

# Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis

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## Abstract

**Objective** To assess the effects of corticosteroids on mortality in patients with severe sepsis and septic shock.

**Data sources** Randomised and quasi-randomised trials of corticosteroids versus placebo (or supportive treatment alone) retrieved from the Cochrane infectious diseases group's trials register, the Cochrane central register of controlled trials, Medline, Embase, and LILACS.

**Review method** Two pairs of reviewers agreed on eligibility of trials. One reviewer entered data on to the computer and four reviewers checked them. We obtained some missing data from authors of trials and assessed methodological quality of trials.

**Results** 16/23 trials (n = 2063) were selected. Corticosteroids did not change 28 day mortality (15 trials, n = 2022; relative risk 0.92, 95% confidence interval 0.75 to 1.14) or hospital mortality (13 trials, n = 1418; 0.89, 0.71 to 1.11). There was significant heterogeneity. Subgroup analysis on long courses ( $\geq 5$  days) with low dose ( $\leq 300$  mg hydrocortisone or equivalent) corticosteroids showed no more heterogeneity. The relative risk for mortality was 0.80 at 28 days (five trials, n = 465; 0.67 to 0.95) and 0.83 at hospital discharge (five trials, n = 465, 0.71 to 0.97). Use of corticosteroids reduced mortality in intensive care units (four trials, n = 425, 0.83, 0.70 to 0.97), increased shock reversal at 7 days (four trials, n = 425; 1.60, 1.27 to 2.03) and 28 days (four trials, n = 425, 1.26, 1.04 to 1.52) without inducing side effects.

**Conclusions** For all trials, regardless of duration of treatment and dose, use of corticosteroids did not significantly affect mortality. With long courses of low doses of corticosteroids, however, mortality at 28 days and hospital mortality was reduced.

## Introduction

Hospital mortality is 30% for severe sepsis and 50-60% for septic shock.<sup>1-3</sup> The prevalence of adrenal insufficiency in septic shock is about 50%, so corticosteroids have been considered potentially beneficial in its management. Initial studies in sepsis and septic shock used short courses of high dose corticosteroids and found no benefit, as shown by two meta-analyses of randomised trials published between 1966-93.<sup>4,5</sup> However, these reviews did not exclude a benefit with longer durations of treatment ( $\geq 5$  days) and lower doses ( $\leq 300$  mg hydrocortisone or equivalent a day), as observed in more recent trials. We systematically reanalysed the effects of corticosteroids in severe sepsis and septic shock, considering all currently available data.

## Methods

### Studies and participants

We searched for randomised or quasi-randomised trials, with or without blinding, on severe sepsis and

septic shock in children or adults.<sup>6</sup> We included data from trials in sepsis, sepsis syndrome, or acute respiratory distress syndrome if separate data were available for septic shock.

### Interventions

We considered all studies reporting on intravenous treatment with any corticosteroid preparation (for example, cortisone, hydrocortisone, methylprednisolone, betamethasone, or dexamethasone). We defined length of treatment at full doses as long ( $\geq 5$  days) or short ( $< 5$  days) and classified daily doses of corticosteroids as low ( $\leq 300$  mg of hydrocortisone or equivalent) or high ( $> 300$  mg).

The control group received a standard treatment (antibiotics, fluid replacement, inotropes or vasopressors, mechanical ventilation, renal replacement therapy), given either alone or with a placebo.

### Outcome measures

The primary outcome measure was all cause mortality at 28 days. Secondary outcome measures included mortality in the intensive care unit and in hospital, number of patients with reversal of shock (stable haemodynamic status for at least 24 hours after weaning from vasopressors) at 7 and 28 days, and number of patients with adverse events (gastrointestinal bleeding, superinfections, hyperglycaemia, and other adverse effects).

