SELECTED ARTICLES

Dexamethasone in acute bacterial meningitis

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Clinical question
In adult patients with acute bacterial meningitis, does adjuvant treatment with corticosteroids increase the chance of a favourable neurologic outcome?

Article chosen
de Gans J, van de Beek D; European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002;347(20):1549-56.

Objective
To determine whether the concurrent administration of dexamethasone with appropriate antibiotics improves the neurologic outcomes in adults with acute bacterial meningitis when compared to antibiotics alone.

Background
The frequency of neurologic sequelae among adult survivors of acute bacterial meningitis is high, especially in patients with pneumococcal meningitis. Evidence from animal models indicates that antibiotic-induced bacterial lysis causes subarachnoid inflammation which may contribute to an unfavorable outcome.[1] Corticosteroids attenuate this inflammatory response, and controlled trials of adjuvant corticosteroid use in children with acute bacterial meningitis have shown benefit for some patients.[2] These trials suggest that dexamethasone decreases severe hearing loss in children with *Haemophilus influenzae* type b meningitis. One study suggests that dexamethasone improves survival in children and adults with pneumococcal meningitis when given prior to or concurrent with antibiotics.[3,4]

Population studied
Consecutive patients, 17 years and older, presenting to 50 participating centres in the Netherlands, Germany, Austria and Denmark with suspected acute bacterial meningitis were evaluated. Eligibility criteria are summarized in Table 1.

Study design
This prospective, double-blind, multicentre, randomized control trial compared dexamethasone to placebo in adults with cerebrospinal fluid (CSF) findings of acute bacterial meningitis. Dexamethasone (10 mg by intravenous [IV]) or placebo was administered 0 to 20 minutes before the first dose of empiric antibiotic therapy and continued every 6 hours for 4 days. Initial antibiotic therapy was based on local guidelines and susceptibility data and altered according to the results of Gram's staining and culture of the CSF.

Table 1. Study eligibility criteria

Inclusion criteria	Exclusion criteria
• Age 17 or older • Clinically suspected meningits with at least one of the following: 1. cloudy cerebrospinal fluid (CSF) or 2. bacteria in CSF or Gram's stain or 3. CSF leukocyte count >100/mm^3	• History of hypersensitivity to β-lactam antibiotics or corticosteroids • Pregnant • CSF shunt • Oral or parenteral antibiotic treatment within the previous 48 hours • History of active tuberculosis or fungal infection • History of recent head trauma, neurosurgery or peptic ulcer disease • Current participation in another clinical trial

Outcomes measured

The primary outcome measured was favourable neurologic outcome at 8 weeks. "Favourable" outcome was defined as a Glasgow Outcome Scale (GOS) score of 5, (mild or no disability allowing the patient to return to work or school). Scores of 1 (death), 2 (vegetative state), 3 (severe disability) or 4 (moderate disability allowing independent living but no return to work or school) were considered "unfavourable" outcomes. Secondary outcomes measured were death, focal neurological abnormalities, hearing loss, gastrointestinal bleeding, fungal infection, herpes zoster and hyperglycemia. Subgroup analysis was performed comparing patients according to infectious etiology.

Results

301 patients were randomized to dexamethasone (n = 157) or placebo (n = 144), and 11 patients in each arm were withdrawn from the study. Overall, 4 patients failed to meet exclusion criteria (3 in dexamethasone group [dex], 1 in the placebo group), 4 did not receive the study medication for a full 4 days (2 dex, 2 placebo), 8 suffered clinical deterioration that led to off-protocol corticosteroid use (2 dex, 6 placebo), 5 suffered unspecified adverse events (4 dex, 1 placebo) and 1 patient in the placebo group withdrew consent. An intention-to-treat analysis was carried out on all 301 patients, including the 22 early withdrawals, 7 patients lost to follow-up (3 dex) and 32 who died (11 dex). Baseline patient characteristics were similar between groups. The main statistically significant outcome difference between the two groups was that the patients treated with dexamethasone had fewer unfavourable neurologic outcomes (15% v. 25%; absolute risk reduction [ARR] = 10; number needed to treat [NNT] 10; p = 0.03) and lower mortality (7% v. 15%; ARR = 8; NNT 13.3; p = 0.04). Other differences included lower rates of impaired consciousness (11 v. 25%; p = 0.002), fewer seizures (5% v. 12%; p = 0.04) and a lower prevalence of cardiorespiratory failure (10% v. 20%; p = 0.02). These dexamethasone benefits were most often seen in sicker patients, and virtually all of the difference in treatment was related to patients with pneumococcal meningitis (Table 2). Dexamethasone treatment did not provide significant benefit for patients with meningitis due to *Neisseria meningitides* or other bacteria, or those who had sterile CSF. Predictors of an unfavourable outcome were coma on admission, hypotension and meningitis due to *Streptococcus pneumoniae*.

