Corticosteroid Administration and Outcome of Adolescents and Adults With Acute Bacterial Meningitis: A Meta-analysis

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OBJECTIVE: To systematically assess the effect of the adjunctive administration of corticosteroids in the treatment of acute bacterial meningitis.

METHODS: We performed a systematic review and meta-analysis by searching several databases for reports (published from January 1966 through February 2008) of placebo-controlled randomized trials of corticosteroid use in the treatment of adolescents and adults with acute bacterial meningitis. We used random-effects models. Sources of heterogeneity were explored by preplanned subgroup analyses.

RESULTS: The 4 eligible trials (published between 1999 and 2007) were of high methodological quality and included 1261 adult patients. Overall, the short-term mortality rate associated with corticosteroid administration was not significantly lower than that associated with placebo (relative risk [RR], 0.81; 95% confidence interval [CI], 0.54-1.20; $P=54\%$). A significant interaction was found between the effect of corticosteroids and the income status of the country ($P=.02$) and the prevalence of infection with human immunodeficiency virus (HIV) among study populations ($P=.03$). The administration of corticosteroids resulted in a lower short-term mortality rate than did the administration of placebo in high-income countries (pooled RR, 0.5; 95% CI, 0.27-0.92; $P=0\%$) and in the studies with a low prevalence of infection with HIV (RR, 0.66; 95% CI, 0.44-0.99; $P=0\%$). In studies from high-income countries, the number needed to treat with corticosteroids to prevent 1 death and 1 neurologic sequela was 12.5 (95% CI, 7.1-100.0) and 11.0 (95% CI, 5.6-100.0), respectively.

CONCLUSION: Our meta-analysis suggests that the adjunctive administration of corticosteroids is beneficial in the treatment of adolescents and adults with bacterial meningitis in patient populations similar to those seen in high-income countries and in areas with a low prevalence of HIV infection.

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CI = confidence interval; CSF = cerebrospinal fluid; HIV = human immunodeficiency virus; NNT = number needed to treat; RR = relative risk

Acute bacterial meningitis can lead to morbidity and mortality, even when highly effective antibiotic therapy is administered.¹ Because neurologic damage is at least partially caused by the host immune response,² anti-inflammatory drug therapy should, in theory, improve outcome. Indeed, cumulative evidence, including the results of a Cochrane review³ and a systematic review and meta-analysis⁴ of adjunctive corticosteroid therapy for adults with acute bacterial meningitis, indicates that early treatment with dexamethasone improves outcome. In these studies, the beneficial effect was most apparent for patients with meningitis caused by *Streptococcus pneumoniae*, the

leading causative pathogen of adult meningitis. Accordingly, practice guidelines currently recommend the adjunctive administration of dexamethasone to all adult patients with pneumococcal meningitis.⁵ However, 2 subsequent large randomized trials^{6,7} that included 900 patients from developing countries did not show similar benefits in terms of mortality and neurologic sequelae. Because the previous meta-analysis⁴ included quasi-randomized and open-label trials,^{8,9} concerns exist about the validity of their pooled estimates. The findings of meta-epidemiological studies^{10,11} suggest that the introduction of cointerventions during the conduct of such trials, even for well-defined end points such as mortality, cannot always be excluded and thus could weaken the inferences based on the pooled results of a meta-analysis.

To further examine the ongoing controversy concerning corticosteroid therapy for bacterial meningitis, we performed a meta-analysis of published reports of randomized, placebo-controlled trials of adjunctive corticosteroid therapy for adolescents and adults with bacterial meningitis.

METHODS

ELIGIBILITY CRITERIA

We included published articles in our analysis if they reported the results of trials that met the following criteria: (1) randomized, placebo-controlled trials, the findings of which were published after 1980; (2) trials including participants aged 14 years or older with clinically suspected or proven bacterial meningitis; (3) trials including patients who were randomly assigned to receive either corticosteroids or placebo and were treated with antibacterial agents; and (4) trials reporting short-term, all-cause mortality rates (death within 2 months after diagnosis) and any additional outcomes, including hearing loss (clinical or audiologic) and any other neurologic sequelae.

