Corticosteroids in acute bacterial meningitis

[Review]

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Date of Most Recent Update: 26-August-2004 Updated

Date of Most Recent Substantive Update: 31-January-2003

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Abstract

Background: Acute bacterial meningitis remains a disease with high mortality rate, ranging from 10 to 30 percent, despite advances in critical care. It has been estimated that between 5 to 40 percent of all patients can suffer hearing loss. The use of corticosteroids as adjuvant therapy in the treatment of acute bacterial meningitis is controversial despite several controlled clinical trials and three meta-analyses. In particular there are few data on the use of corticosteroids in adult meningitis.

Objectives: We conducted a systematic review examining the efficacy and safety of adjuvant corticosteroid therapy in children and adults with acute bacterial meningitis.

Search strategy: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library issue 1, 2003)); MEDLINE (1966 to April 2002); EMBASE (1974 to April 2002); and HEALTHLINE (1988 to April 2002) and Current Contents for trials published before the April 1st 2002, and reference lists of articles. We also contacted manufacturers and researchers in the field.

Selection criteria: Eligible studies were published or non-published randomised controlled trials on corticosteroids as adjuvant therapy in acute bacterial meningitis. Patients of any age and in any clinical condition, treated with antibacterial agents and randomised to corticosteroid therapy (or placebo) of any type, could be included. At least case fatality rate or hearing loss had to be recorded for inclusion.

Data collection and analysis: Two reviewers independently assessed trial quality and extracted data. Study authors were contacted for additional information. Adverse effects information was collected from the trials.

Main results: Eighteen studies involving 1853 people were included. Overall, adjuvant...
corticosteroids were associated with lower case fatality (relative risk (RR) 0.76, 95% confidence intervals (CI) 0.59 to 0.98) and lower rates of both severe hearing loss (RR 0.36, 95% CI 0.22 to 0.60) and long-term neurological sequelae (RR 0.66, 95% CI 0.44 to 0.99). In children, corticosteroids reduced severe hearing loss in bacterial meningitis caused by Haemophilus influenzae (RR 0.31, 95% CI 0.15 to 0.62), as well as in meningitis caused by other bacteria than H. influenzae (RR 0.42, 95% CI 0.20 to 0.89). In adults there was a reduction in case-fatality (RR 0.38, 95% CI 0.18 to 0.78), however there were few data. Adverse events were not increased significantly with the use of corticosteroids.

Conclusions: Adjuvant corticosteroids are beneficial in the treatment of children with acute bacterial meningitis. The limited data available in adults shows a trend in favour of adjuvant corticosteroids but a definite recommendation must await more studies.

ERRATUM
During the review process of this systematic review the results of the European Dexamethasone in Adulthood Bacterial Meningitis Trial were published. (De Gans 2002) In this prospective, randomised, double-blind, multicenter trial, which included 301 adults with bacterial meningitis, treatment with dexamethasone was associated with a reduction in mortality (relative risk of death, 0.48; 95 CI 0.24 to 0.96; p = 0.04). Therefore, dexamethasone should be given to all adults with bacterial meningitis and should be initiated before or with the first dose of antibiotics.

Issue protocol first published
1998 Issue 3

Date of last minor update
02 April, 2003

Date new studies found but not yet included or excluded
31 January, 2003

Issue next stage
Issue 3, 2005

Issue review first published
2003 Issue 3

Background

Acute bacterial meningitis remains a disease with high mortality rate, ranging from 10 to 30 percent, despite advances in critical care (Bohr 1983; Baraff 1993; Durand 1993). Late sequelae such as cranial nerve impairment, especially hearing loss, have been estimated to occur in 5 to 40 percent of all patients (Bohr 1983; Baraff 1993; Durand 1993; Van de Beek 2002). In experimental studies, outcome has been correlated with severity of the inflammatory process in the subarachnoidal space; treatment with corticosteroids has resulted in a reduction of the inflammatory response in the cerebrospinal fluid (CSF) (Scheld 1980; Tauber 1985). These pathophysiological insights prompted investigators to evaluate corticosteroids as adjuvant
therapy in children with acute bacterial meningitis. However, the results of individual studies did not point unequivocally to a beneficial effect. Two meta-analyses, including randomised controlled trials performed in children, showed a beneficial effect of adjuvant dexamethasone on severe hearing loss in *Haemophilus influenzae* type b (Hib) meningitis (Havens 1989; Geiman 1992). As a consequence dexamethasone is recommended for routine use in childhood Hib meningitis (Anonymous 1990). However, childhood Hib meningitis has nearly been eliminated in the Western world following routine vaccination with conjugate Hib vaccines (Schuchat 1997). In 1997, a third meta-analysis showed dexamethasone to be protective for severe hearing loss in children with pneumococcal meningitis in the subgroup of children who received corticosteroids before or with the first dose of antibiotics; no beneficial effect was found for patients with meningococcal meningitis (McIntyre 1997). This third meta-analysis did not include trials published before 1988 and did not evaluate the effect of dexamethasone on mortality. As benefit from corticosteroids was not shown for all categories of children with meningitis, several experts in the field are advising against routine use of dexamethasone in childhood bacterial meningitis (Quagliarello 1997; Coyle 1999; Saez-Llorens 1999; Moller 2000). In adults, data on adjuvant corticosteroids in the treatment of bacterial meningitis are scarce. The only study with significant numbers of adult patients (147 over 13 years old), found that corticosteroids were associated with a significant reduction in mortality rate (Girgis 1989). However, results of this Egyptian study must be interpreted with caution as methodological flaws may have diminished the reliability of its results (Prober 1995). None of the three previous meta-analyses has included all available studies, none has included adult patients and none has evaluated mortality. We therefore conducted a meta-analysis of randomized controlled trials of adjuvant corticosteroids in the treatment of children and adults with acute bacterial meningitis.

