Critical Review Form
Therapy

Dexamethasone in adults with bacterial meningitis
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Objective: **To determine whether adjunctive dexamethasone treatment improves the outcome in adults with bacterial meningitis.**

Methods:

Patients aged 17 years or older referred to research centers in the Netherlands, Belgium, Germany, Denmark or Austria between 1993-2001 were eligible if they had suspected meningitis and cloudy CSF or positive Gram's stain, or CSF WBC >1000 cells/mm^3. Exclusion criteria included hypersensitivity to β-lactams or corticosteroids, pregnancy, cerebrospinal shunt, active TB, fungal infections, antimicrobials within preceding 48°, recent head trauma, neurosurgery, or peptic ulcer disease.

Dexamethasone 10mg IV every 6° for 4 days was administered to the treatment group while the control group received identical appearing placebo. Both groups received the medication 15-minutes before antibiotics until a 1997 data monitoring interim analysis recommended allowing administration of the antibiotic with steroids to enhance enrollment. The interim analysis also permitted local investigators to deviate from the amoxicillin based protocol the Dutch investigators had originally devised based upon their local resistance patterns.

The primary outcome measure was score on the Glasgow Outcome Scale eight weeks after randomization as assessed by the patient's physician (1=death, 5=mild or no disability). The Glasgow Outcome Scale is a well-validated tool with good inter-observer agreement. Secondary outcome measures included death, focal neurological abnormalities (aphasia, cranial nerve palsy, ataxia, monoparesis, hemiparesis), hearing loss, or GI bleed, herpes, fungal infection, or hyperglycemia >144 mg/dL.

Sample size was calculated at 80% power with two-sided α=0.05 to detect a 15% difference in the primary outcome and required 150 patients per group. Logistic regression analysis of baseline variables (gender, age, symptom duration, seizures, coma, CSF WBC, admission hypotension) was performed to identify whether steroid therapy was an independent predictor of the primary outcome.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes, "with the use of a computer-generated list of random numbers in blocks of six" (p.1550)
2.	Was randomization concealed (blinded)?	Yes, until the 8-week evaluation of the last enrolled patient.
3.	Were patients analyzed in the groups to which they were randomized?	Yes, "the analysis of outcomes was performed on an intention-to-treat basis with the use of a last-observation carried forward procedure". (p.1550)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Table I (p.1552) notes similar prognostic baseline characteristics including age, CSF findings, pre-admission symptom duration, and initial clinical appearance.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No. "The code was not broken until the last patient to be enrolled had completed eight weeks of follow-up". (p.1550)
2.	Were clinicians aware of group allocation?	No.
3.	Were outcome assessors aware of group allocation?	No, not until the code was broken eight weeks after the last patient was enrolled.
4.	Was follow-up complete?	Seven patients were lost to follow-up (3 in steroid group). Overall, 97% (262/269) had eight week neurological examination.
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	• Classic signs/symptoms of meningitis were present in a majority of patients: headache 94%, neck stiffness 94%, fever 91%. • CSF cultures were positive in 78%. Among those with sterile CSF, 66% had at least one suspicious CSF finding (glucose <34mg/dL, protein >220mg/dL, CSF WBC >2000 cells/mm^3, CSF neutrophil >1180 cells/mm^3). • Unfavorable outcome favored dexamethasone with ARR 10% NNT=10 (95% CI 5-73), p<.03 (Table 2 p.1553), a benefit which persisted in logistic regression analysis accounting for other significant predictors of unfavorable outcome (coma on admission, hypotension, S pneumoniae causative organism). • Among those with S pneumoniae meningitis the ARR 26% NNT =4 to prevent one unfavorable outcome. • Among patients with N meningitides adjuvant dexamethasone did not provide a significant benefit although only nine unfavorable events occurred in this subgroup (compared with 41 in S pneumonia). • For death among all cases ARR = 8% NNT = 13, but for pneumococcal meningitis mortality decreased from 34% to 14% (ARR 20%, NNT = 5). • The lower mortality rate in the dexamethasone group did not result in an increased rate of severe neurological sequelae (Table 3, p,1554) • Adjuvant dexamethasone did not have a significant beneficial effect on neurologic sequelae including hearing loss.

		• Treatment with dexamethasone did not result in an increased risk of adverse events. • The initial antibiotic regimen provided adequate coverage in 97% of dexamethasone group and 98% of control group.

2.	How precise was the estimate of the treatment effect?	The CI's are sufficiently narrow.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes, although clear-cut adult meningitis is an increasingly rare entity in 2008. Atypical presentation seems more common than text book presentations.
2.	Were all clinically important outcomes considered?	Yes, except for patient/family quality of life (QOL) assessment.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes, if a cheap readily available therapy can reduce devastating results of bacterial meningitis without adverse effects.

Limitations

1. Potential *selection* and *co-intervention bias* of rigidly controlled study setting. However, the mortality rates of the placebo group did not differ from the Netherland's national data so reassured that these biases are less likely.
2. Protocol use of amoxicillin atypical for 2008 U.S. medicine in which Ceftriaxone and Vancomycin are standard of care. Faced with conflicting evidence in children vs. adults regarding the effects of dexamethasone on Vancomycin CSF penetration, the authors recommend following post-steroid Vancomycin patients very closely for evidence of treatment failure.
3. No analysis of steroid before vs. steroids with antibiotics.
4. No long-term follow-up data (beyond eight weeks)
5. No patient QOL assessment.

Bottom Line

Dexamethasone (10mg IV every 6-hours for 4 days) 20 minutes before or with antibiotics independently reduces bacterial meningitis related mortality (NNT=13) without increasing the number with an unfavorable neurological outcome. The benefit of dexamethasone are most pronounced with S pneumonia meningitis (NNT = 5 to prevent one-death). No significant increase in adverse events was noted with dexamethasone therapy.