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METHODS OF FINDING RELEVANT PUBLICATIONS

The literature search strategy was developed by a reference librarian (P.J.E.) with 35 years' experience in working with medical literature. The search strategy for the systematic review used a combination of controlled vocabulary and text words. The search strategy for MEDLINE (January 1966-February 2008) exploded the term *meningitis, bacterial* for each of the bacterial entities associated with the disease, combined with the Medical Subject Headings (MeSH) terms for corticosteroids: explode *adrenal cortex hormones* OR explode *11-hydroxycorticosteroids* OR explode *17-hydroxycorticosteroids* OR explode *glucocorticoids*. We used the Cochrane filter to limit search results to reports of randomized controlled trials.

We used the same strategy to search EMBASE, but we altered the terms to reflect Emtree's more granular subject headings. Thomson Scientific Web of Science (January 1993-February 2008) and Elsevier Scopus (inception to February 2008) are based on text words. We searched these databases for the following words in titles, abstracts, and keywords: (*meningitis* SAME (*bacterial* OR *tubercul** OR *coli** OR *pneumo** OR *meningococ** OR *haemophil** OR *listeri**)) AND (*corticosteroid** OR *glucocorticoid** OR *dexamethasone* OR *hydrocortisone**) AND (*random** OR *trial* OR *cohort** OR *outcome** OR *meta-analysis* OR *systematic** OR *quasi-random** OR *blind** OR *placebo**). The Ovid Cochrane Library is prefiltered to include only systematic reviews or randomized controlled trials. The controlled vocabulary is available, but the hierarchical structure of MEDLINE and EMBASE is not. The MeSH and Emtree terms were augmented with text words. Two authors (A.M.A., F.A.A.) independently assessed the eligibility of identified studies.

DATA COLLECTION

Using a structured form, 2 reviewers (A.M.A., F.A.A.) independently abstracted data about primary outcome measures (mortality, hearing loss, and neurologic sequelae) and adverse events. They also assessed the methodological quality of included studies by using the validity criteria proposed by Jüni et al.¹⁰ These validity criteria assess the possibility of selection, performance, outcome ascertainment, and attrition biases. Disagreements were resolved by consensus.

STATISTICAL ANALYSES

We used a random-effects model, the DerSimonian-Laird method,¹² as the primary model for pooling dichotomous data across trials (for more generalizable results). We estimated pooled relative risk (RR) and its associated 95% confidence interval (CI). We calculated the pooled number needed to treat (NNT) and the 95% CI on the basis of the

inverse of the pooled absolute risk reduction, and we calculated the heterogeneity statistic (I^2) as the proportion of the total variability in results between studies that is due to true heterogeneity rather than to sampling error (chance).¹³ An I^2 value of 50% or higher indicates substantial inconsistency in results. All analyses were performed with Review Manager (RevMan) version 4.2.7 (the Cochrane Collaboration). Inconsistency was explored by prespecified subgroup analyses that tested for a treatment-subgroup interaction by using a statistical test of interaction.¹⁴ Subgroup analyses compared high-income countries with low-income countries and compared populations that had a high prevalence of human immunodeficiency virus (HIV) with populations that had a low prevalence of HIV. Countries scoring less than 0.7 on The United Nations Human Development Index were considered low-income countries and those scoring 0.7 or higher were considered high-income countries.¹⁵

RESULTS

YIELD OF SEARCH STRATEGY AND ELIGIBLE TRIALS

The search strategy yielded 528 publications, including 9 randomized trials. Of these randomized trials,^{6-9,16-20} only 4 were eligible for inclusion in our meta-analysis.^{6,7,16,17} Five studies were excluded because of inappropriate randomization, inappropriate allocation concealment, or both^{8,9,18-20} (Figure 1).