**Objectives**

To determine the effect of adjuvant corticosteroids on mortality, severe hearing loss and neurological sequelae, in the treatment of children and adults with acute bacterial meningitis.

**Criteria for considering studies for this review**

**Types of participants**

Participants of any age and in any clinical condition.

**Types of intervention**

Participants treated with antibacterial agents and randomised to corticosteroid therapy (or placebo) of any type.

**Types of outcome measures**

At least rates of case fatality rate or hearing loss had to be recorded for inclusion of studies.

**Types of studies**

Eligible studies were published or non-published randomised controlled trials on corticosteroids as adjuvant therapy in acute bacterial meningitis.

**Search strategy for identification of studies**

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library issue 1, 2003); MEDLINE (1966 to January 2003); EMBASE (1974 to April 2002);

The Cochrane Collaboration strategy for identifying randomised controlled trials (see the Cochrane Handbook, Appendix 5c) was used in combination with the following specific terms:

#1 'meningitis' AND 'adrenal cortex hormones'
#2 'mening$.tw' AND 'steroid$.tw'
#3 'mening$.tw' AND 'dexameth$.tw'
#4 'mening$.tw' AND 'adrenal cortex hormones'
#5 'meningitis' AND 'steroid$.tw'
#6 'meningitis' AND 'dexameth$.tw'.
#7 OR/1-6

We performed the search without language limitations. In addition, we identified relevant trials by: a search of references listed in published studies, handsearching abstracts of congresses, personal communication with researchers and experts in the field, and from literature lists of pharmaceutical companies (MSD, Organon, and Glaxo-Wellcome). Two investigators (DvdB, JdG) did the assessment for inclusion in the methodological appraisal.

**Methods of the review**

**Methodological appraisal**

We performed the appraisal of studies using the Jadad-scale (Jadad 1996). This is a validated 5-point scale evaluating randomisation (0-2 points), double blinding (0-2 points), and withdrawals and dropouts (0-1 point). Two experienced researchers, not working in the field of infectious diseases, performed the appraisal in a blinded way. We resolved disagreements by consensus (kappa's for the items ranged from 0.6 to 0.8). All trials with 1 or 2 points for randomisation in the Jadad-score were included in the analysis.

**Extraction of data**

Two researchers (DvdB, JdG) independently extracted the data, using a predetermined protocol. We included all patients who were randomised or who started therapy in the intention-to-treat analysis. We included all patients who complied with the study protocol in the per-protocol analysis. Data were cross checked and differences were resolved by discussion. If data were not available, we sent a data extraction form to the principal investigator of the study. Double data entry was used to prevent data entry errors.

**Efficacy**

Primary outcome measures were mortality, severe hearing loss and neurological sequelae. Hearing loss was defined as severe when there was bilateral hearing loss greater than 60 dB or requiring bilateral hearing aids. Neurological sequelae were defined as focal neurological deficits other than hearing loss, epilepsy (not present before meningitis onset), severe ataxia and severe memory or concentration disturbance. Children whose only non hearing deficit(s) were speech or language disturbances were not counted as having non hearing deficits if these problems were associated with severe hearing loss. We analysed both short- and long-term neurological sequelae, other than hearing loss. Short-term neurological sequelae were defined as sequelae assessed between discharge and six weeks after hospital discharge. Long-term neurological sequelae were defined as sequelae assessed between 6 and 12 months after discharge. Whenever possible, we extracted data for both these outcomes.

We performed subgroup analyses regarding age, causative organism and time of administration of steroids. Two age groups were defined: patients younger than 16 years and those of 16 years and older. Four categories of causative organisms were defined: *H. influenzae, Neisseria meningitidis, Streptococcus pneumoniae* and other pathogens (including patients with negative CSF culture).

**Safety**
Adverse events were defined as clinically evident gastrointestinal tract bleeding, reactive arthritis, pericarditis, herpes zoster or herpes simplex virus infection, fungal infection, secondary fever (defined as a temperature of 38 [degrees]C or higher occurring after at least one afebrile day during the course of hospitalisation) and persistent fever (defined as fever that continued longer than 5 consecutive days after initiation of appropriate antibiotic therapy). The total number of adverse events in each treatment group was calculated. The frequency of clinically evident gastrointestinal tract bleeding was evaluated separately.

**Statistical analysis**
Statistical analysis was performed using RevMan 4.01 of the Cochrane Collaboration. Chi squared tests were used to test for heterogeneity on the basis of DerSimonian and Laird Q statistics; p values for heterogeneity among studies ranged from 0.6 to 1, so a fixed effect model was chosen (Mantel-Haenszel visu-ratio method). The effect of steroids was expressed as relative risks (RR), where a value below 1.0 indicates a beneficial effect of steroids. Statistical uncertainty was expressed with 95 per cent confidence intervals (CI).

**Description of the studies**

### Selection of Studies
We identified 28 potential eligible trials, of which two were described in one paper (Jadad 1996). Eight trials which did not obtain the necessary points for randomisation on the Jadad-score were excluded. (see Table 01) (Lepper 1959; Jensen 1969; Passos 1979; Baldy 1986; Marguet 1993; Shembesh 1997; Daoud 1999; Gijwani 2002). Subsequently, one study which compared two dexamethasone regimens, (Syrogiannopoulos1994) and one study with insufficient data, (Farina 1995) were excluded, leaving 18 eligible trials.

