Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data

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CRD summary
This well-conducted individual patient data meta-analysis found no evidence that treating bacterial meningitis with dexamethasone reduced mortality or neurological disability for any particular type of patient. The authors' conclusions are likely to be reliable, although some caution around the generalisability of findings to European healthcare systems may be warranted.

Authors' objectives
To evaluate whether different types of patient treated for acute bacterial meningitis might benefit from adjuvant dexamethasone treatment.

Searching
Relevant trials were identified in a 2007 Cochrane Review (see Other Publications of Related Interest) along with four subsequent trials. Methods of searching for trials published since the Cochrane Review were unstated.

Study selection
Trials were eligible for inclusion in the analysis where individual patient data (IPD) was available from randomised, double-blind, placebo controlled trials of dexamethasone for bacterial meningitis.

Specified outcomes were: mortality at first follow-up; mortality or severe neurological sequelae at one month follow-up; any neurological sequelae at first follow-up; and mortality or severe bilateral hearing loss at first follow-up. Subgroups were defined for: age (stratified); sex; pre-admission symptoms (less than 48 hours); malnutrition; human immunodeficiency virus (HIV) status; active antibiotic before first dose; heart rate (stratified); blood haemoglobin (stratified); consciousness level; cerebrospinal fluid white cell count (stratified); cerebrospinal fluid glucose (stratified); cerebrospinal fluid protein (stratified); pyogenic organism seen on microscopy; causative organism; and bacterial meningitis confirmation.

Included trials were conducted in Europe, Malawi, Vietnam and South America. All trials included patients enrolled with clinically suspected bacterial meningitis and cerebrospinal fluid criteria. Less than half (41%) of patients were under 15 years of age, but 11% were over 55.

A total of 22 eligible studies were identified. Data were available from the five most recent trials, all published since 2001. The authors stated that data were not available for 17 older trials (or that they were not trials). However, no information was given on how collaboration was elicited or whether it was coincidental that all of the five most recent trials were able to provide data and all the older trials were not able to provide data.

The authors did not state how relevant studies were selected for the review.

Assessment of study quality
Individual patient data were obtained from the five trials included in the meta-analysis. Inconsistencies in the data and outliers were discussed between the trial investigators and discrepancies were resolved before analysis. All trials randomised patients using computer generated sequencing; treatment concealment was reported as adequate.

Data extraction
Trial investigators provided individual patient data (IPD) for central re-analysis, including data on outcomes, prognostic factors for unfavourable outcome and potential effect modifiers including antibiotic use prior to admission, HIV infection, and malnutrition status.
Missing data on HIV and malnutrition status were either assigned or left as missing according to local prevalence.

The authors did not state specifically how the summary data used in the sensitivity analysis of unavailable trials were obtained. It seemed likely that these were taken directly from the Cochrane review.

**Methods of synthesis**
A two stage IPD meta-analysis was used to calculate overall treatment effect across the five trials, and for a series of pre-specified patient subgroups. Odds ratios (OR) and confidence intervals (CIs) were calculated for individual trials (stratified by centre), and then pooled using a Mantel-Haenszel fixed-effect model. Heterogeneity statistics ($I^2$) and their associated p-values were reported for all subgroups. Logistic regressions were also used to explore the influence of age (adult, child) and HIV infection on the treatment effect.

Definitions of subgroups and outcomes were agreed by the project group prior to analysis.

**Results of the review**
A total of five trials including 2,029 patients were included in the analysis.

Pre-specified analyses showed that dexamethasone was not associated with a significant reduction in death (OR 0.97, 95% CI 0.79 to 1.19), death or severe neurological sequelae or bilateral severe deafness (OR 0.92, 95% CI 0.76 to 1.11), death or any neurological sequelae or any hearing loss (OR 0.89, 95% CI 0.74 to 1.07).

A post-hoc analysis found that dexamethasone reduced hearing loss among survivors (OR 0.77, 95% CI 0.60 to 0.99).

