

Steroids in adults with acute bacterial meningitis: a systematic review

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Bacterial meningitis is uncommon but causes significant mortality and morbidity, despite optimum antibiotic therapy. A clinical trial in 301 patients showed a beneficial effect of adjunctive steroid treatment in adults with acute community-acquired pneumococcal meningitis, but data on other organisms or adverse events are sparse. This led us to do a quantitative systematic review of adjunctive steroid therapy in adults with acute bacterial meningitis. Five trials involving 623 patients were included (pneumococcal meningitis=234, meningococcal meningitis=232, others=127, unknown=30). Overall, treatment with steroids was associated with a significant reduction in mortality (relative risk 0.6, 95% CI 0.4–0.8, $p=0.002$) and in neurological sequelae (0.6, 0.4–1, $p=0.05$), and with a reduction of case-fatality in pneumococcal meningitis of 21% (0.5, 0.3–0.8, $p=0.001$). In meningococcal meningitis, mortality (0.9, 0.3–2.1) and neurological sequelae (0.5, 0.1–1.7) were both reduced, but not significantly. Adverse events, recorded in 391 cases, were equally divided between the treatment and placebo groups (1, 0.5–2), with gastrointestinal bleeding in 1% of steroid-treated and 4% of other patients. Since treatment with steroids reduces both mortality and neurological sequelae in adults with bacterial meningitis, without detectable adverse effects, routine steroid therapy with the first dose of antibiotics is justified in most adult patients in whom acute community-acquired bacterial meningitis is suspected.

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The most common causative agents in acute bacterial meningitis in adulthood (figure) are *Neisseria meningitidis* and *Streptococcus pneumoniae*, which cause 80–85% of all cases.¹ Fatality rates in patients with meningitis caused by these microorganisms are 10% and 26%, respectively.¹ In addition, adults with good recovery after pneumococcal meningitis are at substantial risk for severe neuropsychological abnormalities.²

In experimental meningitis studies, outcome is correlated with severity of the inflammatory response in the subarachnoid space.^{3,4} Because treatment with steroids reduces inflammation in the subarachnoid space,^{3,4} several clinical trials have assessed these drugs as adjuvant therapy in children with bacterial meningitis. The results of these trials, however, did not point unequivocally to a beneficial effect.^{5,6} In 1997, a meta-analysis of randomised controlled trials since 1988 showed a beneficial effect of adjunctive steroid therapy on severe hearing loss in children with *Haemophilus influenzae* type b meningitis.⁵ A Cochrane

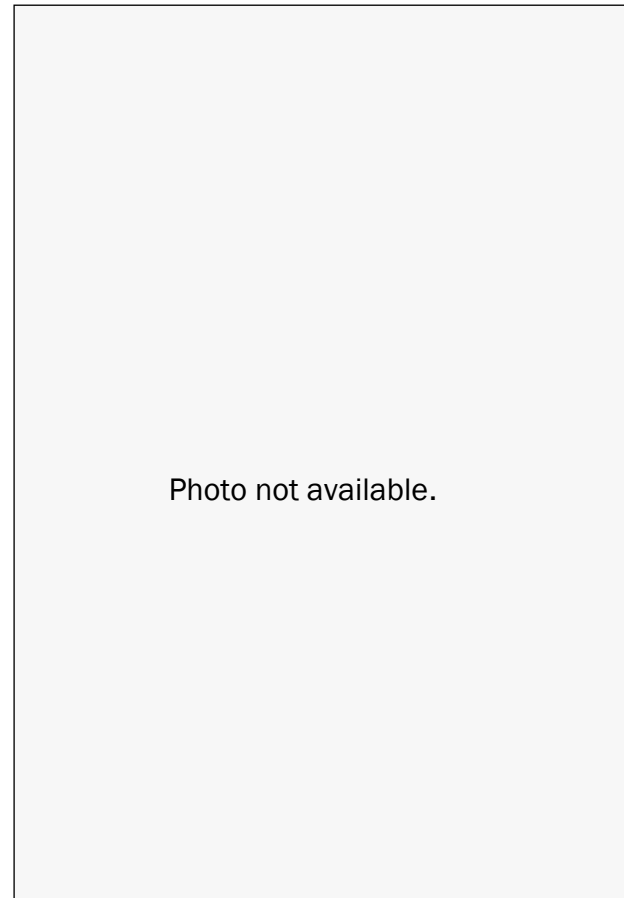


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A patient in intensive care.