### Characteristics of Studies
Subjects over the age of 16 years were included in four studies (Bennett 1963; Girgis 1989; Bhaumik 1998; Thomas 1999). In one of these studies, data could not be derived separately for this age group (Bennett 1963). In two other studies, patients older than 12 years were considered adults (Girgis 1989; Bhaumik 1998). The study intervention consisted of dexamethasone in 15 of 18 studies; dosages ranged from 0.4 to 0.9 mg/kg and duration from two to four days. In the other studies hydrocortisone, prednisolone or a combination of both was given (Bennett 1963; DeLemos 1969; Bademosi 1979). Study-medication was administered with or before the first dose of antibiotic in seven studies (Bademosi 1979; Girgis 1989; Odio 1991; Schaad 1993; Kanra 1995; Kilpi 1995; Qazi 1996) and in seven studies after the first doses. In four studies, the time of administration was not stated. Various antibiotic regimens were used; third generation cephalosporins were most frequently prescribed (Table 02). A sample size calculation was given in two studies (Qazi 1996; Thomas 1999). An intention-to-treat analysis was available from only one study (Bennett 1963); in the other studies only per-protocol data were available to be ascertained. Therefore, the final analysis is based upon per-protocol figures, including 1853 of 2064 (89 percent) randomised patients. Mortality rates ranged between 0 and 45 percent (Table 02). In one study, patients who died during the first 18 hours of admission were excluded (Belsey 1969); nevertheless these results were included in the analysis. Hearing was adequately assessed (by audiometry and/or brainstem auditory evoked potentials) in 1013 children. Definitions of adverse events were heterogeneous and the numbers of events were recalculated for each study.

**Methodological qualities of included studies**

The quality of included studies was high, with a median Jadad-score of 4 (Table 02).

**Results**

### Mortality
The overall number of participants who died was significantly smaller in the corticosteroid group than in the placebo group (79 of 925 [8.5 per cent] versus 108 of 928 [11.6 per cent], RR 0.76, 95% CI 0.59 to 0.97). (Bennett 1963; Belsey 1969; DeLemos 1969; Bademosi 1979; Lebel 1988; Lebel 1988 b; Lebel 1989; Girgis 1989; Odio 1991; Schaad 1993; King 1994; Ciana 1995; Kanra 1995; Kilpi 1995; Wald 1995; Qazi 1996; Bhaumik 1998; Thomas 1999). Forty-eight of the 732 (6.6 per cent)
children in the placebo group died, as compared with 46 of the 742 (6.2 per cent) who received corticosteroids (RR 0.95, 95% CI 0.65 to 1.37) (Belsey 1969; DeLemos 1969; Lebel 1988 a; Lebel 1988 b; Girgis 1989; Lebel 1989; Odio 1991; Schaad 1993; King 1994; Ciana 1995; Kanra 1995; Kilpi 1995; Wald 1995; Qazi 1996) For adult participants, corticosteroids gave significant protection against death: 26 of the 146 (17.8 per cent) adults in the placebo group died, as compared with 9 of the 113 (8.0 per cent) who received corticosteroids (RR 0.38, 95% CI 0.18 to 0.78). (Girgis 1989; Bhaumik 1998; Thomas 1999) So 10 adult participants with bacterial meningitis would need to be treated with steroids to save one additional life. Age was not defined for 120 participants (Bennett 1963; Girgis 1989) Case-fatality rates varied by organism. Of the 535 participants with meningitis due to \textit{H. influenzae}, 22 died (4.1 per cent), compared with 17 of 372 participants with meningococcal meningitis (4.6 per cent) and 64 of 326 participants with pneumococcal meningitis (19.6 per cent). Corticosteroids protected against death in pneumococcal meningitis, as well as in meningitis caused by species other than \textit{H. influenzae} (including participants with negative CSF culture). The relative risk reductions were 39 per cent (RR 0.61, 95% CI 0.39 to 0.94) and 43 per cent (RR 0.57, 95% CI 0.37 to 0.87), respectively. Although not significant, corticosteroids were also associated with a reduction in mortality in meningococcal meningitis (RR 0.75, 95% CI 0.34 to 1.64). Administration of corticosteroids before or with the first dose of antibiotics was associated with a greater relative reduction in case-fatality (RR 0.73, 95% CI 0.51 to 1.03) than administration after the first dose of antibiotics (RR 0.85, 95% CI 0.55 to 1.31).

\textbf{Prevention of Severe Hearing Loss} 

The number of participants with severe hearing loss was significantly smaller in the corticosteroid group than in the placebo group (79 of 703 [2.7 per cent] versus 52 of 674 [7.7 per cent], RR 0.37, 95% CI 0.22 to 0.62). Forty-nine of the 499 (9.8 per cent) children in the placebo group had severe hearing loss, as compared with 15 of the 514 (2.9 per cent) who received corticosteroids (RR 0.31, 95% CI 0.18 to 0.54) (Belsey 1969; Lebel 1988 a; Girgis 1989; Lebel 1989; Odio 1991; Schaad 1993; King 1994; Kanra 1995; Kilpi 1995; Wald 1995; Qazi 1996). Adjuvant corticosteroid treatment of 20 children would prevent one case of severe hearing loss. In meningitis due to \textit{H. influenzae}, hearing loss was significantly reduced by steroids (RR 0.31, 95% CI 0.15 to 0.62). More important, the number of children with severe hearing loss caused by pathogens other than \textit{H. influenzae} was also significantly smaller in the corticosteroid group than in the placebo group (6 of 191 [3.1 per cent] versus 19 of 203 [8.3 per cent], RR 0.42, 95% CI 0.20 to 0.89).