Dexamethasone had no significant interaction effects in any of the pre-specified subgroups including age, sex, pre-admission symptoms, malnutrition status, HIV status, prior treatment with antibiotics, heart rate, haemoglobin levels, consciousness level, cerebrospinal fluid white cell count, cerebrospinal fluid glucose, cerebrospinal fluid protein, microscopic presence or absence of pyogenic organisms, causative organisms, or whether bacterial meningitis was confirmed or probable.

Although a statistically significant benefit of dexamethasone was shown for the adults over 55 years old in analyses of death (OR 0.41, 95% CI 0.20 to 0.84), overall there was no indication of a treatment interaction or trend in the age subgroup analysis. Exploratory analyses, where age was analysed as a continuous variable, did not show any consistent interaction between age and treatment effect. It was difficult to ascertain to what extent the subgroup analysis was confounded by individual trials contributing only to certain categories. An analysis combining the results of the five trials that provided IPD plus the 18 unavailable studies included in the Cochrane review did not demonstrate an overall benefit of dexamethasone (OR 0.88, 95% CI 0.73 to 1.04).

There was no evidence of significant heterogeneity between trials, with an overall $I^2$ value of 4.9% (all but one of the trials included in the Cochrane review were small with very wide confidence intervals).

**Authors' conclusions**
There was no evidence that dexamethasone treatment for bacterial meningitis reduced mortality or neurological disability for any patients or subsets of patients.

**CRD commentary**
This review aimed to establish whether any particular types (subgroups) of patients with acute bacterial meningitis might benefit from dexamethasone and to explain previously noted differences in individual trial findings. An individual patient data approach (generally regarded as a ‘gold standard’ of systematic reviews) was used, bringing benefits of standardisation in definition of outcomes and subgroups, consistent analysis across trials and verification of data. The review was well conducted using appropriate methods.

The five most recent trials (out of 22 potentially eligible trials) were able to provide data and were included in the meta-analysis, accounting for around half the total numbers of patients included in all trials. Given the focus on exploring
possible differential effectiveness in different types of patients, and that a combined analysis of mortality data incorporating aggregate data from the unavailable trials gave broadly similar results, this was not a major concern. There was no clear evidence that the results of the IPD trials differed from the results of the aggregate data trials - the confidence intervals around the combined estimates for each set of trials overlap. However, given that the odds ratio estimates (0.96 for the IPD data and 0.69 for the aggregate data) are quite different, some caution around use of the specific estimates of effect may be prudent. Differences may be attributable to many factors, not least that the IPD permitted thorough data checking and consistent analyses and may ultimately be more reliable.

Pre-specified analyses found no evidence that any subgroups of patients benefited from dexamethasone and that its use was not associated with an increased risk of adverse events. Factors previously considered relevant to the decision to use dexamethasone could not explain differences between the five trials. The conclusion that patients with bacterial meningitis were neither benefited or were harmed by treatment with adjunctive dexamethasone followed from the data and analyses presented.

However, two of the five included trials were conducted in Malawi, one in South America, one in Vietnam and one in Europe. Two trials, one from Europe and one from Malawi, were restricted to adults. The other three trials randomised children. The overall results presented for mortality (figure 4) illustrated the large influence of the two Malawi trials in the analysis - together these contributed three quarters of observed deaths. These trials are also reported to have high mortality in the placebo groups (31% in the trial in children and 53% in the adult trial) compared with the Europe (15%), Vietnam (12%) and South American (16%) trials. Given that results from the small European trial of adult patients favoured the use of dexamethasone, there may be some clinical concern about whether the overall findings are generalisable to other settings with different healthcare systems.

**Implications of the review for practice and research**

**Practice**: The authors stated that there is little to support the routine use of dexamethasone for bacterial meningitis.

**Research**: The authors stated that a large multinational randomised controlled trial would be necessary to establish with certainty whether dexamethasone may have a place in the treatment of adult patients with bacterial meningitis.

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