### Search strategy for identification of studies

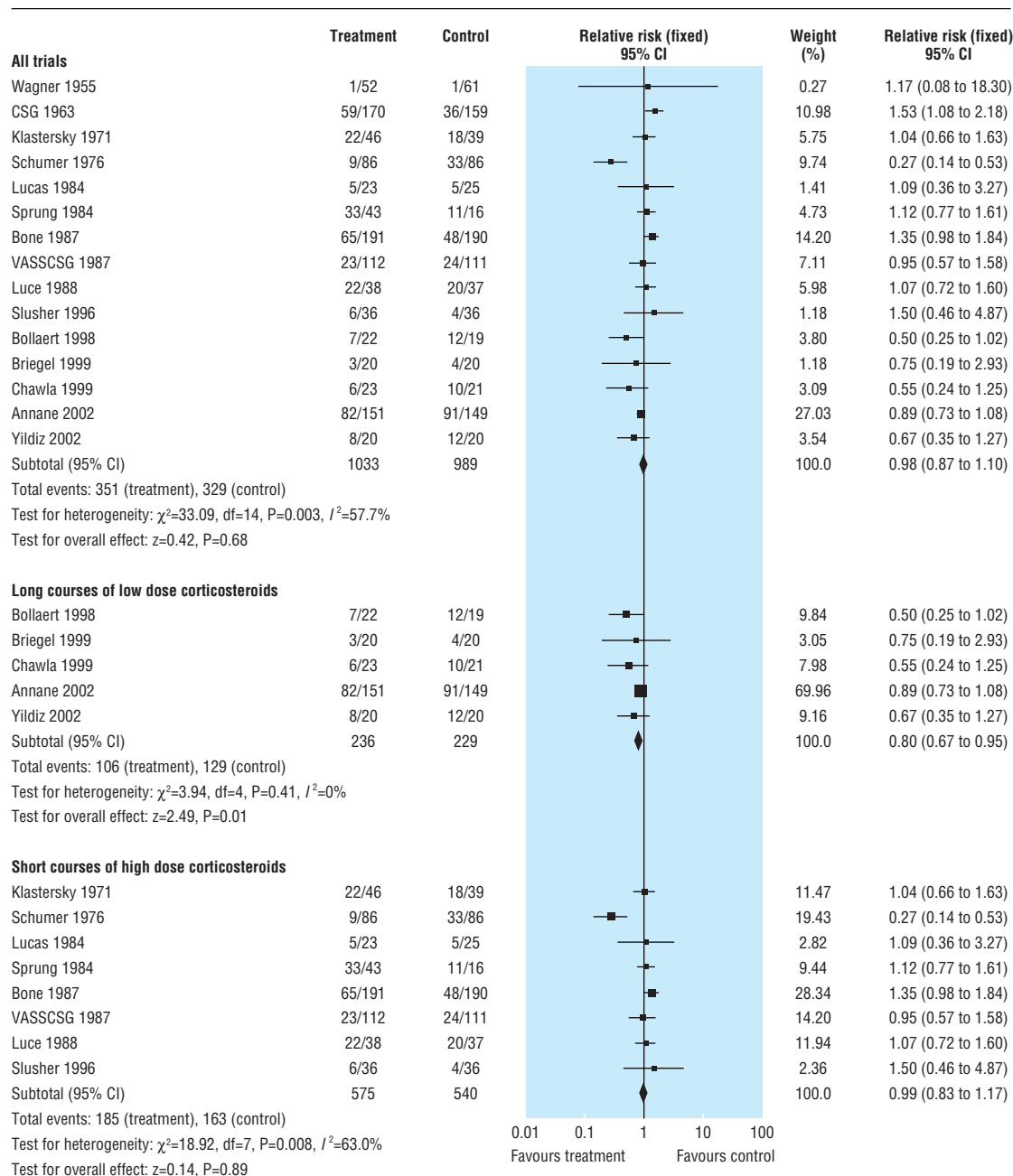
We attempted to identify all studies regardless of language or publication status up until August 2003. We searched the Cochrane infectious diseases group's trials register using the search terms sepsis and septic shock. We searched the Cochrane central register using the search terms sepsis, septic shock, steroids, and corticosteroids; Medline using the search terms sepsis, septic shock, steroids, corticosteroids, adrenal cortex hormones, and glucocorticoids; Embase using the search terms sepsis, septic shock, steroids, and corticosteroids; and LILACS using the search terms sepsis, steroids, and corticosteroids. We also checked the reference lists of resulting trials and, when possible, contacted authors to identify any additional published or unpublished data.