Study conclusions

Early treatment with dexamethasone reduces the risk of unfavourable outcomes and death in adults with bacterial meningitis. The benefit is most apparent in patients with pneumococcal meningitis. No harm was demonstrated in those with other types of bacterial meningitis. Dexamethasone did not impact the prevalence of neurologic sequelae; however, given the improvements in survival a lack of difference may indicate benefit. The authors recommend unequivocal dexamethasone for all patients with CSF findings consistent with bacterial meningitis. They also suggest all patients with suspected meningitis who require computed tomography (CT) of the head prior to lumbar puncture should receive dexamethasone with antibiotics prior to undergoing CT, a practice not tested in the study.

Commentary

Rapid antimicrobial therapy is of undisputed benefit in the treatment of bacterial meningitis. Studies of dexamethasone therapy have yielded conflicting results, and most of the work has been done in children. A meta-analysis of pediatric studies from 1988–1996 conclude that dexamethasone, given early, decreased hearing loss related to *H. influenzae* type b and was neurologically protective in children with pneumococcal meningitis.[2]

This study is the first methodologically sound randomized trial to look at whether dexamethasone adjuvant therapy improves recovery in adults with bacterial meningitis. Using the validated GOS, the authors showed a significant reduction in unfavourable neurologic outcomes in the dexamethasone group. Not only were there fewer deaths (11 v. 21), but the number of patients with favourable outcome scores was also significantly higher: 134 (85%) v. 108 (75%). The study data also suggested that dexamethasone reduced mortality without increasing morbidity. A closer analysis reveals that treatment benefit was limited to patients with pneumococcal meningitis.

Unfortunately, emergency physicians do not have culture results available early enough to drive selective treatment. Based on the results of this study and the minimal harm associated with this therapy, it is reasonable to recommend initiating dexamethasone in conjunction with early antibiotics in patients with suspected meningitis. After the responsible pathogen is identified, the treating physician can determine whether or not to continue treatment.

It is unclear whether the disproportionate benefit seen in patients with pneumococcal meningitis is because this organism produces a more intense CNS inflammatory response or because benefit is easier to demonstrate in sicker patients (in this study, the sickest patients tended to be in the pneumococcal group).

Some previous studies required dexamethasone administration up to 20 minutes prior to starting antibiotics, al-

though work by Thomas and colleagues suggests this practice provides no benefit.[5] The de Gans and coworkers' study protocol described here allowed simultaneous administration of dexamethasone and antibiotics, which is logical given the importance of early antibiotic treatment. At least 3 other randomized controlled trials[3,5,6] have given dexamethasone before, during or shortly after antibiotics in patients with bacterial meningitis, providing further support for this practice, and the resulting meta-analysis, using mortality as the primary outcome, favours the use of steroids (Fig. 1).

An important concern with the de Gans and coworkers' study is that it primarily involved amoxicillin, which is not a first-line agent for adult meningitis in North America, where penicillin-resistant pneumococcus (PRP) is increasingly prevalent (representing up to 20% of isolates in Canada).[7] A particular problem may arise in settings where empiric treatment strategies directed at PRP recommend vancomycin. Vancomycin probably requires CSF inflammation to cross the blood–brain barrier, and experimental models have shown that attenuating the inflammatory response with dexamethasone reduces vancomycin penetration and bactericidal activity in the CSF.[8] Future studies will need to determine whether vancomycin plus dexamethasone or vancomycin alone will provide better outcomes.

Given the absence of serious adverse effects, and potentially large benefits, routine use of dexamethasone before or with the first dose of antibiotics seems reasonable in most adults with suspected bacterial meningitis. Dexamethasone has no benefit for patients who have already received antimicrobial therapy and should be discontinued if cultures reveal an organism other than *S. pneumoniae*. Dexamethasone should also be withheld or discontinued in patients with septic shock because corticosteroid therapy may be detrimental to those with adequate adrenal reserve.[9,10] In patients requiring vancomycin, no good data exists and dexamethasone should be continued at the treat-

