CME CREDIT

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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should adults with suspected acute bacterial meningitis get adjunctive corticosteroids?

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A: Yes. Evidence suggests that adults with competent immune systems who present to the hospital with suspected bacterial meningitis should receive dexamethasone with or immediately before the first dose of antibiotics.

BACKGROUND

Despite significant advances in antibiotic therapy, brain imaging, and critical care, acute bacterial meningitis continues to impose unacceptably high rates of morbidity and mortality. This is particularly true in meningitis due to *Streptococcus pneumoniae* (pneumococcal meningitis), the most common form of bacterial meningitis in adults, with a mortality rate in the United States estimated to be 21% to 28%.[1,2]

Many who survive the infection have significant neurologic deficits, and recent data suggest that even those who have a "good" outcome are at high risk of long-term neuropsychiatric sequelae.[3]

Cascade of damage

Most of the damage in acute bacterial meningitis arises from inflammation in the subarachnoid space, triggered by cell-wall products released by the autolysis of bacteria.

A complex cascade follows, involving the generation of tumor necrosis factor-alpha, interleukins 1 and 6, various chemokines including interleukin 8 and macrophage inflammatory proteins 1 and 2, and matrix metalloproteinases. This in turn leads to the influx of inflammatory cells and the breakdown of the blood-brain barrier, with local vasculitis, loss of cerebral autoregulation, and brain edema.[4]

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

STUDIES IN CHILDREN

Because bacterial meningitis is now known to involve inflammation, trials of corticosteroids, typically dexamethasone, have been conducted in an attempt to blunt inflammatory changes in the subarachnoid space.

The first methodologically sound study, published in 1988, enrolled infants and children and showed a significant reduction in deafness in the treatment group.[5] Other trials followed, most with similar results. Of note, the studies included a high percentage of patients infected with *Hemophilus influenzae* B, and all but one included only children.

A high-quality meta-analysis in 1997 concluded that adjunctive corticosteroids reduce the risk of deafness in meningitis due to *H influenzae* B and that they also appear to protect against neurologic sequelae in pneumococcal meningitis, but only if the corticosteroid is given with or before the first antibiotic dose. Importantly, adverse effects did not appear to be more common in those receiving corticosteroids.[6]

Most of the damage in acute bacterial meningitis arises from subarachnoid inflammation

STUDIES IN ADULTS

Girgis et al,[7] in the first study to include adults, randomized 429 patients in Egypt to receive either "standard" antibiotic therapy alone or antibiotic therapy plus dexamethasone. Patients in this methodologically flawed but intriguing study presented late (64% were

comatose on hospital arrival), and some had received antibiotics prior to presentation.

The overall mortality rate was 10% in the treatment group and 20% in the control group. The difference was even more striking in the subgroup of patients with pneumococcal meningitis, in whom the mortality rates were 13.5% vs 40.7% ($P < .002$).[7]

Thomas et al,[8] in a French-Swiss study, enrolled 60 adults with bacterial meningitis, half of whom were infected with *S pneumoniae*. Unfortunately, the control and treatment groups were not well matched, as the control patients were both older and sicker, and the trial was halted early when France's empiric antibiotic treatment standards for bacterial meningitis were changed. The study has also been criticized for allowing the first dose of corticosteroids to be given up to 3 hours after the first dose of antibiotics.

As a result, it is difficult to draw firm conclusions from the trial, yet a "favorable" outcome was achieved by 74% of the corticosteroid group vs 52% of the control group ($P = .071$).[8]

De Gans et al,[9] in a landmark trial, shed more definitive light on the role of adjunctive corticosteroids in adults with bacterial meningitis. Adult patients with bacterial meningitis were randomized to receive either antibiotics plus placebo or antibiotics plus dexamethasone. A total of 301 patients were randomized and analyzed according to intention to treat. The primary outcome was the score on the Glasgow Outcome Scale 8 weeks after presentation; secondary outcomes included death, focal neurologic deficits, hearing loss, gastrointestinal bleeding, and hyperglycemia.

The first steroid dose should be with or just before the first dose of antibiotics

An unfavorable outcome (defined as moderate or greater disability as judged by the Glasgow Outcome Score) occurred in 15% of the treatment group vs 25% of the control group (relative risk 0.59, $P = .03$). Seven percent of steroid recipients died vs 15% of control patients (relative risk 0.48, $P = .04$).

Differences in the subgroup with pneumococcal meningitis were more striking, with an unfavorable outcome in 26% of treatment patients vs 52% of control patients (relative risk 0.50, $P = .006$), and death in 14% of treated patients vs 34% of control patients (relative risk 0.41, $P = .02$).