review showed a beneficial effect of steroids on severe hearing loss in children with bacterial meningitis caused by *H influenzae* type b, as well as in meningitis caused by bacteria other than *H influenzae*.⁶

Results from a randomised controlled trial of adjunctive steroid therapy in adults with acute bacterial

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Table 1. Quality assessment of studies according to Jadad method and study characteristics

Author (year)	Randomisation 0–2 points	Blinding 0–2 points	Withdrawals 0–1 point	Total 0–5 points	Antibiotic regimen(s)
Excluded for analysis					
Gijwani (2002) ¹⁴	0	0	0	0	Cephalosporin
Included studies for analysis					
Bennett (1963) ¹³	2	2	0	4	NS
Girgis (1989) ¹⁵	1	0	1	2	Ampicillin with chloramphenicol
Bhaumik (1998) ¹⁶	1	0	0	1	Multiple regimens
Thomas (1999) ¹⁷	1	2	1	4	Amoxicillin
De Gans (2002) ⁷	2	2	1	5	Multiple regimens

NS=not stated

meningitis showed that early treatment with dexamethasone improves outcome.⁷ The beneficial effect was most apparent in patients with pneumococcal meningitis. Although no significant beneficial effect was seen in the meningococcal subgroup, a beneficial effect could not be ruled out since the number of patients in this subgroup was small. Nevertheless, several experts advised discontinuing dexamethasone therapy if bacterial meningitis is not caused by *S pneumoniae*.^{8–11} More studies are needed to confirm the results and, moreover, to detect a possible beneficial effect in patients with meningococcal meningitis. However, it took 9 years to complete the European trial,⁷ suggesting that new information on this topic will most likely not be available in the future. Therefore, the aim of our systematic review was to assess the effectiveness and safety of adjunctive steroid therapy in adults with bacterial meningitis.

Methods

Study selection and assessment of methodological quality

We selected trials on steroids as adjuvant therapy in adults with acute bacterial meningitis that were published or unpublished. Eligible patients were adults (predefined as 16 years or older) with bacterial meningitis, treated with antibiotics and randomised to steroid therapy of any type or placebo. For inclusion, at least the case fatality rate had to be recorded. Two investigators did the assessment for inclusion in the methodological appraisal. Studies were appraised by the Jadad scale, a validated five-point scale assessing randomisation (0–2 points), double blinding (0–2 points), and withdrawals and dropouts (0–1 point).¹² Two experienced researchers, not working in infectious diseases, did the blinded appraisal. All trials with one or two points for randomisation on the Jadad scale were included in the analysis.

Assessment of outcome

Primary outcome measures were mortality and neurological sequelae. Neurological sequelae were defined as one or more focal neurological deficits (including hearing loss) and epilepsy not present before meningitis onset. We defined three categories of causative organisms: *N meningitidis*, *S pneumoniae*, and other pathogens (including patients with negative cerebrospinal-

fluid culture). 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°C or higher, occurring after at least 1 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. Two researchers extracted the data independently, with a predetermined protocol. Data were crosschecked and differences were resolved by discussion. Double data entry was used to prevent data entry errors.

Statistical analysis

RevMan 4.1 as supplied by the Cochrane Collaboration was used for the statistical analysis. Chi-square tests for heterogeneity were used on the basis of the DerSimonian and Laird Q statistics; although p values for heterogeneity among studies ranged from 0.3–1.0, we used a random-effect model (Mantel-Haenszel visu-ratio method), because this model provides a more conservative analysis than fixed-effects models. The effect of steroids was expressed as relative risks, where a value below one indicates a beneficial effect of steroids. Statistical uncertainty was expressed with 95% confidence intervals.

