Steroid controversy in sepsis and septic shock: a meta-analysis

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Authors' objectives
To conduct a meta-analysis to assess the clinical evidence for the use of corticosteroids on patients with septic shock, and to evaluate treatment effects in specific subgroups of patients.

Searching
MEDLINE was searched from 1966 to 1992. The authors' own literature file, and references in trial reports and review articles, were also examined. Experts in the field of sepsis research were contacted for additional material.

Study selection
Study designs of evaluations included in the review
Prospective randomised controlled trials (RCTs), which evaluated the effectiveness of corticosteroids in the management of septic shock, were included if they fulfilled the following criteria: a primary intention to assess the effectiveness of corticosteroids, a control group was present, patients were allocated to treatment group by randomisation, patients had to show the general symptoms of sepsis or septic shock, the type of drug, exact dosage and route of administration had to be mentioned, and mortality reported as an outcome. Excluded trials were those with selected types of infection where septic patients were only a subgroup of the whole study population.

Specific interventions included in the review
The following steroids were studied: hydrocortisone, dexamethasone, betamethasone and methylprednisolone. The hypothetical equivalent dose of hydrocortisone was calculated as ranging from 0.3 to 42.0 g for a 70 kg man on the first day. The duration of therapy ranged from 1 to 6 days and the drug was given as a bolus and as a continuous infusion.

Participants included in the review
The participants were patients considered to have septic shock, defined either as having a positive blood culture, clinically, or using the more detailed definition of sepsis ('sepsis syndrome' and 'systemic sepsis'). Where reported, the mean age ranged from 50 to 65 years, with males ranging from 55.3 to 96.7% and mortality in the control group ranging from 7.1 to 78.1%.

Outcomes assessed in the review
The outcomes assessed were absolute mortality, mortality rates excluding patients who died on the first day, with 14-day mortality being preferred to hospital mortality if possible, and adverse effects.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The quality of the primary studies was assessed on quality of design, conduct and presentation using a 33-part questionnaire designed by Evans and Pollock (see Other Publications of Related Interest no.1), which scores quality of trials from 0 (worst) to 100 (best). The quality of the studies was rated by two independent authors, and any disagreements were resolved by discussion.

Data extraction
It is not stated how the data was extracted. The rate difference in mortality rates was calculated for each study, as the mortality rate in the treatment group minus the mortality rate in the control group.
Methods of synthesis

How were the studies combined?
The results were combined using the random-effects model described by DerSimonian and Laird (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Heterogeneity was tested according to the methods of Cochran and Berlin et al. (see Other Publications of Related Interest nos.3 and 4, respectively). The analysis was repeated using 'low-dose' and 'high-dose' regimes: (1) after excluding the one trial (Schumer) whose inclusion lead to statistical heterogeneity; (2) after excluding the trial of Schumer and one other trial whose protocol differed from the other studies; (3) considering trials using dexamethasone and methylprednisolone; and (4) by analysing results separately for Gram-negative and -positive infections. There was a discussion on the possible sources of heterogeneity among studies.

Results of the review

Ten RCTs were used to assess absolute mortality rate difference (N=1,329).

Four RCTs were used to assess mortality rate difference in Gram-negative infection (N=413; N=251 after stated exclusions).

Four RCTs were used to assess mortality rate difference in Gram-positive infection (N=306; N=142 after stated exclusions).

Five RCTs were used to assess 'low-dose' steroids (N=530).

Five RCTs were used to assess 'high-dose' steroids (N=799).

Five RCTs were used to assess gastrointestinal bleeding (N=648).

Six RCTs were used to assess secondary infection (N=1,017).

Four RCTs were used to assess hyperglycaemia (N=529).

Absolute mortality rate difference (treatment minus control): global effect, -0.2% (95% confidence interval, CI: -9.2, 8.8%; test for heterogeneity, P < 0.001).

Mortality rate differences were 4.8% (95% CI: -0.3, 9.9; test for heterogeneity, P > 0.2) after excluding the trial by Schumer, and 3.5% (95% CI: -2.0, 9), after excluding the trial by Schumer and the trial with a different protocol.

Mortality rates difference after excluding patients who died on the first day was -1.7% (95% CI: -11.0, 7.6).

Type and dosage of steroid mortality rate difference: 'low-dose' regime (less than 20 g equivalents of hydrocortisone during the first 24 hours of the study), -1.9% (95% CI: -20.0, 16.2); 'high-dose' regime, 3.6% (95% CI: -2.5, 9.8).

Gram-negative infections:
mortality rate difference was -5.6% (95% CI: -21.4, 10.1), and after excluding the trial by Schumer and the trial with a different protocol, -2.9% (95% CI: -14.7, 8.9).

Gram-positive infections:
mortality rate difference was 1.8% (95% CI: -15.1, 18.6), and after excluding the trial by Schumer and the trial with a different protocol, 9.2% (95% CI: -4.4, 22.7).

Adverse effects of steroids:
gastrointestinal bleeding rate difference was 2.3% (95% CI: -0.7, 5.4), and after excluding the study in which steroids
were administered for 6 days, 1.1% (95% CI: -3.2, 5.4); secondary or 'super infection' rate difference was 0.4% (95% CI: -4.4, 5.2); and hyperglycaemia difference was 0.2% (95% CI: -4.0, 4.4).

The quality assessment scores of the primary studies range from 41 to 97 out of a maximum of 100.

**Authors' conclusions**
No overall beneficial effect of steroids was observed in patients with septic shock, although there was some evidence for a positive effect in patients with Gram-negative septicaemia.

**CRD commentary**
This is a clearly-written review. A more extensive literature search may have revealed more relevant articles though contact with experts in the field should have revealed most of them. The studies were assessed for quality but no details of the factors used were given. The authors highlight problems in the methodology of the primary studies; these include the lack of consistent definition of septic shock, insufficient detail on the patient characteristics, mortality rates defined at different points in time, variable type of steroid, variable duration of steroid therapy, trials over a considerable time period (from 1963 to 1988), lack of information on the time of onset of treatment, and differences in study populations, as reflected in the variability of mortality in the control groups. There was some investigation of heterogeneity but further investigation of the effect of quality assessment and the year of study on the result would have been welcome, as would heterogeneity testing of the studies used to assess the effectiveness of steroids in Gram-negative infections. In view of the lack of statistical significance of the effect of corticosteroids on patients with Gram-negative septicaemia, and the lack of information on the primary studies, it is not possible to support the authors' conclusion that there is evidence of a positive effect of steroids for this subgroup of patients.

**Implications of the review for practice and research**
There is no evidence of a beneficial effect of corticosteroids in patients with septic shock.

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**Other publications of related interest**

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.