

Corticosteroids for Acute Bacterial Meningitis

EBEM Commentator Contact

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SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this review abstract is van de Beek D, de Gans J, McIntyre P, et al. Corticosteroids for acute bacterial meningitis (Cochrane review). *Cochrane Database Syst Rev*. 2007;1:CD004405. DOI: 10.1002/14651858.CD004405.pub2. The *Annals'* EBEM editors assisted in the abstract preparation of this Cochrane systematic review, as well as selection of the Evidence-Based Medicine Teaching Point.

OBJECTIVE

To examine whether or not corticosteroids are effective for reducing mortality and other severe neurologic/long-term sequelae in various populations at risk for acute bacterial meningitis.

DATA SOURCES

The authors searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966 to June 2006), Current Contents (2001 to June 2006), and reference lists of all articles. They also contacted manufacturers and researchers in the relevant fields.

STUDY SELECTION

Studies were selected if they were published and unpublished randomized controlled trials on corticosteroids as an adjuvant therapy for acute bacterial meningitis. Studies included all patient ages, clinical conditions, and treatment with antibiotics. Patients had to be randomized to corticosteroid therapy or placebo. At least 1 case fatality or episode of hearing loss had to be recorded for inclusion.

DATA EXTRACTION AND ANALYSIS

Studies were independently reviewed by 2 review authors for trial quality and data extraction. Information was collected for

the primary efficacy outcomes and adverse effects of adjuvant corticosteroid treatment. Planned subgroup analyses included adults versus children, causative organisms, and low- versus high-income countries. Income categorization of countries was defined by the United Nations Human Development Index: "high" defined by an index of 0.7 or higher, "lower" defined by index less than 0.7.

MAIN RESULTS

Twenty studies with 2,750 patients were included. The overall mortality benefit with adjuvant corticosteroid was favorable (RR=0.83; 95% confidence interval [CI] 0.71 to 0.99). There were lower rates of severe hearing loss (relative risk [RR]=0.65; 95% CI 0.47 to 0.91) and other long-term sequelae (RR=0.67; 95% CI 0.45 to 1.00). In children, there was significantly less hearing loss (RR=0.61; 95% CI 0.44 to 0.86). In adults, there was a significant reduction in mortality (RR=0.57; 95% CI 0.40 to 0.99), as well as short-term neurologic sequelae (RR=0.42; 95% CI 0.22 to 0.87).

For causative organisms, there was a mortality reduction in meningitis caused by *S pneumoniae* (RR=0.59; 95% CI 0.45 to 0.77) and reduced hearing loss in children with *H influenzae* (RR=0.37; 95% CI 0.20 to 0.68). There was a nonsignificant trend to mortality reduction with *N meningitidis* (RR=0.71; 95% CI 0.31 to 1.62).

For patients from high-income countries, the observed benefits were as follows: overall mortality reduction RR=0.83 (95% CI 0.51 to 1.05), short-term neurologic sequelae RR=0.56 (95% CI 0.03 to 0.84), and severe pediatric hearing loss RR=0.61 (95% CI 0.41 to 0.91). There were favorable trends to reduced pediatric severe hearing loss with non-*H influenzae* meningitis (RR=0.51; 95% CI 0.23 to 1.13) and short-term neurologic sequelae (RR=0.72; 95% CI 0.23 to 1.13). For all patients, and specifically children in low-income countries, there were no statistically significant benefits or adverse sequelae observed with corticosteroid use.

CONCLUSIONS

Overall, adjuvant corticosteroid treatment for acute bacterial meningitis is associated with significantly reduced mortality, hearing loss, and neurologic sequelae. In high-income countries with good access to medical services, all adult and pediatric patients should receive adjuvant corticosteroids with their first

dose of antibiotics. These benefits were not statistically significant in patients from low-income countries.

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COMMENTARY: CLINICAL IMPLICATIONS FOR EMERGENCY MEDICINE

Acute bacterial meningitis remains a devastating illness, with the majority of cases affecting neonates and children. Short-term complications in these populations include sepsis, vascular compromise, and death. Long-term complications in these populations include hearing loss, cognitive deficits, epilepsy, and hydrocephalus.¹ Despite the advent of more powerful antibiotics and new vaccines against *H influenzae* that have lowered the incidence of the proportion of cases caused by this microbe,¹ cases caused by *N meningitidis* and *S pneumoniae* remain the common causes of meningitis in children older than 1 month. Concerns about increasing β -lactam resistance of *S pneumoniae* are leading to modification of recommended antibiotic selection patterns in treating these patients.¹

Other options that have been investigated to reduce mortality include corticosteroid use. One purported mechanism of benefit for adjuvant corticosteroids in treating bacterial meningitis is to attenuate the intense inflammatory reaction in the closed brain and spinal cord spaces, which is thought to lead to the destructive secondary effects of bacterial meningitis.² As such, the anti-inflammatory effects of adjuvant corticosteroid (dexamethasone) may help to minimize these effects. Concerns about steroids reducing blood-brain barrier permeability to antibiotic penetration and increases in cognitive deficits have not been borne out in human trials.²

