illness) and the OR of death also exists across the steroid sepsis trials (p 0.03); steroids increase mortality in patient populations with a low control odds of death (less severely ill), and decrease mortality in patient populations with a high control odds of death (more severely ill). As in our previous analysis, a single overly influential trial with methodological differences was identified and removed from these meta-regression analyses [25]. (c) In the subgroup of trials published after 1997 that administered only lower-dose steroids (range in hydrocortisone equivalents: 30–420 mg over first 24 h after enrolment), a similar significant inverse linear relationship between the control odds of death and the OR of death exists (p 0.03), suggesting that low-dose steroids increase mortality in less severely ill patient populations and decrease mortality in more severely ill patient populations.

Previously, we identified nine trials examining the effects of steroids during sepsis published before 1989 [7]. Overall, these trials demonstrated a harmful effect of steroids on mortality after exclusion of a single outlier trial [33]. In our previous analysis, the different effects of steroids in trials published before 1989, as compared with trials published after 1997, could be explained, in part, by a linear relationship between steroid dose and treatment effect [7]. Our current analysis demonstrated similar differences between the

nine trials published before 1989 and the 12 trials published after 1997, and confirmed the relationship between steroid dose and treatment effect. In the trials published before 1989, high-dose steroids were administered to decrease the excessive inflammation associated with sepsis. These earlier trials involved significantly shorter courses of higher-dose steroids, which may have led to harmful immunosuppression. In contrast, the trials published after 1997 involved longer courses of steroids, in a dose range equivalent to the

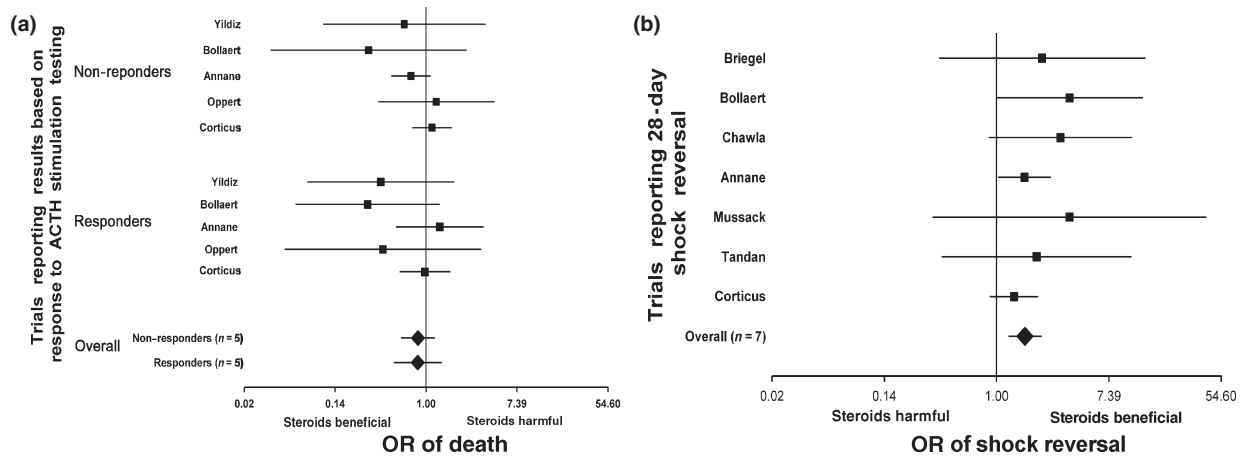


FIG. 4. Effects of low-dose steroids on mortality based on response to adrenocorticotrophic hormone (ACTH) stimulation testing and the effects of steroids on shock reversal. (a) The OR of death and 95% CI with steroid therapy based on patient response to a 250- μ g ACTH stimulation test are shown for the five trials published after 1997 that reported mortality results using these subgroups [8,20,22,26,36]. The treatment effects of steroids on mortality based on response to ACTH stimulation testing were similar (p 0.86) and consistent within both subgroups and combined groups (non-responder, $I^2 = 0\%$; responder, $I^2 = 14\%$; combined, $I^2 = 0\%$). Low-dose steroids demonstrated similar non-significant decreases in mortality in both non-responders (OR of death 0.84, 95% CI 0.59–1.12, p 0.33) and responders (OR of death 0.83, 95% CI 0.50–1.39, p 0.49) to ACTH stimulation testing. (b) The OR of 28-day shock reversal and 95% CI with steroid therapy is displayed for the seven trials published after 1997 reporting this outcome. Low-dose steroids consistently improved 28-day shock reversal (p 0.70, $I^2 = 0\%$), with a significant increase in shock reversal in patients treated with steroids as compared with controls (OR of shock reversal 1.66, 95% CI 1.25–2.20, p <0.001).

amount of steroids produced by the body during a stressful state (c. 300 mg of cortisol per day), to treat critical illness-related corticosteroid insufficiency [38]. The lower doses of steroids administered in the more recent trials do not appear to be immunosuppressive, as evidenced by similar rates of secondary infections in the treatment and control groups in these trials. In addition, low-dose steroids did not lead to higher rates of other steroid-related adverse events, including gastrointestinal bleeding and neuropathy.

