Critical Review Form
Therapy

Dexamethasone in Vietnamese Adolescents and Adults with Bacterial Meningitis, *NEJM* 2007; 357: 2431-40

Objective: **To determine whether adjunctive dexamethasone improves the outcome in adolescents and adults with bacterial meningitis.** (p.2432)

Methods: **From Nov 1996 – June 2005 patients older than age 14 years who presented to Ho Chi Minh City Hospital for Tropical Diseases with suspected bacterial meningitis were considered for inclusion. Clinical evidence of meningitis included nuchal rigidity, elevated CSF protein and CSF WBC, and at least one of the following: positive CSF Gram's stain or acridine orange stain, positive latex agglutination test, positive blood or CSF cultures or cloudy CSF with > 60% neutrophils and CSF: blood glucose ratio <50%. Exclusion included first trimester pregnancy, active pulmonary TB, corticosteroid contraindications, or failure to consent. "Prior treatment with antibiotics was not a criterion for exclusion".**

> **Definite meningitis – bacteria cultured from the CSF or blood or detected on CSF staining.**
> **Probable meningitis – bacteria neither detected nor cultured but without any alternative diagnosis.**

Patients were randomized via a computer-generated sequence in blocks of 100 patients to receive either placebo or dexamethasone (Dxm) 0.4mg/kg IV Q12 hours for 4-days given 15-minutes before the administration of antibiotics. All patients were treated with ceftriaxone (2 gm IV every 12 hours for 10-14 days), although this could be altered at the discretion of the attending physician. All patients were tested for HIV.

The primary outcome was 1-month mortality. Secondary outcomes were death at 6-months, disability at 1- and 6-months, or hearing loss at 1- and 6-months. Disability was assessed with use of the modified Rankin with a scale of 0 = full recovery (no symptoms), 1 or 2 = mild sequelae (symptoms that may impede lifestyle but do not impede independent living), 3 – 5 = severe disability. Deafness was defined as failure to register sounds of 80 dB or less.

With 150 definite bacterial meningitis patients in each group, the study had 80% power to detect a mortality reduction from 25% to 12.5% with (two-tailed) $\alpha = 0.05$. *A priori* subgroup analysis was planned for definite vs. probable bacterial meningitis, gender, age >50 years, prior antibiotic exposure and causative organism. A multivariate Cox regression model was built to identify independent predictors of death during the first month.

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, via a "computer-generated sequence of random numbers" to assign treatment in blocks of 100 patients." (p.2432)
2.	Was randomization concealed (blinded)?	Yes. "The attending physician instructed a nurse to open a numbered envelope containing instructions to give either active drug or placebo. To maintain blinding, a separate team of nurses, who were not otherwise involved in the care of the study patients, opened the envelopes and give the injections".
3.	Were patients analyzed in the groups to which they were randomized?	Intention-to-treat and per-protocol analyses are both reported.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes, as illustrated in Table 1 (p.2434) the Dxm and placebo groups were similar risk populations.
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?	"All patients, the physicians who enrolled them, and study investigators were unaware of the treatment assignments until the last patient had completed follow-up". (p.2432)
2.	Were clinicians aware of group allocation?	No - see above
3.	Were outcome assessors aware of group allocation?	No - see above
4.	Was follow-up complete?	As noted in the CONSORT diagram (Fig 1, p.2433) 6/435 were lost to follow-up (2 in Dxm, 4 in placebo group).

II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect? • No life-threatening adverse events were reported in either group. • Multivariate analysis revealed several independent predictors of 1-month mortality in definite bacterial meningitis = older age, lower GCS, hemiparesis, any bacteria other than S. suis, and assignment to the placebo group (p.2439) • Treatment with Dxm in probable bacterial meningitis was an independent predictor (with an interaction) of 1-month mortality.	• Definite meningitis occurred in 69%, probable meningitis in 28%, and an alternative diagnosis in 2.8% (including TB in nine subjects - 4 Dxm and 5 placebo). • Streptococcus suis was the most frequent pathogen (26%) followed by S. pneumoniae (~ 12.5%), and N. meningitides (4.5%). • Gram stain was positive in 6% when cultures were negative. • Except for pseudomas, S. aureus, and E-coli (one-case each) and 9% of S. pneumoniae isolates, all bacterial isolates were susceptible to ceftriaxone. • Among all patients there was a trend favoring Dxm for 30-day mortality (10% vs. 12.4% mortality, RR 0.79 95% CI 0.45-1.39). • When analyzed as <u>definite bacterial meningitis</u>, Dxm improved 30-day survival (RR 0.43 95% CI 0.20-0.94, NNT=13 (95% CI 8-90), p=0.033), however steroids may have been harmful for probable bacterial meningitis (RR 2.65, 95% CI 0.73-9.63, p=0.139). • 65% of subjects had received previous antibiotics! The authors offer no details about time after antibiotics before Dxm was received, but previous antibiotics did not increase or decrease 1-month mortality. • Among patients with GCS <15 the RR favored Dxm (0.63 95% CI 0.33-1.19). • Steroids decreased one-month mortality from 14% to 6.3% for definite meningitis but <u>increased</u> mortality for probable bacterial meningitis from 3.7% to 14.5%.

		• Among those with definite bacterial meningitis, Dxm decreased death or severe disability at 6-months from 27.4% to 17.4% (OR 0.56, 95% CI 0.32-0.98, NNT=10). • Steroids decreased hearing loss in definite meningitis from 21.8% to 9.6% (p=0.008).

2.	How precise was the estimate of the treatment effect?	Narrow CI described above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	No – Vietnamese patients in socialized medicine setting with limited access to health care and high prevalence of TB and HIV.
2.	Were all clinically important outcomes considered?	No assessment of QOL, though one would presume Rankin Scale would correlate well with this.
3.	Are the likely treatment benefits worth the potential harm and costs?	No, not in this population, unless one can delineate a strategy in the ED to differentiate definite from probable meningitis.

Limitations

1. Limited external validity to US populations with high prevalence of TB (and HIV) and predominant organism *S. suis*.

2. Over 65% of subjects had previously received antibiotics negating the hypothetical benefit of steroids, although pre-treatment was not an independent prediction of failure on multivariable analysis.

3. No sensitivity analysis of results with eleven TB meningitis patients, 6 of which (all treated with Dxm, accounting for half of Dxm-related deaths) died.

Bottom Line

Vietnamese adult patients previously treated with antibiotics for suspected bacterial meningitis only benefit from dexamethasone therapy if bacterial meningitis is subsequently proven by gram stain or culture-positive results. Treating other suspected meningitis patients may be harmful, probably because of the prevalence of TB meningitis. Before recommending routine steroids in such patients clinicians need to be able to reliably distinguish definite from probable meningitis.