Focal neurologic deficits and decreased hearing loss showed a trend toward lower frequency in the treatment group than in the control group (13% vs 20%, $P = .13$). A possible reason for the lack of statistical significance was that more patients with severe disease survived to be assessed in the treatment group. A statistically significant decrease in cardiorespiratory failure and seizures was noted in the treatment group. The incidence of adverse effects did not differ between the two groups.[9]

Van de Beek et al,[10] in a recent meta-analysis, reached conclusions similar to those of de Glans et al: a mortality rate of 12% in adults treated with adjunctive corticosteroids vs 22% in those treated with antibiotics alone. Neurologic sequelae were reported in 14% of those receiving corticosteroids vs 22% of those receiving antibiotics alone. The rate of death in the subgroup of patients infected with *S pneumoniae* was 21% with corticosteroids vs 42% with antibiotics alone.[10]

The heterogeneity of the patient groups and serious methodological flaws in all but one of the studies included in this meta-analysis limit its value. Nevertheless, it provides further modest support for the use of corticosteroids in adults with bacterial meningitis.

OUR RECOMMENDATIONS

On the basis of these studies, we recommend the use of dexamethasone in adults presenting with suspected bacterial meningitis.

The first dose should be given concurrently with or immediately before the first dose of antibiotics. The timing is important, as the theoretical mechanism of benefit of these drugs is by blunting cytokine and chemokine release at the time of initial bacterial killing.[11] We believe the appropriate dose is that used by de Gans et al,[9] ie, 10 mg intravenously every 6 hours.

Most patients presenting with suspected meningitis will prove not to have bacterial meningitis, and in these patients dexamethasone should be halted, with the assumption that abruptly stopping the steroid after only a single dose will not cause significant harm. If the patient proves to have pneumococcal meningitis, steroids should be continued for a

total of 4 days, according to the protocol used in most studies to date.

Although some have suggested that steroid therapy be continued in bacterial meningitis caused by pathogens other than *S pneumoniae*,[10] we agree with authorities who recommend stopping if the causative agent proves to be other than pneumococcal.[11] If no organism is recovered, stopping the steroid is reasonable, although no evidence exists to clearly address this.

Of note, the systematic review of van de Beek et al[10] found no increased incidence of adverse effects in those treated with corticosteroids. Specifically, the incidence of gastrointestinal bleeding, herpes zoster or herpes simplex, and secondary fever was not higher in the corticosteroid group.

UNANSWERED QUESTIONS

Should corticosteroids be used in conjunction with vancomycin?

Given the prevalence of penicillin-resistant and cephalosporin-resistant *S pneumoniae* strains in the United States, the recommended empiric treatment for bacterial meningitis is ceftriaxone combined with vancomycin, even though vancomycin is somewhat unreliable in its penetration into the cerebrospinal fluid. Based on information from rabbit models showing decreased vancomycin penetration into cerebrospinal fluid in the presence of dexamethasone, concern has been raised that this combination may not be appropriate.[12,13]

One very small study supports this argument,[14] but we are not convinced that it permits drawing conclusions, given its small size, the lack of a control group, and vancomycin dosing issues.

Conversely, one small pediatric study reported adequate cerebrospinal fluid vancomycin levels when given together with dexamethasone.[15]

We and others recommend close monitoring if dexamethasone is given with vancomycin to a patient with known or suspected cephalosporin-resistant *S pneumoniae* meningitis, and physicians should have a low threshold for repeating lumbar puncture in this situation. The optimal therapy for *S pneumoniae* meningitis is not clear, but the limited data available support ceftriaxone combined with either vancomycin or rifampin. Most experts use ceftriaxone and vancomycin in this setting.[12,15,16]

Should corticosteroids be given to immunosuppressed patients?

We lack the data to strongly support either giving or withholding corticosteroids in significantly immunosuppressed patients with bacterial meningitis.

A recent study in children with bacterial meningitis in Malawi, many of whom were positive for human immunodeficiency virus, found no benefit in giving corticosteroids, but a number of confounding factors were present.[17]

Is 4 days the optimal treatment duration?

The appropriate duration of adjunctive corticosteroid treatment in patients with pneumococcal meningitis remains somewhat unclear. Based on the available data, it seems most reasonable to give it for the first 4 days of therapy, although one pediatric study suggested that 2 days of therapy might provide the same benefit.[18] In the occasional patient who cannot tolerate dexamethasone, stopping it after 48 hours appears reasonable.

Vancomycin is somewhat unreliable in its penetration into the cerebrospinal fluid

Are corticosteroids the best anti-inflammatory agents?

Although corticosteroids have an adjunctive role in the treatment of at least pneumococcal meningitis, they may not be the ideal anti-inflammatory agents for acute bacterial meningitis. Theoretical concerns persist, based on animal models, that their use in this setting may actually aggravate apoptosis in the dentate gyrus, contributing to neuropsychiatric sequelae.

Potential targets for therapy such as tumor necrosis factor-alpha–converting enzyme and matrix metalloproteinase blockade may provide opportunities for advances in the treatment of bacterial meningitis,[4] but given the difficulty in conducting human trials in bacterial meningitis, further clinical breakthroughs do not appear imminent.

For now, the best treatment is prompt recognition, prompt administration of antibiotics, judicious use of corticosteroids, and meticulous critical care management.

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