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Dana Siegel
Wayne State University, dsiegel@med.wayne.edu

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Early dexamethasone administration in adults with suspected meningitis lowers morbidity and mortality

DANA SIEGEL, Wayne State University School of Medicine, dsiegel@med.wayne.edu

ABSTRACT A critical appraisal and clinical application of de Gans J, van de Beek D, Investigators EDiABMS. Dexamethasone in adults with bacterial meningitis. *New Eng J Med*. 2002;347(20):1549-1556. doi: 10.1056/NEJMoa021334.

Keywords: *bacterial meningitis, dexamethasone, treatment of meningitis*

Clinical Context

This patient is a 30-year-old African American woman with no significant past medical history who presented to the emergency room with headache, nuchal rigidity, photophobia and fever. She had no recent sick contacts. However, the patient lives with her son and husband in an apartment building with many college students. Her husband, who denied having any symptoms himself, brought the patient to the emergency department due to subjective high fever. Her vaccination status was unknown.

Upon presentation to the emergency room, patient's temperature was 104.0° Fahrenheit. She was immediately started on empiric treatment for bacterial meningitis, which included 10mg IV dexamethasone, 2g IV ceftriaxone, 15mg/kg IV vancomycin, and 10mg/kg IV acyclovir. Although this is the standard treatment regimen for ages 18-50 years with suspected meningitis at the hospital in which the patient presented, she was hesitant to accept the dexamethasone treatment due to reported adverse effects of corticosteroids and subjective futility. After appropriate counseling with an explanation of the risks and benefits, the patient agreed to receive the dexamethasone therapy. An image-guided lumbar puncture of cerebrospinal fluid (CSF) for culture studies and gram stain was then obtained.

Gram stain revealed gram-negative diplococci later speciated to be *Neisseria meningitidis* susceptible to penicillin; therefore, patient was continued on 2g IV ceftriaxone every 12 hours for seven days while acyclovir and vancomycin were immediately discontinued. The treatment team questioned whether dexamethasone should be discontinued as well, but ultimately decided to continue until hospital day four per hospital protocol. The patient wished to limit the amount of steroid taken to avoid adverse effects, but also wanted to avoid any neurologic complications from the infection. Over the following days her fever, photophobia, neck stiffness, and headache continued to improve. She was discharged on day seven of her hospital admission with no immediate sequelae.

Clinical Question

Does dexamethasone administration improve morbidity and mortality outcomes in patients with suspected bacterial meningitis?

DANA SIEGEL, B.S., *is a medical student at Wayne State University School of Medicine.*

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Research Article

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Related Literature

Literature review began with a search on UpToDate® for treatment in adults with suspected bacterial meningitis. Keywords included "bacterial meningitis" and "treatment," yielding six relevant resources. An additional search on UpToDate® was then performed, which included complications of bacterial meningitis and neurological sequelae providing four additional resources.

Subsequent investigation included searching PubMed regarding the use of dexamethasone in patients with acute bacterial meningitis. Keywords included "bacterial meningitis" and "dexamethasone." This was restricted to review articles and humans, yielding 66 titles, which were evaluated by reviewing the titles and abstracts. The most relevant systemic reviews and meta-analyses on the topic were ultimately evaluated further for additional relevant citations.[1,2] A total of nineteen randomized, double-blind, placebo-controlled studies were involved in the meta-analyses; however, only six of these studies were relevant to our clinical context and were thus analyzed further.[3-8]

The Advanced Search feature in PubMed was then used to explore all other possible relevant articles with the following search terms: '((bacterial meningitis[Title/Abstract]) AND dexamethasone[Title/Abstract]) AND therapy[MeSH Terms]'. This was restricted to randomized controlled trials and humans, yielding 21 titles. These titles were explored looking for other relevant papers, which resulted in the location of additional papers to evaluate.[9,10]

The de Gans et al. paper was chosen for this critical appraisal over the other relevant studies for multiple reasons. First, the age range of the patients enrolled in their study corresponded with the patient that we encountered. Many of the other studies also included the pediatric population. Secondly, the de Gans et al. study population was from developed countries with similar resources as the United States. Furthermore, the de Gans et al. study was unique in that it performed a subgroup analysis to measure the outcomes based on the causative bacteria of the meningitis. Finally, this study had a large sample size (n=301) with a low number lost to follow-up, as 97 percent of patients followed-up at eight weeks after admission for a last-observation neurologic examination.