CHARACTERISTICS OF THE INCLUDED TRIALS

Between June 1993 and June 2005, the 4 eligible trials enrolled 1261 adolescent and adult patients (Table 1). Two were multicenter trials that included 361 patients from Europe,^{16,17} and 2 were single-center studies that included 900 patients from developing countries (Malawi and Vietnam).^{6,7} Of patients in the Malawian trial,⁶ 90% were infected with HIV vs only 0.7% in the Vietnamese trial.⁷ The HIV infection status was not reported for the 2 European studies; however, the difference in HIV prevalence between Western Europe (0.3%) and Malawi (14.0%) supports our assumption that the rate of HIV infection among patients in the European studies was low.^{21,22} In addition, 2 European meningitis studies reported HIV infection rates of 0.9%²³ and 0.6%,²⁴ rates that were similar to the rate of 0.7% in the Vietnamese study. In all included studies, acute bacterial meningitis was diagnosed by clinical and cerebrospinal fluid (CSF) criteria (cloudy CSF, CSF pleocytosis, bacteria visible on Gram stains, or positive results for bacteria in CSF cultures).

The administration of dexamethasone was initiated before or within 3 hours of the initiation of antibiotic therapy. Dexamethasone was administered at doses ranging from 32

FIGURE 1. Flow diagram of eligible studies.

to 40 mg/d^{7,16,17} or were based on the patient's weight (0.8 mg/kg/d).⁶ Empiric antibiotics administered included either ceftriaxone^{6,7} or amoxicillin.^{16,17} Short-term mortality rates were available for all trials and ranged from 10% to 54%. An audiologic definition of hearing loss was available for 3 of the 4 trials.^{6,7,16} Table 2 outlines the definitions of efficacy and safety outcomes used in the trials included in our analyses.

QUALITY ASSESSMENT OF THE INCLUDED TRIALS

Trials were judged according to key validity components that address biases in selection, performance, detection, and sample attrition. All trials were of high methodological quality, with adequate allocation concealment, randomization, and outcome assessment. Intent-to-treat analysis was performed for all studies, and the proportion of patients lost to follow-up ranged from 0% to 2.3%.

 TABLE 1. Characteristics of Eligible Studies^a

Reference	Location (type of center)	Sample size	Age of patients (y)	Empiric antibiotics administered	Corticosteroid regimen	Corticosteroid initiation	HIV	<i>Streptococcus pneumoniae</i>	<i>Neisseria meningitidis</i>	<i>Streptococcus suis</i>	Mortality rate (%)
Thomas et al, ¹⁷ 1999	France and Switzerland (multi)	60	18-79	Amoxicillin	10 mg of IV DEX every 6 h for 3 d	Within 3 h after antibiotics	NR	52.0	30.0	0	13.0
de Gans et al, ¹⁶ 2002	Europe (multi)	301	>17	Amoxicillin	10 mg of IV DEX every 6 h for 4 d	15-20 min before antibiotics	NR	35.8	21.6	0	10.6
Scarborough et al, ⁶ 2007	Malawi (single)	465	>16	Ceftriaxone	16 mg of IV DEX every 12 h for 4 d	Immediately before antibiotics	90	59.0	4.0	0	54.0
Nguyen et al, ⁷ 2007	Vietnam (single)	435	>14	Ceftriaxone	0.4 mg/kg of IV DEX every 12 h for 4 d	15 min before antibiotics	0.7	12.7	4.4	26.7	10.0

^a For each pathogen type, the percentage of infected patients is provided. DEX = dexamethasone; HIV = human immunodeficiency virus; IV = intravenous; NR = not reported.