\textbf{Prevention of Neurological Sequelae} 

The number of participants with long-term neurological sequelae was significantly less in the corticosteroid group than in the placebo group (36 of 596 [6.0 per cent] versus 51 of 567 [9.0 per cent], RR 0.67, 95% CI 0.45 to 1.00) (Lebel 1988 a; Girgis 1989; Lebel 1989; Odio 1991; Schaad 1993; King 1994; Kilpi 1995; Wald 1995; Qazi 1996). Sub analysis of children and adults gave similar point estimates for risk reduction of long-term sequelae by corticosteroids, which did not reach statistical significance. Short-term neurological sequelae were assessed in seven studies including 425 participants. (Lebel 1988 a; Lebel 1988 b; Lebel 1989; Ciana 1995; Kanra 1995; Kilpi 1995; Bhaumik 1998; Thomas 1999) Although corticosteroids seemed to have a beneficial effect on short-term sequelae, this failed to achieve statistical significance (RR 0.72, 95% CI 0.48 to 1.06). There were too few participants with specified neurological sequelae and a known causative organism to assess pathogen-specific effects.

\textbf{Safety} 

Adverse events were equally divided between the treatment and placebo group (RR 1.06, 95% CI 0.88 to 1.27). (Bennett 1963; Belsey 1969; Lebel 1988 a; Lebel 1988 b; Lebel 1989; Odio 1991; Schaad 1993; King 1994; Kanra 1995; Kilpi 1995; Wald 1995; Qazi 1996; Bhaumik 1998; Thomas 1999) The relative risk for gastrointestinal tract bleeding was increased, but did not reach statistical significance (RR 1.16 for patients treated with steroids).

\textbf{Discussion} 

This meta-analysis showed that in childhood bacterial meningitis caused by pathogens
other than *H. influenzae*, the use of adjuvant corticosteroids reduces the risk of severe hearing loss by 58 percent. Adjuvant corticosteroid treatment of 20 children would prevent one case of severe hearing loss. The clearest effect was seen on severe hearing loss, but a consistent trend in the direction of benefit from corticosteroids in reducing mortality and neurological sequelae was found, in the absence of significant adverse effects. On basis of this analysis of clinical trials, corticosteroid treatment in all children with suspected bacterial meningitis appears justified. For adults, a survival benefit was evident with a relative risk reduction of 62 percent, suggesting one additional life will be saved for every 10 adults treated with adjuvant corticosteroids. However, the results must be interpreted cautiously because the Egyptian study (which included both adolescents and adults) accounted for 62 percent of all adult participants (Girgis 1989). In the Egyptian study, which was not placebo-controlled and not double-blinded, only three pathogens were cultured from the cerebral spinal fluid (CSF) of enrolled participants, suggesting a possible selection bias. Although the results suggest a beneficial effect, this needs to be confirmed by others. The European trial "Dexamethasone in Adulthood Bacterial Meningitis Trial" (De Gans 2002), which has included 300 participants, will soon provide further evidence on the effects of corticosteroids in adulthood bacterial meningitis.

The definitions of neurological sequelae used in the studies included in this analysis were heterogeneous. Therefore the effect of corticosteroids on neurological sequelae, except hearing loss, must be interpreted with caution. Death and severe hearing loss are well-defined measures and therefore are the important outcomes in this meta-analysis.

Two possible biases may have diminished the reliability of our results. The first confounding factor is selection bias. Several included studies on childhood bacterial meningitis had low mortality rates; nine studies had mortality rates of three per cent or less. Mortality rates of childhood bacterial meningitis in previously reported studies ranged from 8 to 20 per cent (Bohr 1983; Baraff 1993; Durand 1993). Inclusion of patients in the meta-analysis with less severe illness, as reflected in low case fatality rates, will probably underestimate the protective effect of corticosteroids (Glasziou 1995). Few included studies had high mortality rates but in two studies mortality rates were over 40 per cent. For patients admitted in a late stage of disease, adjuvant corticosteroids are less protective and might even be harmful (Prasad 1995). Inclusion of such patients will lead to an underestimate of the treatment effect. Recently, a large controlled trial showed no beneficial effect of adjunctive steroids (Molyneux 2002). However, this Malawian study included mainly children in whom treatment began late, HIV-positive children, and children receiving inappropriate antibiotic therapy. The results of this trial are not representative for the typical meningitis population in industrialised countries.

A second bias is introduced when participants are withdrawn (Prasad 1995; Qazi 1996). The analysis was based upon per-protocol figures, as intention-to-treat figures were available for only one study. In total, 211 participants were withdrawn after the randomisation process, often for unknown reasons. Reasons for withdrawal can be ineligibility according to trial criteria or inability to complete the treatment-protocol (Prasad 1995). Withdrawals on the grounds on ineligibility may have been influenced by knowledge of outcome; if so, this would advantage the corticosteroid regimen. Excluding participants because of inability to complete the course of corticosteroids due to side effects, (e.g. upper gastrointestinal bleeding) clearly introduces bias in favour of the study medication, whereas withdrawals due to loss to follow-up might be in favour of the placebo group.

We included only randomised controlled trials as assessed by the previous validated Jadad-scale (Jadad 1996), and excluded studies that used quasi-randomisation, such as alternate allocation. The quality of included studies was high, reflected in a high median Jadad-score. Although quality assessment and methods of its incorporation into systemic reviews remain
controversial, its importance is clearly accepted (Moher 1998). As the included studies were heterogeneous with respect to study protocol and study population effect-sizes were calculated as relative risks. The results showed sufficient statistical homogeneity in a fixed effect-analysis.

The use of steroids was associated with only few side effects. However, definitions of adverse events used in the studies were heterogeneous and most studies had no specified criteria in advance, so under ascertainment is possible. The relative risk for gastro-intestinal bleeding did not reach statistical significance.