The other relevant randomized, double-blind, placebo-controlled studies with an appropriate age range were also evaluated further for comparison.[3-5,7,8] These studies were not chosen for the critical appraisal as they included patients from underdeveloped countries including sub-Saharan Africa, Vietnam, and India. Although the studies had a range of sample sizes (n=30-465), these patients encounter additional obstacles that can lead to worse outcomes such as poor nutrition, delays in presentation, and overall low life expectancy. Additionally, ninety percent of the patients in Scarborough et al.'s study were HIV-positive while Thomas et al. and Bhaumik et al.'s studies had an unequal distribution of baseline characteristics between treatment groups. Furthermore, Thomas et al.'s study outcome measures were limited to only thirty days after initiation of therapy whereas the de Gans et al. study followed patients for eight weeks.

An additional prospective cohort study of community-acquired bacterial meningitis by Heckenberg et al. was also evaluated.[11] Investigators studied whether patient outcomes changed since the implementation of regular dexamethasone use (1998-2002 vs. 2006-2011). The results showed no significance difference in the rate of neurological complications or death between the later dexamethasone cohort compared to the earlier cohort. This study was not chosen for the critical appraisal due to the observational nature.

The above studies showed mixed results concerning the use and effectiveness of dexamethasone in preventing complications of suspected bacterial meningitis in adults. The power was relatively low in all studies and the empiric antibiotic therapies were not standardized. Furthermore, none of the above studies aside from the de Gans et al. study stratified the outcome results based on CSF cultures.

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Critical Appraisal

The study by de Gans and associates was a randomized, prospective, double-blind, multicenter trial comparing the Glasgow Outcome Scale (GOS) at eight weeks in adult patients with acute bacterial meningitis who received dexamethasone or placebo along with their first dose of antibiotics. GOS is a frequently used objective scale in clinical trials, which assigns patients a score based on their respective level of disability. A favorable outcome is defined as a score of 5 and signifies that the patient is able to return to work, which was important for our patient. The study included 301 patients randomly assigned, with 157 to the dexamethasone group and 144 to the placebo group. The study qualifies as a level 1 according to the Oxford Centre for Evidence-Based Medicine. The primary purpose of the study was to determine whether adjunctive dexamethasone treatment improves the functional outcome in adult patients with CSF-proven bacterial meningitis. Specifically, authors were looking at effects on mortality, focal neurologic abnormalities such as aphasia, hemiparesis or ataxia, hearing loss, gastrointestinal bleeding, and hyperglycemia, all of which were concerns of our patient.

Patients were included in the study if they were seventeen years of age or older and had suspected meningitis in combination with bacteria in CSF on Gram staining. Our patient fit the inclusion and exclusion criteria and had similar baseline characteristics to the study population. Patients received either a 10mg IV dose of dexamethasone sodium phosphate (Oradexon) given every six hours for four days, or a placebo delivered in the identical fashion. The standard of care dosing regimen in adult patients with suspected meningitis is 0.15mg/kg every six hours for two-four days simultaneously with the first dose of antimicrobial therapy.[12] The initial antibiotic treatment was 2g IV amoxicillin given every four hours for 7-10 days, which was maintained or changed depending on the results of the Gram stain.