Results

Description of studies

Six potentially eligible studies were identified.^{7,13–17} One trial did not obtain the necessary points for randomisation on the Jadad scale and was excluded,¹⁴ leaving five eligible trials involving 623 patients (table 1 and table 2).^{7,13,15–17} Two studies in this analysis were neither placebo-controlled nor double-blinded.^{15,16} In one study, patients older than 12 years were considered adults.¹⁵ Study intervention consisted of 3-day to 7-day regimens of dexamethasone and dosages ranged from 16–40 mg daily; in one study hydrocortisone was given.¹³ The study medication was started before or with the first dose of antibiotics in two studies;^{7,15} in two other studies it was given after the first dose.^{16,17} For one study the protocol required that therapy with steroids or placebo be instituted at the time that antibacterial agents were first instituted, or

Table 2. Meta-analysis of the effect of steroids on mortality in adults with bacterial meningitis

	Mortality rate (%)		Relative risk	95% CI
	Dexamethasone	Placebo		
Bennett ¹³	16/38 (42)	22/47 (47)	0.9	0.56–1.46
Girgis ¹⁵	5/68 (7)	18/79 (23)	0.3	0.13–0.82
Bhaumik ¹⁶	1/14 (7)	3/16 (19)	0.3	0.04–3.36
Thomas ¹⁷	3/31 (10)	5/29 (17)	0.6	0.15–2.14
De Gans ⁷	11/157 (7)	21/144 (15)	0.4	0.24–0.96
Meta-analysis	36/308 (12)	69/315 (22)	0.6*	0.40–0.81

*p=0.002

at the time that a major change in antibacterial therapy occurred.¹³ Several antibiotic regimens were used (table 1). In two studies a sample size calculation was given^{7,17} but an intention-to-treat analysis was available for only one study.⁷ For the remaining studies only per-protocol data could be ascertained. Mortality rates in the studies ranged from 11–45%. Definitions of adverse events were heterogeneous and the numbers of events were recalculated for each study.

Efficacy of steroids

Overall, the percentage of patients who died was significantly smaller in the steroid (12%) than in the placebo group (22%; RR 0.6, 95% CI 0.4–0.8, p=0.002; table 2). The absolute reduction in risk of a fatal outcome was 10%. Subanalysis for causative organisms was possible for 593 of 623 included patients. There was appreciable variation in mortality rate by causative organism, with 73 of 234 (31%) patients with pneumococcal meningitis dying, 16 of 232 (7%) patients with meningococcal meningitis, and 14 of 127 (11%) patients with meningitis due to other pathogens or with negative cerebrospinal fluid culture.

Among patients with pneumococcal meningitis, 24 of 117 (21%) of those who received steroids and 49 of 117 (42%) of patients who received placebo died (0.5, 0.3–0.8, p=0.001). In meningococcal meningitis, the point estimate for risk reduction was lower and not statistically significant (0.9, 0.3–2.1, p=0.7).

Neurological sequelae could be analysed in three studies, including 340 patients.^{7,16,17} The proportion of patients with neurological sequelae was smaller in the steroid group (26 of 184 [14%]) than in the placebo group (35 of 156 [22%]), with borderline statistical significance (0.6, 0.4–1.0, p=0.05; table 3). Subanalysis for causative organisms did not show a significant benefit for patients treated with steroids; however, point estimates were below

one in all subgroups, and in the 107 patients with meningococcal meningitis the relative risk for neurological sequelae was 0.5 for patients treated with steroids (0.1–1.7, p=0.3).

Safety of steroids

Adverse events were reported in 391 patients and were equally divided between the treatment and placebo group (1.0, 0.5–2, p=0.9). Gastrointestinal bleeding occurred in two of 202 (1%) patients in the steroid group and seven of 189 (4%) in the placebo group.