### Study selection

One reviewer checked all identified titles and abstracts, and three reviewers validated this check. Two pairs of reviewers examined all potential trials, selected eligible trials, and graded their methodological quality. Any disagreement within or between pairs was resolved by discussion within the four reviewers or contact with the authors when necessary.



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**Fig 1** Effects of corticosteroids on all cause mortality at 28 days in patients with severe sepsis and septic shock

### Assessment of methodological quality

We documented the methodological quality of trials using a previously published score<sup>5</sup> and graded generation of allocation sequence and allocation concealment as adequate, unclear, or inadequate. Methods for blinding were considered as double blind, single blind, and open. Loss to follow up was described as adequate (analysis included  $\geq 90\%$  of patients), unclear (not reported), and inadequate (analysis included  $< 90\%$  of patients).

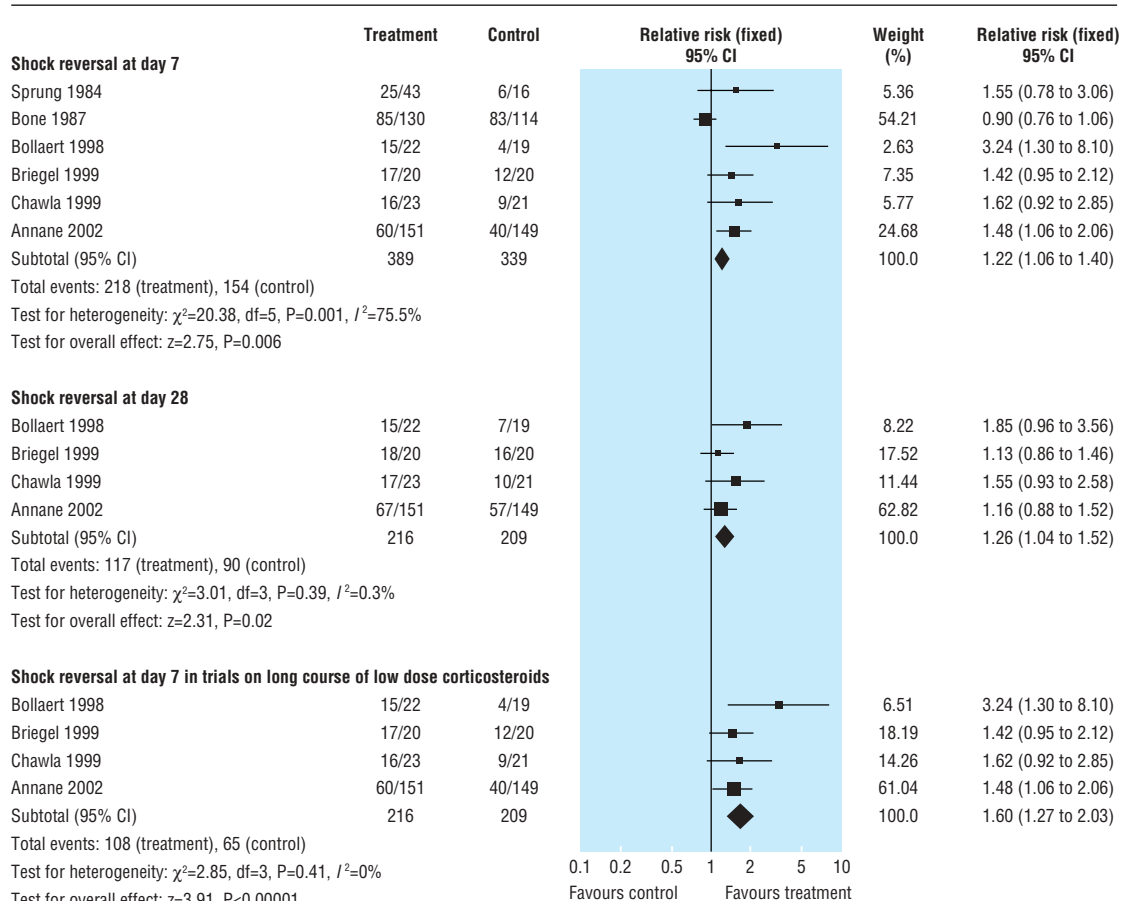
### Data extraction

One reviewer drew up a standard data extraction form and the other reviewers validated it. Four reviewers then independently extracted data and contacted authors of trials for missing data when possible. One

reviewer entered data on to the computer, and four reviewers checked them.

### Data analyses

For each outcome measure, we computed  $2 \times 2$  tables summarising, in each treatment group, the number of patients with the outcome and the total number of patients. We organised the data so that a relative risk  $< 1.0$  favoured corticosteroids (except for shock reversal at days 7 and 28, for which  $> 1.0$  favoured corticosteroids). We performed intention to treat analyses. We calculated a weighted treatment effect (using fixed effects model) across trials. We considered using random effects model only in case of heterogeneity (that is,  $P \leq 0.10$  for  $\chi^2$  test for heterogeneity).



