Critical Review Form
Therapy

Trial of Dexamethasone Treatment for Severe Bacterial Meningitis in Adults, *Intensive Care Med* 1999; 25: 475-480

Objective: **To assess the clinical benefit of an early dexamethasone adjunctive therapy in the management of severe bacterial meningitis in adults. (p.476)**

Methods: **Adults aged 18-79 years admitted to one of 21 French & Swiss ED's or ICU's with clinical signs of bacterial meningitis were eligible. Clinical signs included fever >38°C, cloudy CSF or elevated CSF WBC with > 50% PMN's, "as in whom the first chosen empiric therapy was an aminopenicillin". (p.476) Exclusion criteria included antibiotic > 3 days prior, septic shock, post-traumatic or post-surgical meningitis, brain abscess, prior β-lactam or steroid hypersensitivity, or organ transplants.**

The investigators performed a placebo-controlled, randomized, double-blinded study using dexamethasone 10mg IV every 6-hours for 3-days as the treatment arm. The authors fail to detail how allocation occurred. The initial antibiotic therapy was IV amoxicillin (150-300 mg/kg per day). The primary outcome measure was 30-day cure as measured by Glasgow Coma Scale. Simplified Acute Physiologic Score (SAPS-1) severity of disease, and Mini-mental test as judged by an expert committee blinded to subject groups. Mild sequelae were defined as sensory deficit, ataxia, or memory deficit not requiring hospitalization. Severe sequelae were motor or cognitive deficits requiring hospitalization.

The sample size was calculated based upon a 15% response rate favoring dexamethasone with 90% power and one-sided $\alpha = 0.05$ requiring 256 total subjects. Anticipating difficulty recruiting this number of subjects before the study even began, investigators planned *a priori* to use a triangular test to perform multiple interim analyses for every 20 patients recruited in order to detect a significant difference between dexamethasone and placebo before 256 patients needed to be recruited.

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, although the authors fail to detail how. Therefore, they lose a point on the Jadad scale.
2.	Was randomization concealed (blinded)?	"The complete similarity of the therapeutic units, placebo or Dxm, rendered the trial blind for the patients, nurses, pharmacists, and physicians. The code was only broken by the methodologist at the end of the follow-up period of successive groups of 20 patients". (p.476)
3.	Were patients analyzed in the groups to which they were randomized?	No. Intention-to-treat analysis is reported. In fact, excluded subjects were <u>not</u> analyzed. (p.477)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. Table 1 (p.478) illustrates inadequate randomization in that Dxm subjects were significantly younger (40 vs. 50 years) and healthier (SAPS-1 10.5 vs. 14.3, p=0.018) at baseline. Given the lack of description about allocation concealment in conjunction with this inadequate randomization one wonders whether disbelieving clinicians biased results by awareness of allocation assignment and placement of sicker patients in the placebo arm.
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.
2.	Were clinicians aware of group allocation?	No.

3.	Were outcome assessors aware of group allocation?	No.
4.	Was follow-up complete?	No CONSORT diagram is provided. After exclusion of two subjects by the expert committee, no loss to follow-up is reported.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• Only 60 subjects were recruited. • S. pneumoniae accounted for 52% of cases, N. meningitides 30%. • Mean delay between first meningitis symptom and LP was 31-hours in both groups, while the delay from LP to antibiotics was similar (78' in placebo groups vs. 66' in Dxm, p=0.569). • The first dose of Dxm was 97 ± 78 minutes after the first dose of antibiotics. • 30-day cure was estimated at 52% for placebo vs. 74% for Dxm, though investigators were forced to halt the study prematurely by the expert committee. Review of Table 2 (p.478) reveals a trend favoring Dxm for 30-day mortality, severe or mild neurologic sequelae, and overall cure without neurological sequelae. • Five adverse events were documented (2-Dxm, 3-placebo) although the Dxm side effects (pain at injection site, transient hyperglycemia) seemed milder than the placebo SE (two hemorrhaging ulcers, one zoster).
2.	How precise was the estimate of the treatment effect?	No CI are provided
III.	**How can I apply the results to patient care (answer the questions posed**	

	below)?	
1.	Were the study patients similar to my patient?	French & Swiss ED patients, but uncertain about demographics or baseline prognostic factors.
2.	Were all clinically important outcomes considered?	No assessment of recovery-speed, long-term outcomes, or QOL.
3.	Are the likely treatment benefits worth the potential harm and costs?	Not based upon the current study.

Limitations

1. Inadequate description of allocation concealment and imperfect distribution of prognostic baseline. Were enrolling investigators aware of allocation and did they preferentially place younger, less ill patients in the Dxm arm?

2. Under-powered and halted prematurely with definite possibility of Type II error given the reported trends favoring Dxm.

3. Inappropriate use of single-tailed p-value in power calculation. Steroids could have easily caused harm or benefit so 2-tailed p-value should have been used.

4. Use of amoxicillin first-line is not representative of 2008 meningitis management in the US.

5. No CONSORT diagram provided.

6. No intention-to-treat analysis performed.

7. Steroids administered (average 100 minutes) after antibiotics which contradicts the purported mechanism of action in reducing meningitis related morbidity and mortality.

Bottom Line:

Vastly underpowered, insufficiently randomized, prematurely halted French & Swiss trial which still suggests a benefit of dexamethasone in adult bacterial meningitis patients presenting to the ED when administered 1.5 hours after antibiotics. This paper has too many flaws to be useful in isolation, but might be useful in aggregate as part of a systematic review.