Adjunctive dexamethasone therapy for bacterial meningitis in adults: a meta-analysis of randomized controlled trials
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CRD summary
The authors found that adjunctive dexamethasone treatment was associated with lower mortality in specific subgroups of adults with bacterial meningitis, including those with definite and/or pneumococcal meningitis. Although the authors' conclusions were cautious, it is difficult to be certain of their reliability, given the large number of subgroup analyses in the review, some with very few trials.

Authors' objectives
To assess the role of dexamethasone, and of steroids in general, for the adjunctive treatment of bacterial meningitis in adults.

Searching
PubMed, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Search terms were reported. Reference lists of relevant articles and reviews were checked. The search was restricted to studies in English, French, German, Italian or Greek. Conference abstracts were not included.

Study selection
Randomised controlled trials (RCTs) of adjunctive corticosteroids used for the treatment of patients with acquired acute study-defined bacterial meningitis were eligible for inclusion. Eligible trials had to have a majority of adult patients, defined as having over 70% of patients aged over 16 years and/or median age over 20 years.

The primary review outcome was all-cause mortality during treatment and for a follow-up of up to eight weeks. Secondary endpoints were unfavourable outcomes (e.g. hearing impairment) and drug-related adverse effects (e.g. bleeding). Trials comparing types or doses of corticosteroid were excluded.

The mean or median age of participant groups in most trials ranged from 26 to 50 years (where stated), but in one trial the two comparison groups had mean ages of 12.9 and 14 years. In most of the included trials, meningitis was defined by clinical presentation plus altered white cell, protein and glucose levels in the cerebrospinal fluid, with or without a positive cerebrospinal fluid gram stain or culture (definite diagnosis). Between 50 and 100% of participants in the review had definite meningitis. Some included trials had a few cases of tuberculous or aseptic meningitis. Disease severity was comparable across the trials, with mean or median Glasgow Coma Scale scores ranging from seven to 13 at baseline (where reported). Dexamethasone, hydrocortisone and/or prednisolone were administered in varying doses for three to 14 days before, with or after antibiotics. Half of the trials reported that nearly all pathogens were susceptible to the antibiotics used. Control groups of the included trials received placebo or no comparator. The included trials were conducted in Asia, Europe, Africa or America, in most cases in high or medium Human Development Index countries.

Two reviewers independently selected the studies.

Assessment of study quality
Trials were scored for quality, using two different quality scores (Jadad and Moher), taking into consideration the reporting and methods used for randomisation and sequence generation, double-blinding, withdrawals and allocation concealment. The maximum score for each scoring tool was 5 points, with studies scoring 3 or more points rated as high quality.

The authors did not state how many reviewers performed the assessment.

Data extraction
Odds ratios (ORs) were calculated from the numbers of events in the control and intervention groups of each trial, with 95% confidence intervals (CIs).

Two reviewers independently extracted the data, with disagreements resolved by consensus among all authors.

**Methods of synthesis**

Trials were combined to calculate pooled odds ratios and 95% confidence intervals, using a Mantel-Haenszel fixed-effect model unless there was heterogeneity, when a DerSimonian random-effects model was used. Heterogeneity was assessed using the $\chi^2$ test and $I^2$ statistic ($p<0.10$ or $I^2>40\%$ denoting heterogeneity). Publication bias was assessed using Egger’s test.

Subgroup analyses were conducted to examine the impact of the following variables: use of antibiotics pre-enrolment, early or late presentation, definite or probable meningitis, presence of bacteraemia or septic shock, need for intensive care, Human Development Index of trial setting, and causative organism. Additional analyses excluded an outlying (Malawian) trial, which differed from other trials with respect to Human Development Index status and clinical characteristics of the participants. Sensitivity analyses were conducted according to trial quality.

**Results of the review**

Ten RCTs were included in the review (n=2,125 patients). Six trials were double-blinded. Five trials reported adequate allocation concealment. Six trials were allocated 3 or more points (denoting high quality) for both quality scores. The quality scores were reported in a supplementary table available online. There were some discrepancies between the text and figures; the results cited in this field are based on the figures.

**Dexamethasone versus controls** (eight RCTs): There was no statistically significant difference in mortality between the dexamethasone group and comparator groups (eight RCTs; $I^2=42.8\%$). When the outlying trial from Malawi was excluded from analysis, there was a significantly lower mortality rate in the intervention group (OR 0.59, 95% CI 0.40 to 0.86; seven RCTs; $I^2=2.1\%$). In subgroup analyses, the intervention was associated with significant benefit in trials of patients with definite meningitis (OR 0.55, 95% CI 0.31 to 0.96; six RCTs; $I^2=53.4\%$), where *Streptococcus pneumoniae* was the causative organism (OR 0.26, 95% CI 0.08 to 0.78) and in countries with high Human Development Index settings (OR 0.45, 95% CI: 0.23, 0.95; two RCTs; $I^2=0\%$). There was no statistically significant difference between the groups in unfavourable outcomes or adverse effects. However, dexamethasone was associated with a non-significant trend towards fewer episodes of hearing impairment, and restriction of the analysis to high quality trials resulted in a significant benefit associated with dexamethasone for this outcome (OR 0.64, 95% CI 0.43 to 0.94). Data on intensive care needs, bacteraemia and septic shock were lacking.

**Corticosteroids versus controls** (ten RCTs): There was no statistically significant difference in mortality between corticosteroid and comparator groups (10 RCTs). In subgroup analyses, the intervention was associated with significant benefit where *Streptococcus pneumoniae* was the causative organism (OR 0.45, 95% CI 0.21 to 0.96; eight RCTs) and in trials in high HDI settings (OR 0.56, 95% CI 0.33 to 0.95; three RCTs).

No significant publication bias was detected. Other findings were reported in the review.

**Authors’ conclusions**

Adjunctive dexamethasone treatment was associated with lower mortality in specific subgroups of adults with bacterial meningitis, including those with definite and/or pneumococcal meningitis.

**CRD commentary**

The objectives and inclusion criteria of the review were clear and relevant sources were searched for studies, although the exclusion of conference abstracts meant that some studies may have been missed. At least one trial of children appeared to be included, contrary to the stated inclusion criteria. The restriction of the search to specific languages led to the exclusion of two trials, with unknown potential for bias. Search dates were not reported. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently select studies and extract...
the data. However, few details were provided about the primary studies (e.g. sample numbers, drop-out rates).

Appropriate statistical techniques were used: to combine the trials; to assess for heterogeneity; and to explore differences between the trials. A plausible explanation was proposed for the different findings of the Malawian trial. Some findings reported as statistically significant reached only borderline significance. As the authors acknowledged, the large number of subgroup analyses in the review increased the potential for spurious chance findings. Although the authors' conclusions were cautious, it is difficult to be certain of their reliability, given the large number of subgroup analyses in the review, some with very few trials.

Implications of the review for practice and research

**Practice**: The authors stated that current evidence suggests that dexamethasone should be administered to all adult patients with bacterial meningitis.

**Research**: The authors stated that large studies of dexamethasone for adults with bacterial meningitis are required, to determine the impact of symptom duration, disease severity and administration of antibiotics before commencing dexamethasone.

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