**Fig 2** Effects of corticosteroids on shock reversal in patients with severe sepsis and septic shock

Potential sources of heterogeneity were identified by sensitivity analyses on the basis of high quality trials and by subgroup analysis on the basis of long courses of low dose corticosteroids. This analysis allowed us to evaluate the strategy based on the high prevalence of adrenal insufficiency in septic shock and tested in trials performed after 1992. We sought evidence of publication bias using the funnel plot method.

## Results

### Description of studies

We identified 23 trials on corticosteroids in severe sepsis or septic shock. Of these, we excluded seven and included 16 trials ( $n = 2063$ ) (see [bmj.com](http://bmj.com) for details of trials and their methodological quality).

### All cause mortality at 28 days

There were 351/1033 (34%) deaths in the treated group compared with 329/989 (33%) in the control group (fig 1). There was significant heterogeneity in the results. The relative risk of dying at 28 days was 0.92 (95% confidence interval 0.75 to 1.14,  $P=0.46$ ; random effects model).

The subgroup analysis on trials with long courses of low dose corticosteroids no longer showed heterogeneity, and the all cause mortality at 28 days was lower (0.80, 0.67 to 0.95,  $P=0.01$ ). In contrast, the subgroup analysis on trials with short courses of high dose corticosteroids did not show any difference (0.97,

0.72 to 1.31,  $P=0.84$ ; random effects model). Subgroup analyses based on high quality trials failed to explain heterogeneity.

### Mortality in intensive care unit

We extracted data for mortality in intensive care units from four trials ( $n = 425$ ), all of which investigated the effects of long courses of low dose corticosteroids. There were 108/216 (50%) deaths in the intensive care unit in the treated group compared with 127/209 (61%) in the control group (0.83, 0.70 to 0.97,  $P=0.02$ ).

### Mortality in hospital

We extracted data for hospital mortality from 13 trials ( $n = 1418$ ). There were 279/730 (38%) hospital deaths in the treated group compared with 271/688 (39%) in the control group. There was significant heterogeneity in the results ( $\chi^2 = 27.68$ ,  $P=0.006$ ). The relative risk of dying in hospital was 0.89 (0.71 to 1.11,  $P=0.30$ ; random effects model).

