Corticosteroids in Acute Bacterial Meningitis

Sanjit R. Konda* Barry M. Diner, MD^

** Medical Student, Emory University, Atlanta, Georgia, United States*
^ Assistant Professor Emory University, Atlanta, Georgia, United States

SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, which will be a regular feature of the Israeli Journal of Emergency Medicine Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews (http://www.cochrane.org/index0.htm) and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: van de Beek J, de Gans J, McIntyre P, and Prasad K. Corticosteroids in acute bacterial meningitis (Cochrane Review). In: The Cochrane Library. Issue 2. Chichester, United Kingdom: John Wiley & Sons, Ltd; 2004.

MeSH words: Meningitis, Steroids, Treatment

Objective

To evaluate the efficacy and safety of adjuvant corticosteroids on mortality, severe hearing loss, and neurological sequelae in children and adults with acute bacterial meningitis.

Data Sources

The following databases were searched: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library issue 1, 2003); MEDLINE (1996 to January 2003); EMBASE (1974 to April 2002); and HEALTHLINE (1998 to April 2002) and Current Contents for trials published before April 1st 2002. Additional relevant trials were identified by searching references listed in published studies, searching abstracts of congresses, personal communication with researchers and experts in the field, and from literature lists of pharmaceutical companies (MSD, Organon, and Glaxo-Wellcome).

Study Selection

Published or non-published randomized controlled trials on corticosteroids as adjuvant therapy in acute bacterial meningitis. Studies were included if the participants (of any age and in any clinical condition) were treated with antibacterial agents and then randomized to

corticosteroid therapy (or placebo) of any type. Outcome measures of case fatality or hearing loss had to be recorded for inclusion.

Data Extraction

The Jadad-scale was used to appraise the quality of the studies, and all trials with 1 or 2 points for randomization (0-2 Jadad randomization scale) were included in the analysis. Two researchers independently extracted data to include all patients who were randomized or who started therapy in the intention-to-treat analysis. Data were cross checked and differences were resolved by discussion. If data was not available, then data extraction forms were sent to the principal investigator of the study in question. Data was reported as relative risk (RR) with 95% confidence interval (CI); a fixed-effect model was used based on the heterogeneity among the studies (p-value ranged from 0.6 to 1).

Main Results

From a total of 28 potentially eligible trials, 18 published peer reviewed trials involving 1853 people were selected for inclusion in this review. The analysis of the included studies was accomplished by looking at the primary outcomes (mortality, hearing loss, and neurological sequelae) and secondary outcome (adverse effects) from the perspective of all participants and from the perspective of participants subdivided into children (< 16 yo) and adults (>/= 16 yo). Further subgroup analyses regarding causative organism (H. influenzae, Neisseria meningitides, Streptococcus pneumoniae, and other pathogens) and time of administration of corticosteroids (before or after administration of first dose of antibiotics) was also performed.

With regards to all participants (adults and children): mortality was significantly reduced with corticosteroids as compared to placebo (RR 0.76; 95% CI 0.59 to 0.97); as well as severe hearing loss (RR 0.37; 95% CI 0.22 to 0.62) and long-term neurological sequelae (6-12 months after discharge) (RR 0.67; 95% CI 0.45 to 1.00). In addition, there was a non-significant reduction of short-term neurological sequelae (discharge to six weeks); and there was almost no difference in risk for adverse events (clinical evidence of GI bleed, reactive arthritis, pericarditis, herpes zoster or simplex, fungal infection or fever) with corticosteroids compared to placebo (RR 1.06; 95% CI 0.88 to 1.27).

In the subgroup analysis of children, there was little difference in mortality with corticosteroids compared to placebo (RR 0.95; 95% CI 0.65 to 1.37), but severe hearing loss was significantly reduced in both H.infleunzae meningitis and pathogens other than H. influenzae with RR (0.31; 95% CI 0.18 to 0.87) and (0.42; 95% CI 0.20 to 0.89), respectively. In addition, long-term neurological sequelae was non-significantly reduced with corticosteroids compared with placebo.

In the subgroup analysis of adults, mortality was significantly reduced with corticosteroids compared to placebo (RR .38; 95% CI 0.18 to 0.78), but long-term neurological sequelae was non-significantly reduced.

With regards to the different causative organisms of bacterial meningitis, case-fatality rates varied by organism; however, a statistically significant reduction in mortality was found with corticosteroid use against meningitis caused by Streptococcus pneumoniae (RR 0.61; 95% CI 0.30 to 0.94) as well as against all other species other than H. influenzae (RR 0.57; 95% CI 0.37 to 0.87). Although not statistically significant, corticosteroids also reduced mortality in meningococcal meningitis (RR 0.75, 95% CI 0.34 to 1.64).

It was also noted that administration of corticosteroids before or with the first dose of antibiotics was associated with a greater relative reduction in mortality (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).

Conclusion:

The authors of this review recommend the use of corticosteroids before or during the first dose of antibiotics in both childhood and adult meningitis.