Concern have been raised over the interference by corticosteroids on CSF eradication of meningeal pathogens by reducing the blood brain barrier (BBB) permeability and thereby the penetration of antibiotics in the subarachnoid space. Although in children with bacterial meningitis, treatment of dexamethasone did not reduce vancomycin levels in the CSF (Klugman 1995), therapeutic failures have been described in adults treated with standard doses of vancomycin and adjunctive dexamethasone (Viladrich 1991). Therefore, patients with pneumococcal meningitis who are treated with vancomycin and dexamethasone should be carefully observed throughout therapy.

In adults who survive bacterial meningitis, cognitive impairment occurs frequently (Van de Beek 2002). As corticosteroids may potentiate ischaemic injury to neurons (Sapolsky 1985), it is important to know whether corticosteroids have beneficial effects on hearing loss and mortality but worsen cerebral cortical functioning. Further studies are needed to evaluate long-term cognitive functioning of patients treated with and without adjuvant corticosteroids.

The available studies do not address two important issues - the minimum duration of corticosteroid therapy or the maximum length of time after parenteral antibiotic therapy for commencement of steroid therapy. In most studies, a four-day regimen dexamethasone (0.4 or 0.6 mg/kg/day) divided in four daily doses was used. Although one study showed a two-day and four-day regimen of dexamethasone to be similarly effective (Syrogiannopoulos1994), the results of this meta-analysis are only applicable to a four-day regimen. In agreement with previous reports (King 1994; McIntyre 1997) administration of steroids before or with the first dose of parenteral antibiotics seemed more effective than administration after the first dose of antibiotics. However, many trials included participants where steroids were commenced (at a variable time) after parenteral antibiotics (McIntyre 1997), so it is possible that benefit may still accrue although the maximum delay after parenteral antibiotics is not clear. In settings where late presentation, especially after antibiotic therapy, is common any benefit may be reduced or absent (Qazi 1996).

In the United Kingdom (UK), general practitioners are often advised to give (parenteral) antibiotics before transferring the patient to the hospital if meningitis is suspected (Heyderman 2003). Although in the UK retrospective data showed a favourable outcome in patients who were treated early with parenteral antibiotics (Cartwright 1992), pre-hospital antibiotic treatment remains controversial. A Danish study found a considerable higher mortality rate in pre-hospital treated patients with suspected meningococcal meningitis (Sorensen 1992). A meta-analysis of all available studies showed no beneficial effect of pre-hospital antibiotic treatment (OR 0.82, 95%CI 0.43 to 1.56) (Sorensen 1998), however, prospective data are lacking. If general practitioners decide to treat a patients with suspected bacterial meningitis with antibiotic agents, dexamethasone should also be given before or with the first dose of antibiotics.

The role of steroids for patients who present with both evidence of bacterial meningitis and septic shock remains unclear. Lower doses of steroids have shown to be beneficial in septic shock, (Annane 2002) while higher doses have shown to be either of no benefit or have even a trend towards increased mortality (Cronin 1995; Lefering 1995).
Conclusions

Implications for practice

In summary, even though several methodological and design flaws of included studies diminish the reliability of results, the consistency and degree of benefit identified in this analysis merits the use of corticosteroids in childhood bacterial meningitis in industrialised countries with good access to services. We recommend a four-day regimen of dexamethasone (0.6 mg/kg daily), preferably given before or with the first dose of antibiotics. Although, the pathophysiology of meningeal inflammation is the same in all age groups, the paucity of data in adults with meningitis precludes a definitive recommendation in this age group. (see ERRATUM)

Implications for research

(1) It is hopeful that the large European trial of adjuvant dexamethasone in adult bacterial meningitis will soon yield clearer conclusions.

ERRATUM
During the review process of this systematic review the results of the European Dexamethasone in Adulthood Bacterial Meningitis Trial were published. (De Gans 2002) In this prospective, randomised, double-blind, multicenter trial, which included 301 adults with bacterial meningitis, treatment with dexamethasone was associated with a reduction in mortality (relative risk of death 0.48; 95% CI 0.24 to 0.96; p = 0.04). Therefore, dexamethasone should be given to all adults with bacterial meningitis and should be initiated before or with the first dose of antibiotics.

(2) Further studies are needed to evaluate long-term cognitive functioning of patients treated with and without adjuvant corticosteroids.

(3) Case series are needed to determine whether adjunctive dexamethasone therapy may be harmful in patients with pneumococcal meningitis caused by highly penicillin- or cephalosporin-resistant strains.

Internal sources of support to the review

* Dept. of Neurology, Academic Medical Center, University of Amsterdam NETHERLANDS

External sources of support to the review

* Potential conflict of interest

None known

Acknowledgements

We thank J Stam and I van Schaik for their methodological appraisal of included studies, and CJJM Schouten for her support in the data-management.

Contribution of Reviewer(s)

Design of study (DvdB, JdG)

Protocol (DvdB, JdG, PM, KP)
Synopsis

The corticosteroid dexamethasone can reduce hearing loss and death after meningitis for both children and adults.

Bacterial meningitis is an infection of the membrane lining the brain that often causes hearing loss and is frequently fatal. It is usually caused by bacteria spreading from an ear or throat infection. Meningitis is most common in adolescents and children. Corticosteroids are drugs that can reduce inflammation caused by infection. Research on the use of corticosteroids for meningitis has had conflicting results, so they are often not used. However, the review of trials found that the corticosteroid dexamethasone leads to a major reduction in death in hearing loss and death in both children and adults, without major adverse effects.