TABLE 2. Definitions of Outcome in Eligible Studies

Reference	Short-term mortality	Neurologic sequelae	Hearing loss	Adverse events	Gastrointestinal bleeding	Hyperglycemia
Thomas et al, ¹⁷ 1999	Death within 30 d after diagnosis	<i>Mild</i> : sensory deficit (visual disturbances, hearing loss), mild ataxia, or memory deficit that did not prolong hospitalization <i>Severe</i> : objective motor deficit, mental or consciousness changes requiring hospitalization, or both	Not defined	Gastrointestinal bleeding, hyperglycemia, <i>Herpes zoster</i> infection	Clinically evident gastrointestinal bleeding	Not defined
de Gans et al, ¹⁶ 2002	Death at 8 wk after diagnosis	Focal neurologic abnormalities: aphasia, cranial-nerve palsy, monoparesis, hemiparesis, and severe ataxia	Clinical hearing loss at 8 wk after diagnosis	Gastrointestinal bleeding, hyperglycemia, <i>Herpes zoster</i> infection, fungal infection	Clinically relevant bleeding with a decreased serum hemoglobin concentration	Serum glucose concentration >144 mg/dL ^a
Scarborough et al, ⁶ 2007	Death at 40 d after diagnosis	Glasgow Outcome Scale score $\leq 3^b$ at 40 d after diagnosis	Hearing loss confirmed by audiometry at 40 d after diagnosis	Gastrointestinal bleeding, hyperglycemia, <i>Varicella zoster</i> infection, abdominal pain, transient pruritus, <i>Herpes labialis</i> infection, pulmonary tuberculosis during follow-up	Proven gastrointestinal bleeding	Random serum glucose concentration >200 mg/dL ^a
Nguyen et al, ⁷ 2007	Death at 1 mo after diagnosis	Modified Rankin Scale score $\geq 1^c$	Hearing loss confirmed by audiometry	Gastrointestinal bleeding, hyperglycemia, <i>Herpes labialis</i> infection, hypertension	Clinically evident gastrointestinal bleeding	Not defined

^a SI conversion factor: To convert serum glucose concentration to mmol/L, multiply by 0.0555.

^b Glasgow Outcome Scale: 4 = no disability; 3 = disabled but able to live independently and return to school or work; 2 = disabled but dependent on others for routine daily tasks; 1 = minimally responsive; 0 = dead.

^c Modified Rankin Scale: 0 = no symptoms; 1 = minor symptoms not interfering with lifestyle; 2 = symptoms restricting lifestyle but not impeding independent living; 3 = symptoms restricting lifestyle and interfering with independent living; 4 = symptoms clearly preventing independent living, although constant care is not required; 5 = symptoms resulting in complete dependence on others.

FINDINGS OF META-ANALYSES

Overall Efficacy and Safety of Corticosteroids. In the overall pooled analysis, the reduction in short-term mortality associated with the administration of corticosteroids (165 [25.9%] of 636 patients) was not significantly different than that associated with the use of a placebo (173 [27.9%] of 619 patients; pooled RR, 0.81; 95% CI, 0.54-1.20; $P=54\%$; $P=.29$) (Figure 2). However, the number of neurologic sequelae other than hearing loss was lower among groups treated with corticosteroids (114 [23.5%] of 486 patients) than among groups given a placebo (143 [30.8%] of 465 patients; pooled RR, 0.67; 95% CI, 0.45-1.01; $P=56\%$; $P=.05$). Three trials^{6,7,16} assessed clinical or audiologic hearing loss and found that its incidence was significantly lower in the corticosteroid group than in the placebo group (pooled RR, 0.73; 95% CI, 0.55-0.97; $P=0\%$). Overall, the incidence of adverse events, gastrointestinal bleeding, and hyperglycemia was not higher in groups treated with corticosteroids than in those given a placebo (Table 3).

Subgroup Analyses. Inconsistency in effect estimates between studies was explained by subgroup analyses, which showed statistically significant interactions and a decrease in I^2 . Specifically, in high-income countries but not in low-income countries ($P=.02$), the administration of corticosteroids resulted in a lower short-term mortality rate than did the administration of placebo (pooled RR, 0.5; 95% CI, 0.27-0.92; $P=0\%$). The NNT to prevent 1 death in high-income countries was 12.5 (95% CI, 7.1-100.0). In patients with *Streptococcus pneumoniae* meningitis, the NNT was 4.8 (95% CI, 2.9-14.3). We were unable to perform subgroup analyses for *Streptococcus suis* because this strain was found in only 1 study.