Table 2. Outcomes eight weeks after admission, according to culture results*

Outcome and culture results	Dexamethasone group, %	Placebo group, %	Relative risk (and 95% CI)	*p* value	ARR	NNT
Unfavourable outcome						
All patients	15	25	0.59 (0.37–0.94)	0.03	10%	10
Streptococcus pneumoniae	26	52	0.50 (0.30–0.83)	0.006	26%	4
Neisseria meningitidis	8	11	0.75 (0.21–2.63)	0.74	–	–
Other bacteria	17	6	2.83 (0.29–27.8)	0.55	–	–
Negative bacterial culture†	5	13	0.41 (0.08–2.06)	0.40	–	–
Death						
All Patients	7	15	0.48 (0.24–0.96)	0.04	8%	13.3
S. pneumoniae	14	34	0.41 (0.19–0.86)	0.02	20%	5
N. meningitidis	4	2	1.88 (0.76–20.1)	1.00	–	–
Other bacteria	8	6	1.42 (0.10–20.5)	1.00	–	–
Negative bacterial culture	–	7	–	0.20	–	–
Focal neurologic abnormalities						
All Patients	13	20	0.62 (0.36–1.09)	0.13	–	–
S. pneumoniae	22	33	0.67 (0.33–1.37)	0.32	–	–
N. meningitidis	7	11	0.57 (0.15–2.26)	0.48	–	–
Other bacteria	27	19	1.45 (0.36–5.92)	0.66	–	–
Negative bacterial culture	3	19	0.14 (0.02–1.13)	0.07	–	–
Hearing loss						
All Patients	9	12	0.77 (0.38–1.58)	0.54	–	–
S. pneumoniae	14	21	0.67 (0.25–1.69)	0.55	–	–
N. meningitidis	7	11	0.57 (0.15–2.26)	0.48	–	–
Other bacteria	18	6	2.91 (0.30–28.3)	0.55	–	–
Negative bacterial culture	3	4	0.70 (0.05–10.7)	1.00	–	–

*The analyses of unfavourable outcome and death included all patients and were performed with a last-observation-carried forward procedure. The analyses of neurologic abnormalities and hearing loss included all surviving patients who underwent neurologic examination at eight weeks.
†Included in this category are two patients in whom cerebrospinal fluid culture was not performed.
CI = confidence interval; ARR = absolute risk reduction; NNT = number needed to treat.
Adapted with permission from de Gans J, van de Beek D; European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002;347(20):1549-56.

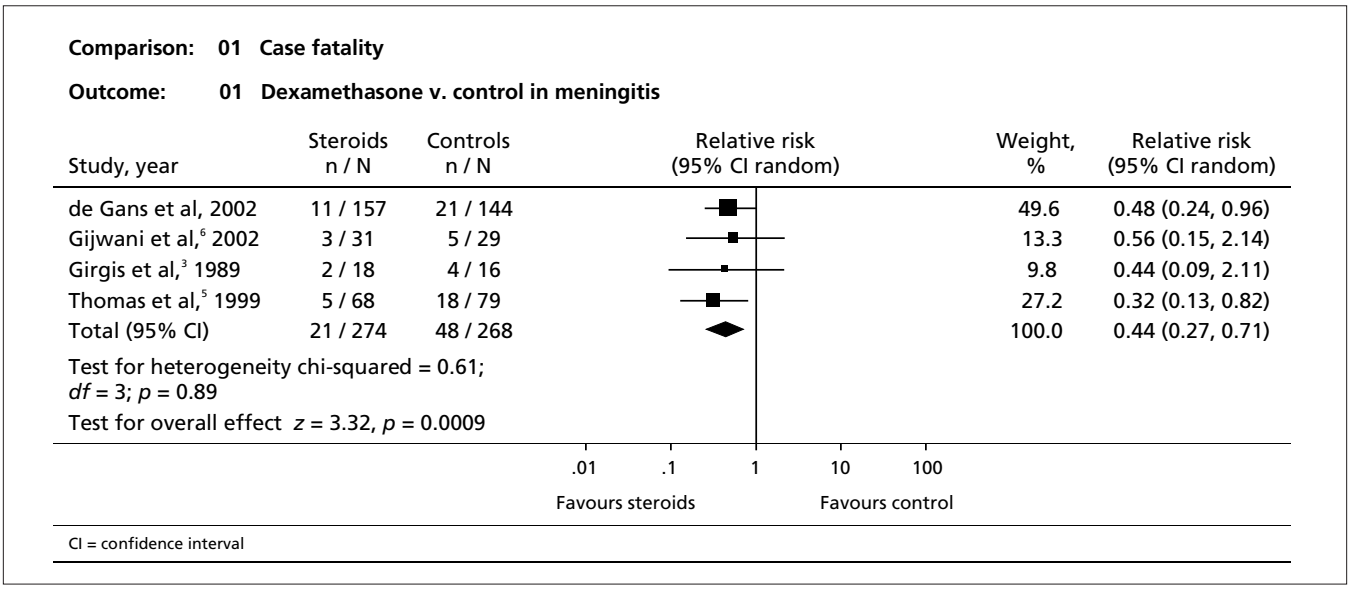

Fig. 1. Effect of corticosteroids on mortality.

ing physician's discretion and with close monitoring of the patient for signs of treatment failure.

Competing interests: None declared.

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