ERRATUM

During the review process of this systematic review the results of the European Dexamethasone in Adulthood Bacterial Meningitis Trial were published. (De Gans 2002) In this prospective, randomised, double-blind, multicenter trial, which included 301 adults with bacterial meningitis, treatment with dexamethasone was associated with a reduction in mortality (relative risk of death, 0.48; 95% confidence interval 0.24 to 0.96; p = 0.04). Therefore, dexamethasone should be given to all adults with bacterial meningitis and should be initiated before or with the first dose of antibiotics.

Table of comparisons

Fig 01 all patients
mortality

severe hearing loss
short-term neurological sequelae

long-term neurological sequelae
adverse events

Table of comparisons

Fig 02 children

mortality
severe hearing loss

Table of comparisons

Fig 03 different causative species
### Table of comparisons

#### Fig 04 adults

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<td><strong>Test for heterogeneity chi-square=1.61 df=3 p=0.752</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect=0.16 p=0.9</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><em>Neisseria meningitidis</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cima 1995</td>
</tr>
<tr>
<td>Delmos 1989</td>
</tr>
<tr>
<td>Girgis 1990</td>
</tr>
<tr>
<td>Lebl 1988 a</td>
</tr>
<tr>
<td>Lebl 1988 b</td>
</tr>
<tr>
<td>Schaad 1990</td>
</tr>
<tr>
<td>Thomas 1999</td>
</tr>
<tr>
<td>Wadd 1995</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
</tr>
<tr>
<td><strong>Test for heterogeneity chi-square=0.00 df=0</strong></td>
</tr>
<tr>
<td><strong>Test for overall effect=0.07 p=0.5</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><em>Streptococcus pneumoniae</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bademos 1979</td>
</tr>
<tr>
<td>Delmos 1980</td>
</tr>
<tr>
<td>Girgis 1990</td>
</tr>
<tr>
<td>Kama 1995</td>
</tr>
<tr>
<td>Klpi 1995</td>
</tr>
<tr>
<td>Lebl 1988 a</td>
</tr>
<tr>
<td>Lebl 1988 b</td>
</tr>
<tr>
<td>Odde 1991</td>
</tr>
<tr>
<td>Schaad 1990</td>
</tr>
<tr>
<td>Wadd 1995</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
</tr>
<tr>
<td><strong>Test for heterogeneity chi-square=0.04 df=2 p=0.999</strong></td>
</tr>
<tr>
<td><strong>Test for overall effect=0.77 p=0.0002</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><em>all other species than H. influenzae</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bademos 1979</td>
</tr>
<tr>
<td>Delmos 1980</td>
</tr>
<tr>
<td>Girgis 1990</td>
</tr>
<tr>
<td>Klpi 1995</td>
</tr>
<tr>
<td>Lebl 1988 a</td>
</tr>
<tr>
<td>Lebl 1988 b</td>
</tr>
<tr>
<td>Odde 1991</td>
</tr>
<tr>
<td>Schaad 1990</td>
</tr>
<tr>
<td>Wadd 1995</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
</tr>
<tr>
<td><strong>Test for heterogeneity chi-square=2.48 df=2 p=0.2246</strong></td>
</tr>
<tr>
<td><strong>Test for overall effect=2.79 p=0.005</strong></td>
</tr>
</tbody>
</table>

---

**Table of comparisons**

Fig 04 adults
Characteristics of included studies

Study: Bademosi 1979

Methods: see add. table 2

Participants:

Interventions:

Outcomes:

Notes:

Allocation concealment: D

Study: Belsey 1969

Methods:

Participants:

Interventions:

Outcomes:

Notes:

Allocation concealment: D

Study: Bennett 1963

Methods:

Participants:

Interventions:

Outcomes:
Notes:

Allocation concealment: D

Study: Bhaumik 1998

Methods:

Participants:

Interventions:

Outcomes:

Notes:

Allocation concealment: D

Study: Ciana 1995

Methods:

Participants:

Interventions:

Outcomes:

Notes:

Allocation concealment: D

Study: DeLemos 1969

Methods:

Participants:

Interventions:

Outcomes:

Notes:

Allocation concealment: D

Study: Girgis 1989

Methods:

Participants:

Interventions:
Outcomes:

Notes:

Allocation concealment: D

Study: Kanra 1995

Methods:

Participants:

Interventions:

Outcomes:

Notes:

Allocation concealment: D

Study: Kilpi 1995

Methods:

Participants:

Interventions:

Outcomes:

Notes:

Allocation concealment: D

Study: King 1994

Methods:

Participants:

Interventions:

Outcomes:

Notes:

Allocation concealment: D

Study: Lebel 1988 a

Methods:

Participants:
Interventions:

Outcomes:

Notes:

Allocation concealment: D

Study: Lebel 1988 b

Methods:

Participants:

Interventions:

Outcomes:

Notes:

Allocation concealment: D

Study: Lebel 1989

Methods:

Participants:

Interventions:

Outcomes:

Notes:

Allocation concealment: D

Study: Odio 1991

Methods:

Participants:

Interventions:

Outcomes:

Notes:

Allocation concealment: D

Study: Qazi 1996

Methods:
Participants:
Interventions:
Outcomes:
Notes:
Allocation concealment: D

Study: Schaad 1993

Methods:
Participants:
Interventions:
Outcomes:
Notes:
Allocation concealment: D

Study: Thomas 1999

Methods:
Participants:
Interventions:
Outcomes:
Notes:
Allocation concealment: D

Study: Wald 1995

Methods:
Participants:
Interventions:
Outcomes:
Notes:
Allocation concealment: D

Characteristics of excluded studies

http://gateway.ut.ovid.com/gw2/ovidweb.cgi
Study: Baldy 1986

Reason for exclusion: see additional table 1

Study: Daoud 1999

Reason for exclusion:

Study: Farina 1995

Reason for exclusion:

Study: Gijwani 2002

Reason for exclusion:

