Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature

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Authors' objectives
To determine the effect of corticosteroid therapy on morbidity and mortality in patients with sepsis.

Searching
MEDLINE and EMBASE were searched from 1966 to 1993 using the following MeSH terms: 'sepsis' and 'steroids' or 'corticosteroids', and 'septic shock' and 'steroids' or 'corticosteroids'. The Science Citation Index was searched using the terms 'sepsis' and (explode) 'corticosteroid', and 'septic shock' and (explode) 'corticosteroid'. Index Medicus was handsearched from 1951 onward using the terms 'corticosteroids', 'steroids', 'sepsis' and 'septic shock'. Personal files, reference lists of relevant primary and review articles, and contact with primary investigators were used to locate additional published and unpublished material.

Study selection
Study designs of evaluations included in the review
Randomised clinical trials were included.

Specific interventions included in the review
Intravenous corticosteroids (methylprednisolone, dexamethasone, betamethasone and hydrocortisone).

Participants included in the review
Adults with signs of sepsis or septic shock, including at least 2 of the following: shaking chills and/or temperature greater than 38.9 or less than 35.5 C; heart beat greater than 100 beats/min; systolic blood-pressure less than 90 mmHg; bacteraemia; organ dysfunction.

Outcomes assessed in the review
Mortality. Complications of corticosteroid therapy (secondary infection, upper gastrointestinal bleeding, progression of organ dysfunction, hyperglycaemia).

How were decisions on the relevance of primary studies made?
Two investigators independently reviewed the titles and abstracts of all relevant articles. Three investigators (one of whom was blinded to the journal, authors, institution, and the magnitude and direction of results) independently applied the study selection criteria to full manuscripts. The selection criteria were based on study design, population, intervention and outcome. Any discrepancies were resolved by consensus.

Assessment of study quality
The validity assessment was based on patient selection, patient characteristics at baseline, randomisation, blinding, intervention, contamination, cointervention, explicit description of complications of steroids, withdrawals, use of intention to treat protocol, and explicit definition of septic shock. A methodological quality scoring system was applied independently by two reviewers (one was blinded to the journal, authors, institution, and the magnitude and direction of results). The authors of the primary studies were consulted regarding the accuracy of methodological scores, and additional information was requested if necessary. Any disagreements between reviewers were resolved by discussion and consensus.

Data extraction
Data were extracted on population, intervention, outcome, and methodological quality by two investigators. Any disagreements were resolved by consensus. Information was requested from primary investigators when data were missing or unclear.
Methods of synthesis
How were the studies combined?
The relative risk (RR) and associated 95\% confidence intervals (CIs) were estimated across the studies.

How were differences between studies investigated?
Heterogeneity across the studies was tested using the method of Fleiss (see Other Publications of Related Interest no 1).

Results of the review
Nine randomised clinical trials (1,297 participants) were included.

Mortality:
Treatment with corticosteroids produced a trend toward increased mortality (RR 1.13, 95\% CI: 0.99, 1.29). There was significant heterogeneity across studies (p=0.02); sensitivity analysis revealed that this could not be explained by the variation alone in the methodological quality of primary studies.

Subgroup analysis on 6 trials (730 participants) of patients with septic shock showed that treatment with corticosteroids had no effect on mortality (RR 1.07, 95\% CI: 0.91, 1.26). Heterogeneity across these studies can be explained by differences in methodological quality. The higher quality studies (n=4) suggested a trend toward increased mortality (RR 1.12, 95\% CI: 0.95, 1.32), while the lower quality studies (n=2) suggested significant benefit (RR 0.49, 95\% CI: 0.25, 0.98).

Adverse effects:
Heterogeneity was not identified across any studies of adverse effects, although data were not always presented in a manner that allowed statistical pooling. Overall, no increase in secondary infections (911 patients) was found with corticosteroid use (RR 0.92, 95\% CI: 0.67, 1.26).

There was a trend toward increased gastrointestinal bleeding (527 patients) with corticosteroid use (RR 1.17, 95\% CI: 0.79, 1.73), but the definition of gastrointestinal bleeding varied across studies.

Authors' conclusions
Current evidence provides no support for the use of corticosteroids in patients with sepsis or septic shock, and suggests that their use may be harmful.

CRD commentary
In general this is a well-conducted and clearly presented systematic review. The authors acknowledge that the heterogeneity across studies, particularly with respect to study populations and methodological quality, limits interpretation of the review's findings.

Implications of the review for practice and research
The authors stated that these trials underscore the need for future methodologically rigorous trials evaluating new immune-modulating therapies in well-defined critically ill patients with overwhelming infection.

Bibliographic details

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Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
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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.