

Dexamethasone improved disability in acute bacterial meningitis

de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med*. 2002;347:1549-56.

QUESTION

In patients with acute bacterial meningitis, does adjunctive treatment with dexamethasone improve outcomes more than placebo?

DESIGN

Randomized (allocation concealed*), blinded {clinicians, patients, data collectors, outcome assessors, data analysts, data monitoring committee, and manuscript writers}†, * placebo-controlled trial with 8-week follow-up.

SETTING

52 centers in the Netherlands, Belgium, Germany, Denmark, and Austria.

PATIENTS

301 patients (mean age 45 y, 56% men) who had suspected meningitis in combination with cloudy cerebrospinal fluid, bacteria in cerebrospinal fluid on Gram staining, or cerebrospinal fluid leukocyte count > 1000/mm³. Exclusion criteria included hypersensitivity to β -lactam antibiotics or corticosteroids; cerebrospinal shunt; antibiotics in the past 48 hours; and history of active tuberculosis or fungal infection, head trauma, neurosurgery, or peptic ulcer disease. All patients were included in the analysis.

INTERVENTION

Patients were allocated to intravenous dexamethasone, 10 mg every 6 hours for 4 days ($n = 157$), or placebo ($n = 144$). All patients received parenteral antibiotics.

MAIN OUTCOME MEASURES

The primary outcome was score on the Glasgow Outcome Scale (score of 5 = favorable outcome [mild or no disability], and 1 to 4 = unfavorable outcome [range, death to moderate disability]). Secondary outcomes were death, focal neurologic abnormalities, hearing loss, gastrointestinal bleeding, fungal infection, herpes zoster, and hyperglycemia.

MAIN RESULTS

Analysis was by intention to treat. Fewer patients who received dexamethasone had an unfavorable outcome than did patients who

received placebo (Table). Also, fewer patients in the dexamethasone group died than in the placebo group (Table). The groups did not differ for any other secondary outcomes. Dexamethasone and placebo groups did not differ for adverse effects.

CONCLUSION

In patients with acute bacterial meningitis, adjunctive treatment with dexamethasone was more effective than placebo in improving disability and reducing death.

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*See Glossary.

†Information provided by author.

Dexamethasone vs placebo for bacterial meningitis at 8 weeks‡

Outcomes	Dexamethasone	Placebo	RRR (95% CI)	NNT (CI)
Unfavorable outcome	15%	25%	41% (7 to 63)	10 (5 to 73)
Death	7%	15%	52% (5 to 75)	13 (7 to 163)

‡Unfavorable outcome = score of 1 to 4 on the Glasgow Outcome Scale: death, vegetative state, severe disability, or moderate disability. Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

Before the study of de Gans and van de Beek, only 3 randomized trials evaluated dexamethasone in adults with bacterial meningitis. The first (1), done in Egypt, showed a survival benefit in a subset of adults with pneumococcal meningitis. However, 60% of the patients were comatose at entry, and antibiotics were administered intramuscularly. The second study (2), which showed a trend to better outcomes with dexamethasone, enrolled only 60 patients of a planned 256, and dexamethasone could be administered up to 3 hours after the first dose of antibiotics. The third study (3), done in India, enrolled only 30 patients, and dexamethasone was started after antibiotics.

The study by de Gans and van de Beek addresses the limitations of the previous studies. The sample size was 301, and dexamethasone was given before or at the same time as the first antibiotic dose. The benefit of dexamethasone was largely restricted to those with pneumococcal meningitis.

The study was done principally in the Netherlands, where strains of *Streptococcus pneumoniae* with reduced susceptibility to penicillin are rare. In centers where reduced susceptibility of *S. pneumoniae* to a third-generation cephalosporin exists, it is common for vancomycin to be used with a third-generation cephalosporin for empirical treatment of bacterial meningitis pending culture and susceptibility results.

However, evidence from animal studies shows that dexamethasone reduces penetration of vancomycin into infected cerebrospinal fluid (4).

Thus, there is concern that use of dexamethasone with vancomycin could compromise the efficacy of vancomycin in third-generation

cephalosporin-resistant strains (5). However, the vast majority of cases of bacterial meningitis are not caused by *S. pneumoniae* with reduced susceptibility to third-generation cephalosporins. Thus, even if adjunctive dexamethasone was deleterious in patients with meningitis caused by *S. pneumoniae* resistant to third-generation cephalosporins (which has not been established), many more patients would benefit from dexamethasone. Dexamethasone should now be considered the standard of care, provided that it is initiated before or at the same time as antibiotics.

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