Study: Gupta 1996

Reason for exclusion:

Study: Jensen 1969

Reason for exclusion:

Study: Lepper 1959

Reason for exclusion:

Study: Marguet 1993

Reason for exclusion:

Study: Passos 1979

Reason for exclusion:

Study: Shembesh 1997

Reason for exclusion:

Study: Syrogiannopoulos1994

Reason for exclusion:

Table 01 Quality assessment and characteristics of excluded studies

<table>
<thead>
<tr>
<th>year (author)</th>
<th>1. randomisation (0-:</th>
<th>2. blinding (0-2):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1959 (Lepper)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
3. withdrawals (0-1): 0
   total Jadad (0-5): 0
   age pts: all ages
   antibiotics (AB): pen or pen/strep
   DXM before/with AB: NS
   death %: 13
   year (author): 1969 (Jensen)

1. randomisation (0-): 0
2. blinding (0-2): 0
3. withdrawals (0-1): 0
   total Jadad (0-5): 0
   age pts: all ages
   antibiotics (AB): sulf/pen
   DXM before/with AB: NS
   death %: 19
   year (author): 1979 (Passos)

1. randomisation (0-): 0
2. blinding (0-2): 0
3. withdrawals (0-1): 0
   total Jadad (0-5): 0
   age pts: all ages
   antibiotics (AB): pen
   DXM before/with AB: NS
   death %: 0
   year (author): 1986 (Baldy)
3. withdrawals (0-1): 0

total Jadad (0-5): 0

age pts: all ages

antibiotics (AB): amp or pen

DXM before/with AB: NS

death %: 0

year (author): 1993 (Marguet)

1. randomisation (0-): 0

2. blinding (0-2): 0

3. withdrawals (0-1): 0

total Jadad (0-5): 0

age pts: 1 mo-14 yrs

antibiotics (AB): ceph

DXM before/with AB: No

death %: 5

year (author): 1994 (Syrogian)

1. randomisation (0-): 2

2. blinding (0-2): 0

3. withdrawals (0-1): 0

total Jadad (0-5): 2

age pts: 2 mo-15 yrs

antibiotics (AB): various

DXM before/with AB: No

death %: 0

year (author): 1995 (Farina)

1. randomisation (0-): 1

2. blinding (0-2): 1
3. withdrawals (0-1): 0

total Jadad (0-5): 2

age pts: NG

antibiotics (AB): NG

DXM before/with AB: No

dead %: NG

year (author): 1996 (Gupta)

1. randomisation (0-): 0

2. blinding (0-2): 0

3. withdrawals (0-1): 0

total Jadad (0-5): 0

age pts: 12-70 yrs

antibiotics (AB): pen/chlor/gent

DXM before/with AB: NS

dead %: 23

year (author): 1997 (Shembesh)

1. randomisation (0-): 0

2. blinding (0-2): 0

3. withdrawals (0-1): 0

total Jadad (0-5): 0

age pts: all ages

antibiotics (AB): ceph

DXM before/with AB: NS

dead %: 13

year (author): 1999 (Daoud)

1. randomisation (0-): 0

2. blinding (0-2): 0
3. withdrawals (0-1): 0

total Jadad (0-5): 0

age pts: neonates

antibiotics (AB): amp+ceph

DXM before/with AB: Yes

deaht %: 25

year (author): 2002 (Gijwani)

1. randomisation (0-): 0

2. blinding (0-2): 0

3. withdrawals (0-1): 0

total Jadad (0-5): 0

age pts: adults

antibiotics (AB): ceph

DXM before/with AB: Yes

deaht %: 15

year (author):

1. randomisation (0-):

2. blinding (0-2):

3. withdrawals (0-1):

total Jadad (0-5):

age pts:

antibiotics (AB):

DXM before/with AB:

deaht %:

year (author):

1. randomisation (0-):

2. blinding (0-2):
<table>
<thead>
<tr>
<th>Year (Author)</th>
<th>Randomisation</th>
<th>Blinding</th>
<th>Withdrawals</th>
<th>Total Jadad</th>
<th>Age</th>
<th>Antibiotics</th>
<th>DXM before/with AB</th>
<th>Death %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963 (Bennet)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>all ages</td>
<td>NS</td>
<td>No</td>
<td>45</td>
</tr>
<tr>
<td>1969 (deLemos)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. randomisation (0-): 1
2. blinding (0-2): 1
3. withdrawals (0-1): 0

**Total Jadad (0-5):** 2

**Age pts:** 1 mo-17 yrs

**Antibiotics (AB):** chlor/sulf/pen

**DXM before/with AB:** No

**Deaths %:** 3

**Year (Author):** 1969 (Belsey)

1. randomisation (0-): 1
2. blinding (0-2): 1
3. withdrawals (0-1): 0

**Total Jadad (0-5):** 2

**Age pts:** 0-17 yrs

**Antibiotics (AB):** chlor/sulf/pen

**DXM before/with AB:** NS

**Deaths %:** 3

**Year (Author):** 1979 (Bademosi)

1. randomisation (0-): 1
2. blinding (0-2): 0
3. withdrawals (0-1): 0

**Total Jadad (0-5):** 1

**Age pts:** 10-59 yrs

**Antibiotics (AB):** sulf/pen

**DXM before/with AB:** Yes

**Deaths %:** 44

**Year (Author):** 1988 (Lebel)
1. randomisation (0-): 2
2. blinding (0-2): 2
3. withdrawals (0-1): 1
total Jadad (0-5): 5
age pts: 2 mo-16 yrs
antibiotics (AB): ceph
DXM before/with AB: No
deaths %: 2
year (author): 1991 (Odio)