The study outcome showed that after eight weeks of enrollment, the percentage of patients with an unfavorable outcome as measured by the GOS was significantly smaller in the dexamethasone group (15%) than in the placebo group (25%) (absolute risk reduction, 0.59; p=0.03). Out of the 301 patients included in the final analysis, CSF cultures revealed that 110 had *Streptococcus pneumoniae*, 95 had *Neisseria meningitidis*, 29 had "other" bacteria, and 65 had negative bacterial cultures. Among the patients with pneumococcal meningitis, 26% in the dexamethasone group had an unfavorable outcome, as compared with 52% in the placebo group (relative risk, 0.50; p=0.006). The number of patients with pneumococcal meningitis who needed to be treated to prevent one bad outcome (NNT) at eight weeks was four. Among the patients with meningitis due to *N. meningitidis*, however, adjuvant treatment with dexamethasone did not provide a significant benefit (p=0.74) and the NNT was thirty-eight. The overall proportion of patients who died was significantly smaller in the dexamethasone (7%) group overall than in the placebo group (15%) (relative risk, 0.48; p=0.04). The death rate of patients with *N. meningitidis* or "other bacteria," however, was not significant (p=1.00). Adjunctive dexamethasone treatment did not have a significant effect on focal neurological abnormalities (p=0.13) or hearing loss (p=0.54) but patients in the dexamethasone group were significantly less likely to have impaired consciousness (p=0.002), a seizure (p=0.04), or cardiorespiratory failure (p=0.02). There were no significant adverse effects encountered in the treatment group.

The study definitely had several strengths. It demonstrated appropriate randomization via a computer-generated list of random number assignments. The blinding was also appropriate as neither the patients nor researchers were aware of the treatment assignment. The primary outcome assessment used was the standardized and objective Glasgow Outcome Scale, which is a well-validated scale with good inter-observer agreement. Furthermore, there were no significant differences between the two groups' baseline characteristics.

However, there are also several weaknesses. For example, the authors chose not to stratify the results based on antibiotic treatment regimens, which is a potential confounding factor. A total of twenty-two patients were withdrawn from treatment early for several reasons such as severe hyperglycemia, flushing, suspected cerebral abscess, and suspected stomach perforation. Seven patients were lost to follow-up after discharge from the hospital. However, the characteristics of the withdrawn and lost to follow-up patients were similar and were equally distributed across both treatment groups. Furthermore, as the patients were only followed for eight weeks, longer-term sequelae could potentially have been missed.

Despite these weaknesses, the results of this prospective trial provide sufficient evidence that early treatment with dexamethasone can improve the outcome in adults with acute bacterial meningitis. Although the benefit of therapy was most apparent in the patients with pneumococcal meningitis, there was insufficient power in the meningococcal meningitis subgroup to rule out the potential benefit. Because there were no significant adverse effects encountered in the treatment group, it was reasonable to

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provide our patient with adjunctive dexamethasone, and to recommend providing the same to all adults with suspected meningitis during the first dose of antibiotics.

Clinical Application

The patient in question is a 30 year-old female with no significant past medical history who presented to the emergency department with signs and symptoms of acute bacterial meningitis, and who was immediately started on empiric antibiotic therapy along with dexamethasone treatment, despite the patient's hesitation. Although the patient was reluctant to receive corticosteroid therapy due to perceived adverse effects and added cost to the hospital stay, the potential benefits reported by studies such as the one described in this appraisal as well as an explanation of Medicaid benefits led to an informed consent and a shared decision-making process. The antibiotics were de-escalated when the patient was diagnosed with meningococcal meningitis and the dexamethasone continued until hospital day four with discharge on hospital day seven.

Learning points:

1. Adjunctive dexamethasone therapy can significantly reduce morbidity and mortality in adult patients with pneumococcal meningitis. Adjunctive dexamethasone therapy is also recommended to all patients with suspected bacterial meningitis as it does not result in any significant adverse effects and can improve the neurological outcomes overall in adults.

2. I have gained an invaluable understanding regarding proper application of research-driven data to patient care, such as ensuring that my patient in question relates to the study population.

3. I have learned that it is always important to critically assess the power of each study as well as balancing the strength of evidence with the risk of treatment before making any applications to patient care.

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