Discussion

Our results show that adjunctive treatment with steroids significantly reduces mortality in adults with bacterial meningitis. The consistency and degree of benefit identified in this analysis warrants routine steroid therapy in adult patients with suspected meningitis. Although the beneficial effect was statistically significant only in pneumococcal meningitis, where the number of deaths was greatest, subgroup analysis for patients with meningococcal and other bacterial meningitis also showed a favourable trend in mortality and neurological sequelae in the absence of any excess adverse events. Therefore, on the basis of overall benefit and no detrimental effects by subgroup, steroid therapy should be begun with the first dose of antibiotic and continued in all patients with acute community-acquired bacterial meningitis.

Two possible biases may have diminished the reliability of our results—selection bias and patient withdrawal. In the Egyptian study,¹⁵ only two different pathogens were isolated in the adult group, suggesting possible selection bias. A second bias is introduced when patients are withdrawn.¹⁸ The analysis was based on per-protocol figures, since intention-to-treat data were available for only one study. An unknown number of patients were

Table 3. Meta-analysis of the effect of steroids on neurological sequelae in adults with bacterial meningitis

	Rate neurological sequelae (%)		Relative risk	95% CI
	Dexamethasone	Placebo		
Bennett ¹³	NS	NS
Girgis ¹⁵	NS	NS
Bhaumik ¹⁶	3/13 (23)	2/13 (15)	1.5	0.30–7.55
Thomas ¹⁷	5/28 (18)	9/24 (38)	0.5	0.18–1.23
De Gans ⁷	18/143 (13)	24/119 (20)	0.6	0.36–1.09
Meta-analysis	26/184 (14)	35/156 (22)	0.6*	0.40–1.00

*p=0.05. NS=not stated.

withdrawn after randomisation, often for unknown reasons. Reasons for withdrawal can be ineligibility according to trial criteria or inability to complete the treatment protocol.¹⁹ If withdrawal on the grounds of ineligibility were affected by knowledge of outcome, this could advantage the steroid regimen. In addition, excluding patients because of inability to complete the course of steroids due to side-effects (eg, upper gastrointestinal tract bleeding), clearly introduces bias in favour of the study medication, whereas withdrawal due to loss to follow-up might favour the placebo group.

For the analysis we only included randomised controlled trials as assessed by the previous validated Jadad scale and excluded studies that used quasi-randomisation, such as alternate allocation.¹² Although quality assessment and methods of its incorporation into systematic reviews remain controversial, its importance is clearly accepted.²⁰ Since the included studies were heterogeneous with respect to study protocol and study population, effect-sizes were calculated as relative risks. A random effect model was chosen because it accounts for the possibility of interstudy as well as intrastudy heterogeneity and provides a more conservative analysis than fixed-effect models.

In adults who survive bacterial meningitis cognitive impairment occurs frequently.² In experimental meningitis, steroids as an adjunct to antibiotic treatment aggravate neuronal damage in the hippocampal formation,²¹ and may potentiate ischaemic injury to neurons,²² so it is important to assess adverse effects—eg, whether steroids may prevent death but worsen cerebral cortical functioning. In the studies in this analysis, adverse effects were equally divided between the treatment and placebo group; there was a statistically significant reduction in mortality and neurological sequelae overall with no evidence of heterogeneous outcome among subgroups. This finding suggests that, in human beings, there is no detrimental effect in survivors that counterbalance reduced mortality from adjunctive steroid therapy. However, definitions of adverse events used in the studies were heterogeneous and in most studies no specified criteria were used in advance, so underascertainment is possible.

Concern has been expressed that steroids reduce the blood–brain permeability and thereby the penetration of antibiotics into the subarachnoid space.^{8–11} Although in children with acute bacterial meningitis, treatment with steroids did not reduce vancomycin concentrations in cerebrospinal fluid,²³ therapeutic failures have been described in adults treated with standard doses of vancomycin and adjunctive steroids.²⁴ Therefore, patients with pneumococcal meningitis who are treated with vancomycin and steroids should be carefully monitored throughout therapy.