This Cochrane review has addressed the role of corticosteroids in acute meningitis. Using a comprehensive search strategy to avoid publication bias and an independent assessment process that avoids selection bias, the authors identified 18 studies involving 2,750 meningitis patients. Corticosteroid agents considered included dexamethasone, hydrocortisone, and methylprednisolone, with a variety of dosing strategies. The review identified considerable clinical and statistical benefit associated with adding corticosteroids to acute meningitis treatment. The statistically significant results for clinical outcomes are summarized in the Table, with accompanying numbers needed to treat. These results show modest benefits in overall populations treated for a number of clinically important outcomes, but higher benefits specifically for adult mortality, long-term neurologic sequelae, and children's severe hearing loss. The authors recommend dexamethasone adjuvant treatment as the corticosteroid

Table. Summary of clinical effect estimates and numbers needed to treat.

Outcome	Absolute Risk Reduction, %	Numbers Needed to Treat
Overall mortality	2.7	36
Overall hearing loss	3.3	30
Overall long-term sequelae	3.0	32
Child hearing loss	4.4	22
Adult mortality	10.2	9
Adult short-term sequelae	9.6	10

treatment of choice for acute bacterial meningitis. The recommended dosage is 0.6 mg/kg daily for 4 days, administered before or with the administration of antibiotics. There were no significant adverse effects reported for giving adjuvant corticosteroids.

Two important points must be added to the systematic review. First, there are clear subgroups that may benefit from this treatment more than comparisons: patients in developed countries and children from higher-income countries. Second, a number of treatment-timing trials have recommended that adjuvant corticosteroid be given with or just before intravenous antibiotics.² The authors recommend that the first dose be loaded either before or with the first antibiotic dose. This review provides no recommendations for the common emergency department (ED) situation in which the first dose of antibiotics has been delivered before the return of the cerebrospinal fluid test results.

TAKE-HOME MESSAGE

Adjuvant corticosteroids are a key intervention for all patients with acute bacterial meningitis during the early ED phase of treatment, to be delivered concomitantly with the first dose of antibiotics. The benefits for mortality reduction, severe hearing loss, and neurologic sequelae are statistically significant for patients in high-income countries, although not so for patients from lower-income countries. However, given the devastating sequelae of bacterial meningitis from a mortality and morbidity perspective, it is intuitively evident that all patients with acute bacterial meningitis should receive early adjuvant corticosteroids with the first dose of antibiotics (in addition to optimal supportive care).

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EBEM TEACHING POINT

Statistical versus clinical significance. A reader may struggle with the difference between *statistical* significance and *clinical*

significance of reported results.^{3,4} Statistical significance is a mathematical concept that demonstrates that the difference between 2 interventions being compared is mathematically “true,” such that it is unlikely that the difference is due to chance. For example, a comparison of antibiotics versus analgesics for acute otitis media may show a statistically significant improvement of 10% (ranging from 4% to 14%), favoring the use of antibiotics to prevent pain on day 1 of treatment. Clinical significance, however, is a subjective concept based on the importance of the outcome of interest to clinicians and patients and how beneficial the treatment effect really is. Using another example, a 1-mm Hg difference in blood pressure may be statistically significant in a large sample of patients; however, the result is not clinically important. The point here is that mathematical significance must be interpreted in the context of the clinical situation. Confusion between the 2 concepts can be minimized by selecting the primary and secondary outcomes carefully, limiting the number of statistical comparisons performed, describing the power calculations, and limiting the discussions to the most important benefits or harm of the interventions being compared.

In this review, number of important clinical outcomes for patients showed statistically significant benefits for the use of adjuvant corticosteroids: mortality reduction, decreased severe hearing loss, and long-term neurologic sequelae in high-income

countries. These outcomes were not statistically significant in patients treated from lower-income countries, although the effect estimates all demonstrated similar trends toward benefit. This was also reflected in mortality reduction related to *N meningitidis*.

If the clinical stakes of not treating a disease are potentially devastating, even trends in benefits for morbidity and mortality reduction may offer clinicians an opportunity to help their patients. In this study, the real and potential benefits for important clinical outcomes may motivate physicians to offer adjuvant corticosteroids to meningitis patients, even if the other components of medical services are suboptimal.

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**The 2008 Pediatric Emergency Medicine Initial Certifying Examination
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The new applicant regular registration period for the 2009 Pediatric Emergency Medicine initial Certifying Examination commences April 4, 2008, and will end October 1, 2008, at 3:00 pm Eastern Daylight Savings Time. Applicants must ensure that they apply online at www.abp.org at least 24 hours before the deadline so that any technical difficulties can be addressed.

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