In our earlier meta-analysis, we were unable to identify a relationship between severity of illness and treatment effects [7]. At that time, we noted that this relationship may exist, but may not have been identified, secondary to the influence of drug dose, a limited range of severity of illness, or a lack of power. In the current analysis, there was no relationship between severity of illness and the effects of steroids on shock reversal; however, there was a relationship between severity of illness and the effects of steroids on mortality, both within the group of the trials published after 1997 and when examining all of the trials combined. The increased power and range of severity of illness provided by the addition of the seven studies published since 2003 allowed for the identification of this relationship in the current analysis. The relationship between severity of illness and treatment effect identified in this analysis is consistent with the reported effects of severity of illness on the treatment

effects of other adjunctive therapies for sepsis, including mediator-specific anti-inflammatory agents and recombinant activated protein C, in both preclinical and clinical trials [6,39]. However, this relationship could not be reproduced prospectively in an antibiotic-treated mouse pneumonia model, which was used to investigate the effects of hydrocortisone over a wide range of risk of death [40].

Potential mechanisms responsible for the beneficial effects of low-dose steroids include an increase in vascular smooth muscle sensitivity to both exogenous and endogenous vaso-pressors, treatment of critical illness-related corticosteroid insufficiency, and attenuation of dysregulated inflammation and coagulation associated with sepsis [41,42]. The steroid-associated increase in vascular smooth muscle sensitivity may lead to improved shock reversal in patients with septic shock, regardless of their risk of death. However, similar to what occurs with other adjunctive therapies, the potential anti-inflammatory effects of low-dose steroids may explain their effects on mortality [6,39]. In severely ill patients who are likely to die from sepsis, attenuation of sepsis-associated dysregulated inflammation by low-dose steroids may decrease mortality. In contrast, in septic patients for whom the likelihood of survival is high, the potential anti-inflammatory and immunosuppressive effects of low-dose steroids may impair host defence mechanisms and lead to worse outcome.

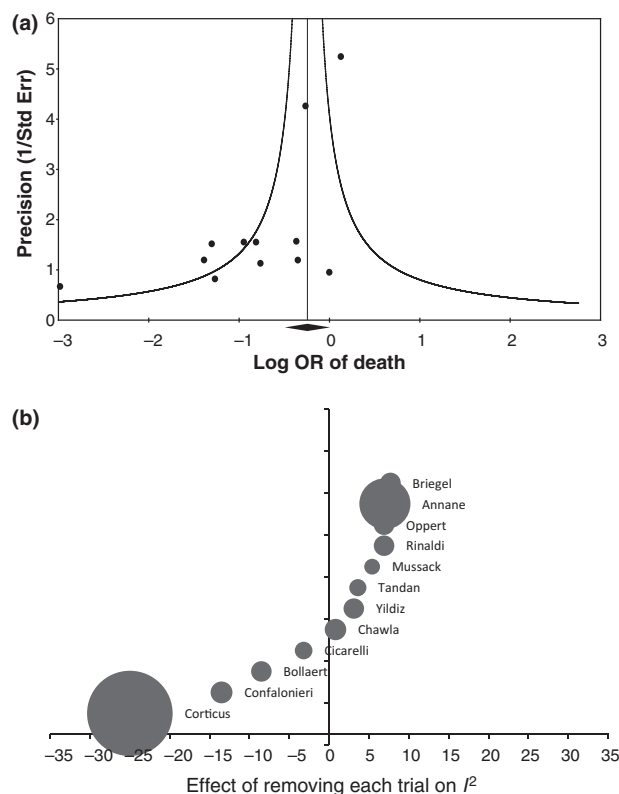


FIG. 5 Publication bias and jackknife sensitivity analysis in the steroid trials published after 1997. (a) A funnel plot of precision versus the log odds ratio of death with steroid therapy for the trials published after 1997 is presented; visual inspection of the plot suggests potential publication bias. There are a disproportionately high number of published small trials demonstrating beneficial treatment effects of steroids (demonstrated by the solid circles with negative log odds ratios of death on the lower left of the vertical line in the middle of the graph) than published small trials demonstrating harmful effects of steroids (reflected by paucity of solid circles with positive log odds ratios of death on the lower right of the vertical line in the middle of the graph). (b) A jackknife sensitivity analysis examining the heterogeneity of the treatment effects of steroids on mortality in the group of trials published after 1997 is displayed. The individual trials are ordered on the X-axis by the change in I^2 in when each trial is removed one at time. This analysis identified that eight studies increased heterogeneity (I^2 increased; represented by the corresponding circle with the study name to the right of the vertical line at zero) and four studies decreased heterogeneity (I^2 decreased; represented by the corresponding circle with the study name to the left of the vertical line at zero) when the individual study was removed. The two studies with the largest effects on the heterogeneity among these 12 trials are on the far left of the figure. When the CORTICUS trial [22] is removed, the I^2 goes from 25% to 0%; when the trial Confalonieri et al. [18] is removed, I^2 goes from 25% to 11%. Of note, these trials represent the largest randomized controlled trial and the trial with the largest beneficial treatment effect of steroids respectively. Circle size is proportional to overall study size.