The available studies do not address two other important issues—the minimum duration of steroid therapy or the maximum length of time after parenteral antibiotic therapy for commencement. Study medication consisted of dexamethasone in all but one of the included studies. Although one study showed a 2-day and 4-day

Search strategy and selection criteria

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library issue 1, 2003), Medline (1966 to June 2003), Embase (1974 to April 2002), and Healthline (1988 to April 2002). We used the following specific terms: “meningitis” AND “adrenal cortex hormones”, “mening\$.tw” AND “steroid\$.tw”, “mening\$.tw” AND “dexameth\$.tw”, “mening\$.tw” AND “adrenal cortex hormones”, “meningitis” AND “steroid\$.tw”, “meningitis” AND “dexameth\$.tw”, and “ OR/1–6”. We did the search without language limitations. In addition, we identified relevant trials by a search of references listed in those published studies, hand searching abstracts of congresses, personal communication with researchers and experts in the field, and from literature lists of pharmaceutical companies.

regimen of dexamethasone to be similarly effective in childhood bacterial meningitis,²⁵ the 4-day regimen has been used in most clinical trials. Starting steroids before or with the first dose of parenteral antibiotics is more effective than starting after the first dose of antibiotics.^{5,6} Although it is possible that benefit may still accrue, the maximum allowable delay after parenteral antibiotics is not clear. For patients admitted in a late stage of disease adjuvant steroids are less protective and might even be harmful.¹⁹ A large controlled trial in children with bacterial meningitis that included mainly children who began treatment late showed no beneficial effect of adjunctive steroid therapy.²⁶

Even though methodological and design flaws of some studies included in this analysis diminish the reliability of results, the consistency and degree of benefit identified in this analysis and the presence of one large well-performed clinical trial merit early steroid therapy in most adults with suspected acute bacterial meningitis. We recommend a 4-day regimen of dexamethasone, at a dose of 10 mg given every 6 h intravenously, started before or with the first dose of antibiotics. We do not recommend the use of adjunctive (high-dose) steroid treatment in patients who have already received parenteral antimicrobial therapy. Similarly, we do not recommend adjunctive steroid therapy in meningitis patients with septic shock, because high-dose steroids may be detrimental in patients with septic shock if they have an adequate adrenal reserve.^{8,27} Patients with postneurosurgical meningitis were excluded in all included studies,^{7,13,15–17} and since postneurosurgical meningitis has different pathophysiology and predominant bacteria,²⁸ we do not recommend routine use of steroids in this patient group. Neither do we recommend the use of steroids in immunosuppressed patients with acute bacterial meningitis such as those with haematological malignancy or those receiving immunosuppressive therapy.

In the UK, family doctors are advised to give (parenteral) antibiotics before transferring the patient to hospital if meningococcal meningitis is suspected.²⁹ A first difficulty is how to identify a patient with meningococcal meningitis. The second dilemma is whether patients benefit from such pre-hospital treatment. Although

retrospective data from the UK showed a favourable outcome for patients who were treated early with parenteral antibiotics,³⁰ pre-hospital antibiotic treatment of such patients remains controversial. A Danish study reported considerably higher mortality in pretreated patients with suspected meningococcal meningitis.³¹ Subsequent analysis of available studies showed no beneficial effect of pre-hospital parenteral antibiotic treatment (odds ratio 0.8, 95% CI 0.4–1.6);³² however, those data were presented in a rather short communication and prospective data are lacking.

The desirability of giving dexamethasone before or with the first parenteral dose of an antimicrobial agent complicates recommendations for routine management of suspected acute bacterial meningitis, both in general and hospital practice. In our opinion, if general practitioners decide to treat a patient with suspected

bacterial meningitis with a parenteral antibiotic, dexamethasone should be given before or with this first dose. Similarly, hospitals will require protocols to include dexamethasone with initial antibiotic therapy, since the causative organism will not be known in many cases when treatment is begun. The reduction in mortality and neurological sequelae and absence of detectable adverse effects from short-term steroid therapy in this setting gives confidence that such therapy will be advantageous to such patients overall.

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Conflicts of interest

We have no conflicts of interest.

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