Moreover, the administration of corticosteroids was associated with a significantly lower rate of neurologic sequelae (other than hearing loss) in high-income countries than in low-income countries (pooled RR, 0.58; 95% CI, 0.36-0.94; $P=0\%$; $P=.60$). The NNT to prevent 1 neurologic sequela in high-income countries was 11.0 (95% CI, 5.6-100.0).

FIGURE 2. Forest plot showing the effect of corticosteroids on short-term mortality in adults with bacterial meningitis. CI = confidence interval; RR = relative risk.

A significant interaction was also found between the effect of corticosteroids and the prevalence of HIV among study populations ($P=.03$) (Table 4). In studies with a population that could be presumed to have a low prevalence of HIV, the short-term mortality rates were significantly lower for patients treated with corticosteroids than for patients given a placebo (pooled RR, 0.66; 95% CI, 0.44-0.99; $I^2=0\%$).

DISCUSSION

The results of our systematic review and meta-analysis, which were limited to placebo-controlled randomized trials, suggest that adjunctive treatment with corticosteroids improves both survival and neurologic recovery in adults with acute bacterial meningitis when patient populations are similar to those seen in high-income countries and in

TABLE 3. Relative Risk of Negative Patient Outcome After Meningitis Treatment: Overall and Stratified by High-Income vs Low-Income Countries^a

Outcome	Overall RR (95% CI)	I^2 (%)	High-income countries RR (95% CI)	I^2 (%)	Low-income countries RR (95% CI)	I^2 (%)	P value
Mortality rate	0.81 (0.54-1.20)	54	0.50 (0.27-0.92)	0	1.04 (0.88-1.22)	0	.02
Mortality rate (<i>Streptococcus pneumoniae</i>)	0.50 (0.20-1.28)	72	0.38 (0.19-0.77)	0	0.49 (0.05-4.54)	64	.80
Neurologic sequelae	0.67 (0.45-1.01)	56	0.58 (0.36-0.94)	0	0.71 (0.36-1.42)	77	.60
Hearing loss	0.73 (0.55-0.97)	0	0.77 (0.38-1.58)	0	0.71 (0.47-1.09)	45	.85
Adverse events	1.11 (0.94-1.31)	0	1.19 (0.89-1.58)	0	1.07 (0.88-1.31)	NA ^b	.55
Gastrointestinal bleeding	0.71 (0.22-2.27)	36	0.31 (0.08-1.31)	0	1.57 (0.60-4.16)	2	.06
Hyperglycemia	1.26 (0.94-1.69)	0	1.25 (0.88-1.79)	0	1.29 (0.77-2.13)	NA ^b	.92

^a CI = confidence interval; NA = not applicable; RR = relative risk.

^b Only 1 study available.

TABLE 4. Relative Risk of Negative Patient Outcome After Corticosteroid Treatment for Meningitis in Study Populations With High vs Low HIV Prevalence^a

Outcome	Study with high HIV prevalence, RR (95% CI)	I ² (%)	Studies (n=3) with low HIV prevalence, RR (95% CI)	I ² (%)	P value
Mortality rate	1.06 (0.90-1.26)	NA ^b	0.66 (0.44-0.99)	0	.03
Neurologic sequelae	0.47 (0.25-0.88)	NA ^b	0.77 (0.52-1.13)	43	.20

^a CI = confidence interval; HIV = human immunodeficiency virus; NA = not applicable; RR = relative risk.

^b Only 1 study available (Scarborough et al⁶).

populations with a low prevalence of HIV. These benefits are achieved without a significant increase in adverse events.