The subgroup analysis on five trials ( $n = 465$ ) with long courses of low dose corticosteroids no longer showed heterogeneity across the trials and showed reduced mortality in hospital (0.83, 0.71 to 0.97,  $P=0.02$ ). In contrast, the subgroup analysis on six trials ( $n = 511$ ) with short courses of high dose corticosteroids did not show any difference in hospital mortality (0.89, 0.57 to 1.37,  $P=0.59$ ; random effects model). Subgroup analyses based on high quality trials failed to explain heterogeneity.

### Shock reversal at day 7

There were 218/389 (56%) shock reversals at day 7 in the treated group compared with 154/339 (45%) in the control group (1.43, 1.01 to 2.01,  $P=0.04$ ; random effects model). There was significant heterogeneity in the results (fig 2).

The subgroup analysis on trials with long courses of low dose corticosteroids no longer showed heterogeneity across the trials, and showed increased rate of shock reversals at 7 days (108/216 (50%) *v* 65/209 (31%); 1.60, 1.27 to 2.03,  $P<0.0001$ ).

### Shock reversal at day 28

There were 117/216 (54%) shock reversals at day 28 in the treated group compared with 90/209 (43%) in the control group (1.26, 1.04 to 1.52,  $P=0.02$ ) (fig 2).

### Adverse events

There was no evidence that corticosteroids increased the risk of gastroduodenal bleeding (10 trials,  $n=1321$ ; 1.16, 0.82 to 1.65,  $P=0.40$ ), superinfections (12 trials,  $n=1705$ ; 0.93, 0.73 to 1.18,  $P=0.54$ ), or hyperglycaemia (6 trials,  $n=608$ ; 1.22, 0.84 to 1.78,  $P=0.30$ ). One trial reported a significant rise in serum sodium concentration ( $>155$  mmol/l) in 6/20 (30%) patients in the treated group and in 1/20 (5%) patients in the placebo group.

## Discussion

For all the trials, regardless of duration of treatment and dose, we found no evidence of a beneficial effect of corticosteroids on all cause mortality at 28 days and mortality in hospital. With long courses of low doses of corticosteroids, however, mortality at 28 days and hospital mortality was reduced.

For both outcomes, the results showed strong heterogeneity that was not explained by the quality of the trials. Sorting the trials by year of publication showed that before 1992 almost all trials showed a relative risk of dying  $>1.0$ , whereas after 1992 all trials had a relative risk of dying  $<1.0$ . This date coincides with the consensus definition for sepsis<sup>6</sup> and with the observation that septic shock is often complicated by adrenal insufficiency.<sup>22</sup> More recent trials also used long courses of low dose corticosteroids, with the aim of treating adrenal insufficiency<sup>23 22</sup> or because of cortisol tissue resistance.<sup>24</sup> The preferred drug was hydrocortisone, with doses of 200-300 mg used to reproduce the cortisol concentrations achieved at maximum exercise in healthy people.<sup>7 8 25</sup> Treatment lasted about a week, corresponding roughly to the mean time that patients with septic shock take vasopressors.

Improvement in survival with corticosteroids may result from reduced duration of shock, severity of inflammation,<sup>25</sup> and number of organ dysfunctions.<sup>8 25</sup> The benefits we have shown are in line with findings from studies on animals, isolated vascular smooth muscles, and inflammatory cells and on healthy volunteers challenged with endotoxin.<sup>26</sup> Finally, there was no evidence of increased rates of gastroduodenal bleeding, superinfections, or hyperglycaemia associated with the use of corticosteroids.

