Glucocorticoids in Central Nervous System Bacterial Infection

P. K. Coyle, MD

Objective: To evaluate evidence-based data on adjunctive glucocorticoid therapy in central nervous system bacterial infections.

Design: A literature review of studies, particularly controlled trials, that have evaluated dexamethasone therapy for acute bacterial meningitis and glucocorticoid therapy for tuberculous meningitis.

Main Outcome Measures: Clinical outcomes were mortality and morbidity rates. Morbidity involved sensorineural hearing loss and other neurologic deficits (motor or behavioral disturbances, epilepsy, cranial nerve palsy, hydrocephalus, and psychomotor retardation).

Results: The evidence-based data support adjunctive dexamethasone therapy for children with *Haemophilus influenzae* meningitis. However, the optimal duration of therapy is not defined. Data are supportive but not conclusive that dexamethasone benefits meningitis caused by other bacterial agents and meningitis in adults. The evidence-based data are supportive but not conclusive that adjunctive glucocorticoid therapy benefits patients with tuberculous meningitis, particularly those with more severe infection.

Conclusions: Although adjunctive glucocorticoid therapy may be beneficial in both acute bacterial meningitis and more severe tuberculous meningitis, there are conclusive data only for *H influenzae* meningitis in children. For acute bacterial meningitis, further studies are needed to clarify the optimal duration of dexamethasone therapy (2 vs 4 days), whether this therapy should be used routinely for adults with meningitis, and whether it should be used for pathogens other than *H influenzae*. For tuberculous meningitis, further studies are needed to provide conclusive evidence of benefit.

Arch Neurol. 1999;56:796-801

Despite advances in diagnosis and management, bacterial infections of the nervous system continue to have substantial morbidity and mortality. Recent studies on the pathogenesis of neural tissue injury in these infections found that inflammatory and toxic factors, produced by the host immune system in response to the invading pathogen, are responsible for much of the damage. This host response is accentuated at the time bactericidal antibiotic treatment is initiated, organisms are lysed, and there is abrupt release of inflammatory cell wall components, lipopolysaccharides, and outer membrane vesicles from the organisms.

In animal studies of meningitis, morbidity and mortality are decreased when anti-inflammatory adjunctive or partner drug therapy is used along with antibiotics. Glucocorticoids such as dexamethasone and, to a lesser extent, prednisone are potent anti-inflammatory and immunomodulatory agents. They have a number of effects that mitigate damaging host factors (Table 1). They shut off transcription of proinflammatory cytokines and chemokines, decrease synthesis of many inflammation mediators, decrease cell activation and recruitment, stabilize lysosomes, decrease adhesion molecule expression and matrix metalloproteinase activity, and temporarily repair the leaky blood-brain barrier. Glucocorticoids have been used as adjunctive therapy in both acute bacterial meningitis and tuberculous (TB) meningitis, but their use is controversial. They raise a number of theoretic concerns, such as interference with the ability of the host to clear the infection, decreased antibiotic penetration across a repaired blood-brain barrier, activation of extraneural disease, masking of signs to judge therapeutic response, and iatrogenic complications. This article will examine the evidence on adjunctive corticosteroid therapy for acute bacterial meningitis and TB meningitis. To put this dis-
cussion in context, pertinent basic features of these 2 central nervous system (CNS) infections will be reviewed.

**ACUTE BACTERIAL MENINGITIS**

**Basic Features**

The overall mortality rate of bacterial meningitis remains around 20%. In addition to mortality, bacterial meningitis causes morbidity such as hearing loss, seizures, hydrocephalus, stroke, and other complications. The morbidity rate can be as high as 40% to 60% in survivors. Previously this infection was largely a pediatric problem, with an average patient age of 15 months.  