An outcome disparity between high-income and low-income countries was previously reported for children with acute bacterial meningitis.²⁵ In our meta-analysis, the lack of benefit in low-income countries was primarily affected by the inclusion of the study from Malawi.⁶ Although *S pneumoniae* was the predominant pathogen, the 40-day mortality rate was substantially higher than that found by other studies, and the administration of corticosteroids did not improve outcome. Differences in the study populations may explain this disparity. First, most patients in the Malawian study were infected with HIV and were likely to have had advanced disease, anemia, malnutrition, or some combination thereof. At least in children, HIV-infected patients with meningitis exhibit higher pneumococcal bacterial loads in blood and CSF and higher chemokine concentrations than patients not infected with HIV.²⁶ Second, delayed presentation to hospital could help explain outcome differences. The duration of illness before presentation was 72 to 96 hours in studies from low-income countries^{6,7} vs less than 24 hours in a European study.¹⁶ In fact, the timing of corticosteroid treatment relative to infection is important for achieving strong inhibition of the inflammatory cytokine responses.²⁷

The study from Vietnam showed that the administration of corticosteroids improved outcome in the subset of patients with proven bacterial meningitis.⁷ The number of patients contributed to the pooled analysis by the Vietnamese⁷ and the Malawian⁶ studies was similar, as was the antibiotic regimen. However, the prevalence of HIV in the Vietnamese study was low.

Although the classes of antibiotics used in low-income countries differ from those used in high-income countries, we think that antibiotic selection is unlikely to explain the discrepancy in outcome. First, the European trials used amoxicillin, and all of the tested *S pneumoniae* isolates (72%) were susceptible to it. In the Malawian study, ceftriaxone resistance was detected in only 0.5% of the screened *S pneumoniae* isolates. Accordingly, both antibiotics should have been effective at least against the *S pneumoniae* isolates. Second, randomization resulted in an

equal distribution of differing organisms (including nonpneumococcal and drug-resistant isolates) between the placebo arm and the corticosteroid arm. Therefore, the choice of antibiotic in a particular study should not have affected the results. Third, the subgroup analysis (Table 3) favored corticosteroid use in high-income countries (the same studies that used amoxicillin as empiric therapy) rather than in low-income countries (studies that used ceftriaxone as empiric therapy). This fact argues against the hypothesis that amoxicillin therapy is suboptimal or that its use explains the between-studies heterogeneity.

It is noteworthy that 6 of 8 Vietnamese patients in the dexamethasone group who had probable meningitis and who were subsequently treated for tuberculosis meningitis died. In areas with a high incidence of tuberculosis, initiating the administration of corticosteroids for patients with probable meningitis (not supported by the results of Gram staining) may be detrimental.

Our meta-analysis has several strengths. To enhance the robustness of the analyses, we excluded studies performed before 1980 because of the advances in diagnostic and treatment methods that have become available since then. The heterogeneity of earlier studies could have negatively affected the validity of the results. In addition, we included only recent placebo-controlled randomized trials. The included studies were relatively homogeneous in design and interventions. Empirical evidence from meta-epidemiological studies¹¹ suggests that when meta-analyses include studies with inadequate randomization methods or with open-label design, such as those included in previously reported meta-analyses, the true effect size can be overestimated. Accordingly, we included only studies with adequate randomization methods and allocation concealment.

Our analysis was limited by the small number of studies available, and this limitation was complicated by the fact that the mortality rate found in the Malawian study was substantially higher than that found in the other studies. However, similarly high mortality rates (41%-50%) were found in other studies from low-income countries.²⁸⁻³⁰ The inclusion of patients with more severe illness, as reflected by the high case fatality rate, may have resulted in an underestimation of the protective effect of corticosteroids.

CONCLUSION

Our meta-analysis suggests that the administration of adjunctive corticosteroids to adolescents and adults with bacterial meningitis is justified for patients with characteristics similar to those who live in high-income countries and in areas in which the prevalence of HIV infection is low. Infection with HIV can be an indirect indicator of other factors that contribute to the lack of benefit with such treatment; these factors include access to health care and nutritional status. However, HIV infection should not preclude the use of corticosteroids for early treatment if patients are otherwise healthy, even in resource-poor areas in which HIV is prevalent. Early access to health care and prompt administration of corticosteroids and antibiotics, in addition to advanced management interventions, may partially explain why the improvement in the outcome of patients with bacterial meningitis is limited to high-income countries. Further studies are needed to determine why the administration of corticosteroids does not improve the survival rates of HIV-infected patients with bacterial meningitis, even though an intense chemokine response is achieved.

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