

Critical Review Form

Meta-analysis

Corticosteroids for Acute Bacterial Meningitis:
Cochrane Database of Systematic Reviews, 2007, Issue 1,
Art. No.: CD004405. DOI: 10.1002/14651858. CD004405.pub 2

Objective: “To examine the efficacy and safety of adjuvant corticosteroid therapy in acute bacterial meningitis.” (p.2)

Methods: Studies were considered for inclusion if they were a RCT of steroids as adjuvant therapy in acute bacterial meningitis with at least one outcome measure of case-fatality or hearing loss. The authors searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and HEALTHLINE through June 2006 without any language restrictions. They also hand searched article reference lists, scientific meeting abstracts and pharmaceutical company literature lists. Finally, they also personally contacted researchers and experts in the field.

Articles were methodologically graded using Jadad’s scale by two experienced researchers not working in Infectious Disease fields. Primary outcome measures included mortality, severe hearing loss and neurological sequelae as defined by:

Severe hearing loss – bilateral hearing loss > 60 d B or requiring bilateral hearing aids.

Neurological sequelae – epilepsy (not present before meningitis), severe ataxia, or severe memory/concentration disturbance.

Short-term neurological sequelae – within 6 weeks of hospital discharge.

Long-term neurological sequelae – problems identified up to 12 months after hospital discharge.

Additionally, the authors performed several subgroup analyses: children vs. adults; causative organism; country income level; and time of steroid administration (in relationship to antibiotics). Adverse events were defined as GI bleed, reactive arthritis, pericarditis, herpes zoster, herpes simplex, or fungal infection, or fever > 38°C for over one-day.

Guide	Question	Comments
I	<i>Are the results valid?</i>	
1.	Did the review explicitly address a sensible question?	Yes, are steroids of benefit in acute bacterial meningitis? If so, how much do they benefit individual population subsets?
2.	Was the search for relevant studies details and exhaustive?	Yes, the authors explored multiple electronic and conference proceedings databases in addition to contacting research and industry experts.
3.	Were the primary studies of high methodological quality?	“The quality of included studies was high with a median Jadad score of 4” (on a scale up to 5). (p.4). However, when the <u>adult</u> (4 studies) meningitis studies included are analyzed separately, they have median Jadad score of 2.5 (and mean of 2.75) vs. pediatric studies which have a median Jadad score of 5 (and mean 3.8).
4.	Were the assessments of the included studies reproducible?	Yes. “Two experienced researchers – not working in the field of Infectious Disease - performed a blinded appraisal”. (p.3)
II.	<i>What are the results?</i>	

1.	What are the overall results of the study?	<ul style="list-style-type: none"> • 17/20 studies used dexamethasone. • Four studies included patients over age 16 years. • Nine studies administered steroids with or before the first dose of antibiotics and seven studies after antibiotics. Four studies did not state when the steroids were administered. • Various antibiotic regimens were used in studies spanning from 1963-2002. • The final analysis was based upon per-protocol (93% of subjects) rather than intention-to-treat in most cases. • Definitions of adverse events were heterogeneous and the numbers of events were recalculated for each study. <p><u>Overall:</u></p> <ul style="list-style-type: none"> ▪ Steroids decreased mortality (13.4% vs. 16.1%, NNT = 37), severe hearing loss (5.7% vs. 9.8%, NNT = 24) and long-term neurological sequelae (6.0% vs. 9.0%, NNT = 33). Short-term neurological sequelae had a non-significant trend favoring steroids. ▪ The risk of GI bleeding was not increased in patients treated with corticosteroids. <p><u>Children:</u></p> <ul style="list-style-type: none"> ▪ Overall, no effect on mortality (13.5% vs. 13.6%). ▪ Corticosteroids prevented hearing loss (6.6% vs. 11.0%, NNT = 23), although when analyzed by country income level, children in low-income countries had no benefit of steroids for hearing loss or short-term neurological sequelae. <p><u>Adults:</u></p> <ul style="list-style-type: none"> ▪ Significant mortality benefit (11.7% vs. 21.9%, NNT = 10). ▪ Steroids prevent short-term neurological sequelae (RR 0.42, 95% CI 0.22 – 0.78) <p><u>Organism:</u></p> <ul style="list-style-type: none"> ▪ Case fatality rates were higher with pneumococcal meningitis (25%) than H. influenza (9.9%) or meningitis (4.3%). ▪ Steroids protected against death in S. pneumoniae and all other non-H. influenza bacteria (including participants with negative CSF cultures). ▪ Significant heterogeneity was noted in studies comparing causative organism and country income levels and for time of steroid administration. ▪ Timing of steroids revealed no differences between before/with antibiotics (RR 0.84, 95% CI 0.70-1.02) and after antibiotics (RR 0.80, 95% CI 0.70-1.02).
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2.	How precise are the results?	The CI's are impressively narrow
3.	Were the results similar from study to study?	No, significant heterogeneity was noted in studies comparing causative organism, income level, or timing of antibiotics.
III.	<i>Will the results help me in caring for my patients?</i>	
1.	How can I best interpret the results to apply them to the care of my patients?	Except for low-income country children, steroids are beneficial in acute bacterial meningitis in all age groups regardless of causative organism without recognized adverse effects.
2.	Were all patient important outcomes considered?	No quality of life assessments were performed, nor were any pragmatic clinical trials reported.
3.	Are the benefits worth the costs and potential risks?	Yes, particularly given the devastating consequences of bacterial meningitis.

Limitations

1. Poor quality adult studies (only 4 studies with median Jadad score 2.5).
2. Poorly defined adverse effects study-to-study with possible *ascertainment bias* since you won't find what you're not looking for.
3. Significant heterogeneity between studies for causative organism, timing of steroids, and national income level suggesting results ought not to have been combined into meta-analysis for these subgroup analyses.
4. Authors of Cochrane review also the investigators in one of the included trials opening possibility of *inclusion bias* or *reporting bias*.

Bottom Line

In adults, steroids in acute bacterial meningitis save lives (NNT=10) and prevent long-term neurological sequelae whether administered before or after antibiotics. Except for low-income countries, steroids in children reduced hearing loss (NNT=23) regardless of the causative organism. Based upon the proposed mechanism of action, the authors advocate giving steroids before or with antibiotics. Future research should identify factors restricting benefit in poorer nations (Late presentation? Inappropriate antibiotics? HIV? Malnutrition?).