1. randomisation (0-): 2
2. blinding (0-2): 2
3. withdrawals (0-1): 0
total Jadad (0-5): 4
age pts: 6w-16 yrs
antibiotics (AB): ceph
DXM before/with AB: Yes
deaths %: 2
year (author): 1993 (Schaad)

1. randomisation (0-): 2
2. blinding (0-2): 2
3. withdrawals (0-1): 1
total Jadad (0-5): 5
age pts: 3 mo-16 yrs
antibiotics (AB): ceph
DXM before/with AB: Yes
deaths %: 0
year (author): 1994 (King)
1. randomisation (0-): 1
2. blinding (0-2): 2
3. withdrawals (0-1): 0

total Jadad (0-5): 3

age pts: 1 mo-13 yrs

antibiotics (AB): various

DXM before/with AB: No

deaths %: 1

year (author): 1995 (Kilpi)

1. randomisation (0-): 2
2. blinding (0-2): 0
3. withdrawals (0-1): 0

total Jadad (0-5): 2

age pts: 3 mo-15 yrs

antibiotics (AB): ceph

DXM before/with AB: Yes

deaths %: 2

year (author): 1995 (Ciana)

1. randomisation (0-): 1
2. blinding (0-2): 0
3. withdrawals (0-1): 1

total Jadad (0-5): 2

age pts: 2 mo-6 yrs

antibiotics (AB): ampi/chlor

DXM before/with AB: NG

deaths %: 28

year (author): 1995 (Wald)
1. randomisation (0-2): 2
2. blinding (0-2): 2
3. withdrawals (0-1): 1

total Jadad (0-5): 5

age pts: 2 mo-12 yrs

antibiotics (AB): ceph

DXM before/with AB: No

deaths %: 1

year (author): 1995 (Kanra)

1. randomisation (0-2): 2
2. blinding (0-2): 2
3. withdrawals (0-1): 1

total Jadad (0-5): 5

age pts: 2-6 yrs

antibiotics (AB): sulf/amp

DXM before/with AB: Yes

deaths %: 5

year (author): 1996 (Qazi)

1. randomisation (0-2): 2
2. blinding (0-2): 2
3. withdrawals (0-1): 1

total Jadad (0-5): 5

age pts: 2 mo-12 yrs

antibiotics (AB): ampi/chlor

DXM before/with AB: Yes

deaths %: 19

year (author): 1998 (Baumik)
1. randomisation (0-): 1
2. blinding (0-2): 0
3. withdrawals (0-1): 0
total Jadad (0-5): 1
age pts: 12-75 yrs
antibiotics (AB): pen/chlor or ceph
DXM before/with AB: No
deaths %: 13
year (author): 1999 (Thomas)
1. randomisation (0-): 1
2. blinding (0-2): 2
3. withdrawals (0-1): 1
total Jadad (0-5): 4
age pts: 17-99 yrs
antibiotics (AB): amox
DXM before/with AB: No
deaths %: 13
year (author):
1. randomisation (0-):
2. blinding (0-2):
3. withdrawals (0-1):
   total Jadad (0-5):
   age pts:
   antibiotics (AB):
   DXM before/with AB:
   deaths %:

Progress

Is the review due for publication in the near future? I note it was submitted over 12 months ago.

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

It will be published 07-21-2003.

Contact address D.vandeBeek@amc.uva.nl

Dr Anna Holdgate

References to studies included in this review

Bademosi 1979


Belsey 1969


Bennett 1963


Bhaumik 1998


Ciana 1995

DeLemos 1969


Girgis 1989


Kanra 1995


Kilpi 1995


King 1994


Lebel 1988a


Lebel 1988b


Lebel 1989


Odio 1991


Qazi 1996

Schaad 1993


Thomas 1999


Wald 1995


References to studies excluded in this review:

Baldy 1986


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Gijwani 2002


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Lepper M, Spies HW. Treatment of pneumococcic meningitis. Archives of Internal Medicine 1959;104(3):253-9. [Context Link]

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Coyle PK. Glucocorticoids in central nervous system bacterial infection. Archives of Neurology 1999;56(7):796-801. [Context Link]

**Cronin 1995**


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**Klugman 1995**


**Lefering 1995**


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McIntyre PB, Berkey CS, King SM, Schaad UB, Kilpi T, Kanra GY et al. Dexamethasone as adjunctive therapy in

Moher 1998


Moller 2000


Molyneux 2002


Prasad 1995


Prober 1995


Quagliarello 1997


Saez-Llorens 1999


Sapolsky 1985


Scheld 1980


Schuchat 1997


Sorensen 1992

**Sorensen 1998**

Sorensen HT, Steffensen FH, Schonheyder HC, Nielsen GL, Olsen J. Clinical management of meningococcal disease. Prospective international registration of patients may be needed. BMJ 1998;316:1016. [Buy Now](http://contextlink.com) [Context Link]

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Tauber MG, Khayam-Bashi H, Sande MA. Effects of ampicillin and corticosteroids on brain water content, cerebrospinal fluid pressure, and cerebrospinal fluid lactate levels in experimental pneumococcal meningitis. Journal of Infectious Diseases 1985;151(3):528-34. [Context Link]

**Van de Beek 2002**


**Viladrich 1991**


Medical Subject Headings (MeSH): Human; Adolescent; *Adrenal Cortex Hormones/tu (therapeutic use); *Anti-Inflammatory Agents/tu (therapeutic use); Child; Dexamethasone/tu (therapeutic use); Hearing Loss/et (etiology); Hearing Loss/pc (prevention & control); Meningitis, Bacterial/cp (complications); *Meningitis, Bacterial/dt (drug therapy); Prednisolone/tu (therapeutic use); Randomized Controlled Trials

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