Cochrane Systematic Review Author Contact
Diederic van de Beek, MD
Department of Neurology
Academic Medical Center University of Amsterdam
Amsterdam, Netherlands
Email D.vandeBeekAamc.uva.nl

Commentary: Clinical Implication

Bacterial meningitis is a worldwide disease with an unacceptably high morbidity and mortality rate ranging from 10 to 30 percent.[1] The mortality rate is about 5 percent in children beyond infancy, 25 percent in neonates, and 25 percent in adults.[2] In the United States, a 1995 study of acute care hospitals from four states showed that the incidence of this disease had decreased to as low as 0.2 cases per 100,000 population, primarily as a result of increased use of meningococcal vaccine.[3]. Elsewhere in the world, incidence rates remain high predominantly in developing countries such as West African where 213,658 cases of meningitis caused 21,830 deaths from 1996-1997.[4]

The question facing the medical community concerning treatment for bacterial meningitis is how to most effectively treat children and adults affected with this disease so as to minimize fatality and reduce associated problems such as hearing loss and neurological sequelae. Long-term complications, such as cognitive deficits, epilepsy, hydrocephalus, and hearing loss, affect about a quarter of survivors.[2] Antibiotics have been the standard of care for affected patients, but the use of adjuvant corticosteroid therapy has been questioned. It has been shown in animal models that antibiotic induced bacterial lysis is the cause of subarachnoid inflammation which subsequently leads to increased mortality and co-morbidities.[5,6] The reasoning behind corticosteroid therapy is to minimize this inflammatory process, but until the van de Beek et. al. meta-analysis, the data collected over several decades as far back as the 1960's had not been synthesized and analyzed to definitively show the effectiveness of this means of therapy.

The review summarizes a number of comparisons, and space does not permit a full discussion of these. The main questions for emergency physicians will be reviewed: what is the evidence for and against adjuvant corticosteroid therapy in children and adults presenting to the ED with bacterial meningitis. In children, there was a similar risk of mortality for the corticosteroid group and the placebo group (RR 0.95; 95% CI 0.65 to 1.37), however, the use of adjunctive corticosteroids did significantly reduce the risk of severe hearing loss in meningitis caused by H. infleunzae (RR 0.31, 95% CI 0.15 to 0.62) and pathogens other than H. influenzae by 58% (RR 0.31; 95% CI 0.18 to 0.54). This means that for every 20 children treated with adjuvant corticosteroids, severe hearing loss would be prevented in one child. With regards to adults, there were fewer studies from which to gather data, but the review concluded that adjuvant corticosteroid therapy significantly reduced mortality as compared to placebo by a relative risk of 62% (RR 0.38; 95% CI 0.18 to 0.78) though there was no demonstration of statistically significant *reduction in* long-term neurological sequelae. This translates into 1 adult life saved for every 10 adults treated with adjuvant corticosteroids. It must be noted that mortality and severe hearing were clearly defined outcomes among the included studies whereas the definition for neurological sequelae was heterogenous. Therefore, the results presented in this review regarding long-term and short-term neurological sequelae should be interpreted critically. For all participants, there was a reduction in mortality when the adjuvant corticosteroid therapy was administered before or during the first dose of antibiotics when compared to administration afterwards, and there was almost no difference in adverse events associated with corticosteroid therapy and placebo. However, again it should be noted that adverse events were heterogeneously defined among included studies, thus under ascertainment is possible.

During the review process the results of the European Dexamathosone in Adulthood Bacterial were published. There were 301 adults randomized to placebo or dexamethasone. The results were not included in this review but the treatment arm demonstrated a reduction in mortality (RR 0.48; 95% CI 0.24to 0.96)[7]

Take Home Message

Adjuvant corticosteroid therapy should be strongly considered for patients of all ages who are afflicted with bacterial meningitis. For children, although corticosteroid therapy may not

decrease mortality, it will significantly decrease the risk for severe hearing loss and reduce the risk of neurological sequelae. In adults, corticosteroid therapy does significantly reduce mortality and reduce neurological sequelae. In addition, administration of steroids) before or with first dose of parental antibiotics seems to be more effective.

References

[1] *Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS, Jr et al. Acute bacterial meningitis in adults. A review of 493 episodes. New England Journal of Medicine 1993;328(1):21-8.*

[2] Loring KE, Anderson DC, Kozak AJ, Menigitis, Encephalitis and Brian Abscess. Ch 227 in Emergency Medicine, J.E. Tinitinalli,ed, McGraw-Hill, New York, 2000, 1485-1491.

[3] Schuchat A, Robinson K, Wenger JD, et al. Bacterial meningitis in the United States in 1995. N Engl J Med. 1997;337:970-976.

[4] Center for Disease Control and Prevention: Nation Center for Infectious Diseases – Division of Bacterial and Mycotic Disease. Website: http://www.cdc.gov/ncidod/dbmd/diseaseinfo/meningococcal_t.htm

[5] Tuomanen E, Tomasz A, Hengstler B, et al. The relative role of bacterial cell wall and capsule in the induction of inflammation in pneumococcal meningitis. J Infect Dis. 1985;151:535-540.

[6] Tuomanen E, Liu H, Hengstler B, et al. The induction of meningeal inflammation by components of the pneumococcal cell wall. J Infect Dis. 1985;151:859-868.

[7] De Gans J, Van de Beek D. Dexamethasone in adults with bacterial meningitis. New England Journal of Medicine 2002;347:1549-56.

Competing interest: None declared
Funding: This review did not receive direct funding.

This article has been peer reviewed.

Correspondence to:

Dr. Barry Diner
Emory University
Department of Emergency Medicine
49 Jessie Hill Jr. Drive #120
Atlanta, GA 30303
(404) 616-5208
bdiner@emory.edu