*Hae-mophilus influenzae* was the single most common pathogen, causing 70% of meningitis infections in patients younger than 5 years. Introduction of the conjugate vaccines for *H influenzae* has transformed this pattern. In the United States, bacterial meningitis cases have dropped by 55% and *H influenzae* cases by 94%. The average patient with meningitis is now 23 years of age. *Streptococcus pneumoniae* is now the major pathogen. It accounts for 47% of all meningitis cases and is the most common agent in adults older than 18 years and children aged 1 to 2 years. *Neisseria meningitidis* is the second leading pathogen. It accounts for 25% of all cases and is the most common agent in children aged 2 to 18 years. *Streptococcus agalactiae* (group B streptococcus) and *Listeria monocytogenes* account for 12% and 8% of meningitis cases, respectively, while *H influenzae* is responsible for only 7% of cases. In the modern medical era, *S pneumoniae* has a case fatality rate of 21%, compared with 3% for *N meningitidis*. The cell wall of *S pneumoniae*, which contains both peptidoglycan and teichoic acid, is a potent inducer of cerebrospinal fluid (CSF) inflammation. This whole picture is further complicated by the occurrence in recent years of antibiotic-resistant strains. Perhaps 25% of *S pneumoniae* bacteria are resistant to penicillin, and 9% are resistant to third-generation cephalosporins. This resistance has implications for antibiotic selection. Current recommendations for empiric treatment of meningitis in adults and in children older than 2 months involve 2 to 3 antibiotics, for empiric treatment of meningitis in adults and in children older than 2 months involve 2 to 3 antibiotics, a third-generation cephalosporin (ceftriaxone sodium or cefotaxime sodium) and vancomycin, with or without rifampin. In animal studies, dexamethasone decreases CSF penetration of both ceftriaxone and vancomycin. Although studies in children found that dexamethasone had no effect on ceftriaxone, vancomycin, or rifampin levels, there are no clinical data on adults that address this concern.

**Evidence-Based Data**

Glucocorticoid treatment for bacterial meningitis dates to the 1950s, but the first controlled trials to document a benefit on hearing loss were published in 1988. A recent meta-analysis identified all clinical trials carried out to evaluate dexamethasone therapy in childhood bacterial meningitis between 1988 and November 1996. There were 16 studies, 11 of which were randomized and had concurrent controls. These 11 studies, consisting of more...
There is general consensus that adjunctive dexamethasone benefits children older than 2 months who than 1300 patients, were used for the meta-analysis. All the studies used dexamethasone, but the protocols and antibiotic treatments were not standardized. Well-defined clinical outcomes (death, hearing loss at 6 weeks or later, other neurologic deficits) were evaluated. Not surprisingly, the major causal agent in these cases was H influenzae (62.0%), followed by N meningitidis (14.7%) and S pneumoniae (14.4%). For all studies, combined mortality was lower with dexamethasone treatment, but the difference did not reach significance at the \( P < .05 \) level. Overall mortality in 9 of the studies was only 1.4%, compared with a mortality rate of 20.5% in 2 of the studies, from Egypt and Mozambique. With regard to hearing loss, severe impairment (defined as bilateral sensorineural hearing loss greater than 60 dB or loss requiring the use of hearing aids) was almost twice as common with S pneumoniae than with H influenzae and did not occur with N meningitidis infection. Combined analysis using all available data from these trials found that dexamethasone treatment had a significant benefit in decreasing severe hearing loss from H influenzae meningitis (Table 2). Benefit was independent of the antibiotic chosen or the timing of the dexamethasone therapy, and was noted whether corticosteroids were given early, just before or at the time of the first antibiotic dose, or later after antibiotics had been started. The data for S pneumoniae meningitis showed a trend in favor of dexamethasone, but the difference was not statistically significant. When stratified by timing of treatment, however, early dexamethasone significantly decreased severe hearing loss. Neurologic deficits other than hearing loss (such as ataxia, behavioral disturbances, epilepsy, cranial nerve palsy, hydrocephalus, paralysis, and psychomotor retardation) were evaluable in 757 children, and there was a suggestive but nonsignificant benefit in favor of dexamethasone. In 7 of the 9 evaluable studies, the rate of neurologic deficits was lower in the group who received adjunctive corticosteroids. In 5 studies, organism-specific data were available to determine treatment effect on hearing or other neurologic deficit. There was a trend in favor of dexamethasone therapy in H influenzae and N meningitidis meningitis, and in S pneumoniae meningitis when corticosteroids were given early. Duration of dexamethasone therapy (2 vs 4 days) was also examined; if anything, the short course was preferable (Table 3).