### Recommendations

Hydrocortisone (or equivalent) should be given to patients with septic shock immediately after they

### What is already known on this topic

Short courses of high dose corticosteroids do not affect mortality from severe sepsis and septic shock

Long courses of low dose corticosteroids improve systemic haemodynamics and reduce the time on vasopressor treatment

### What this study adds

Long courses of low dose corticosteroids reduce mortality at 28 days, in intensive care units, and in hospital

Long courses of low dose corticosteroids do not significantly alter the risk of gastroduodenal bleeding, superinfections, or hyperglycaemia

undergo an adrenocorticotropin hormone test, at a dose of 200-300 mg, and should be continued for 5-11 days, only when absolute (random cortisol concentration  $\leq 414$  nmol/l) or relative (cortisol response to adrenocorticotropin hormone  $\leq 248$  nmol/l) adrenal insufficiency is present.

A longer version of this review has been published in the Cochrane Library.<sup>27</sup>

Contributors: See bmj.com

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Competing interests: Authors of this review have been involved in randomised controlled trials of low dose hydrocortisone that are included in this review.

Ethical approval: Not required.

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## The long term clinical course of acute deep vein thrombosis of the arm: prospective cohort study

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### Introduction

The diagnosis and treatment of deep vein thrombosis of the arm are documented extensively.<sup>1,2</sup> The long term clinical course of the condition is, however, poorly defined.

### Participants, methods, and results

Fifty three consecutive patients with a first, symptomatic deep vein thrombosis of the arm, confirmed by ultrasonography or venography—including six cases related to catheter insertion—were treated with high dose heparin, followed by at least three months of warfarin (targeted international normalised ratio 2.0-3.0) (table).

Follow up visits were scheduled after three and six months, and then every six months up to five years. At each visit, patients underwent a clinical evaluation, for which we used a standardised scale previously validated in patients with venous thrombosis in the leg,<sup>3,4</sup> and an ultrasound assessment of the affected venous segments. Each of five symptoms (heaviness, pain, itching, physical limitation, and paraesthesia) and six signs (pretibial oedema, skin induration, discoloration, venous ectasia, redness, and pain during compression) received a score ranging from 0 to 3. We defined post-thrombotic syndrome as severe in the case of a score higher than 14 and as mild in the case of a score of 5-14, on two consecutive examinations. We considered veins as recanalised if they measured less than 2.0 mm in diameter in a single examination or less than 3.0 mm in two consecutive examinations at least three months apart.

Symptomatic recurrent thrombosis in the same arm was diagnosed in case of a (new) intraluminal defect on venography, while symptomatic recurrences

in other limbs were diagnosed in case the vein could not be compressed on ultrasonography.<sup>1,5</sup>

We used Kaplan-Meier estimates to assess the risk of recurrent thromboembolism and post-thrombotic syndrome. We used stepwise Cox regression models to calculate hazard ratios for these outcomes in relation to age, sex, extension of thrombosis (single spot versus axillary or subclavian involvement), modality of clinical presentation (idiopathic versus secondary), thrombophilic status, acquired risk factors of thrombosis, and persistent venous obstruction. All patients gave written informed consent.

Two patients were lost to follow up after two and three years, respectively, and 11 died because of cancer progression, pulmonary embolism, and congestive heart failure.<sup>1</sup> Median follow up was 48.3 months.

Three patients developed a recurrent thromboembolism (recurrence in the same arm in two, and a thrombosis in the leg in one). The cumulative incidence of recurrent thromboembolism after one, two, and five years was 2.0% (95% confidence interval 0.0 to 5.9), 4.2% (0.0 to 9.9), and 7.7% (0.0 to 16.5), respectively. Thirteen patients developed post-thrombotic syndrome, one severely so. Ten cases occurred within six months, two after one year, and one after two years. The cumulative incidence of post-thrombotic syndrome was 20.8% (9.3 to 32.3) at six months, 25.1% (12.8 to 37.4) at one year, and 27.3% (14.6 to 40.0) at two years. It remained stable afterwards. The incidence of these outcomes in patients with and without vein catheter is shown in table A on bmj.com.

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An additional table showing outcomes in patients with and without vein catheters is on bmj.com