Some authors have suggested that a patient's response to ACTH stimulation testing should be used to determine which septic patients should receive steroids, on the basis of reports that only patients with a blunted response to ACTH stimulation testing derived benefit from steroid therapy [8]. However, other authors have challenged the reliability and reproducibility of the results of ACTH stimulation testing [43–46]. The current analysis demonstrates no difference in the effects of steroids on mortality according to the results of ACTH stimulation testing, and therefore does not support the use of ACTH stimulation testing to determine which septic patients should receive steroid therapy. This recom-

mendation is consistent with a recent consensus statement for the use of steroids in sepsis from the American College of Critical Care Medicine, stating that "ACTH stimulation testing should not be used to identify those patients with septic shock ... who should receive glucocorticoids" [38].

Conclusions regarding the benefits of low-dose steroids in sepsis derived from this analysis are limited by the potential influence of publication bias and by increased heterogeneity among the trials. The funnel plot and Egger's regression suggest that a disproportionately high number of the published small trials demonstrated beneficial effects of steroids on mortality and may be influencing the estimate of the overall

effect of low-dose steroids on mortality. In addition, the jack-knife sensitivity analysis suggests that the small trial by Confalonieri *et al.* disproportionately increases the heterogeneity within the group of low-dose trials [18]. This trial reported the largest decrease in mortality with steroids, and is fundamentally different from the others, considering that the enrolment criterion was pneumonia and not, specifically, sepsis. Removal of this trial does not substantially change the overall relationship between severity of illness and the effects of steroids on mortality.

The jack-knife sensitivity analysis also suggests that CORTICUS [22], the largest and most recent randomized controlled trial of low-dose steroids in sepsis, disproportionately increases the heterogeneity within the group of low-dose trials. This multicentre trial is the only study to report increased mortality with low-dose steroids during sepsis. Multiple issues surrounding the interpretation of the CORTICUS [22] results have been raised. First, according to the authors, this trial was terminated early, "due to a combination of slow enrollment, termination of funding, and time expiry of the drug". The early termination decreased the power of the study to detect a treatment effect of steroids on mortality to <35% [47]. In addition, the power of this trial was also limited by a lower than expected control mortality rate (expected, 40%; actual, 31%). Furthermore, the slow enrolment and less severely ill patient population may have been due to a loss of equipoise during the study, secondary to the publication of treatment guidelines recommending low-dose steroid therapy for patients with vasopressor-dependent septic shock [48]. It is possible that clinicians chose to treat more severely ill septic patients with steroids rather than allow them to participate in the randomized controlled trial; this could account for the lower than expected control mortality rate in the trial, the slow enrolment, and an undetectable treatment effect. It is of note that the results of the CORTICUS trial are consistent with the relationship between severity of illness and the effects of steroids on mortality demonstrated in our analysis. In addition, removal of this trial does not substantially change the overall relationship between severity of illness and the effects of steroids on mortality. Interpreted together, these results suggest that low-dose steroids may improve survival in severely ill septic patients and that further clinical trials of low-dose steroids in septic patients with high mortality rates are warranted.

Conclusions

The effects of steroids in sepsis are dependent on both steroid dose and severity of illness. High-dose steroids during

sepsis increase mortality. Low-dose steroids improve shock reversal during sepsis, independently of severity of illness; however, the effects of low-dose steroids on mortality appear to be dependent on severity of illness, with low-dose steroids decreasing mortality in more severely ill patients. Additional clinical trials with severely ill patients with refractory septic shock who require high-dose vasopressors are necessary to definitively determine the role of low-dose steroids during sepsis. Until such data are available, the decision to administer low-dose steroid therapy to a septic patient must be made on an individual basis, taking into account the patient's severity of illness and the risk of adverse events due to therapy. ACTH stimulation testing should not be used to determine which patients should receive steroid therapy. The currently available data suggest that a 5–7-day course of hydrocortisone (200–300 mg daily, either in divided doses or as a continuous infusion), followed by a taper over 3–5 days, may reduce mortality in patients with septic shock who are at high risk of death (i.e. patients with refractory septic shock requiring high-dose vasopressors).

Transparency Declaration

The authors have no conflicts of interest to report.

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