When adverse events were examined, only secondary fever (defined as recurrence of fever after at least 24 afibrile hours) was significantly higher in the corticosteroid-treated group (Table 4). Overall, gastrointestinal tract bleeding was not significantly increased. However, it was more common with longer duration of dexamethasone treatment. With 4-day regimens, 13 (2.8%) of 466 patients bled, compared with 1 (0.8%) of 122 patients treated for 2 days and 2 (0.4%) of 450 control patients. The difference in the 4-day group was significant compared with controls (\( P = .008 \)).

Although there were differences between the 11 trials evaluated, the consistent trend suggested a benefit with dexamethasone. This was also true for the 5 excluded trials. The final conclusions from this meta-analysis were that adjunctive dexamethasone therapy is beneficial in H influenzae meningitis and may be beneficial if used early in S pneumoniae meningitis. Although the clearest effect was on hearing loss, the consistent direction of effect favored a broader benefit of dexamethasone therapy. Adverse effects were less, and benefit just as good, with a 2-day as opposed to a 4-day treatment regimen.

Subsequent to this meta-analysis, a randomized controlled trial from Pakistan reported greater mortality in the corticosteroid-treated group (12/48 vs 3/41), but this study included culture-negative cases (55%), partially treated cases (44%), and cases that began treatment late (42%),\(^9\) which would not represent the typical meningitis population.

Copyright ©1999 American Medical Association. All rights reserved.
have *H influenzae* meningitis. The recommended dosage is 0.15 mg/kg every 6 hours for 4 days, to begin shortly before the first dose of antibiotic. There is no consensus on adult meningitis or on meningitis caused by other agents, although the American Academy of Pediatrics recommends that treatment be considered for *S pneumoniae* infection. One recent review suggested that it was reasonable to use dexamethasone in adults with a high infection load (positive Gram stain) and evidence of increased intracranial pressure.

**Future Studies**

There are a number of unresolved issues. First, it is possible that shorter treatment (2 days) is superior to 4 days. A study with sufficient statistical power (up to several hundred patients per group) is needed to address optimal duration of dexamethasone. Second, bacterial meningitis is becoming an adult infection, yet there are few data available on adults. An Egyptian study included both adolescents and adults. For those aged 13 to 25 years, the mortality rate was 3% (1/31) in the group treated with dexamethasone compared with 5% (2/39) in the control group. For those older than 25 years, the mortality rate was 11% (2/18) in the group receiving dexamethasone compared with 20% (4/20) in the control group. The results are suggestive of benefit, but the numbers are small. An ongoing study in the Netherlands is evaluating community-acquired meningitis in adults (Dutch Dexamethasone in Adulthood Bacterial Meningitis Trial). This study is using 4 days of dexamethasone (at 0.6 mg/kg per day); the primary end point is outcome based on the Glasgow Outcome Scale at 2 months. Seventy centers are participating in this study. As of November 1998, 200 patients were enrolled, with 100 more patients needed (written communication, Jan de Gans, MD, November 1998). Finally, there are few data on the current major pathogens, *S pneumoniae* and *N meningitidis*. The data for *S pneumoniae* are suggestive but not conclusive. In theory, the same pathogenetic mechanisms apply for children and adults. The same benefits of corticosteroid treatment should hold, since all the major pathogens trigger the same basic immune and inflammatory response. In animal models, glucocorticoids benefit *S pneumoniae* meningitis. It would be expected that adjunctive corticosteroid treatment, particularly if timed early rather than later, should benefit most patients with meningitis. It is reasonable, based on available data, to consider dexamethasone for *S pneumoniae* meningitis. If dexamethasone is used, then rifampin should be added to the antibiotic regimen. Unlike vancomycin, rifampin penetrates uninflamed meninges well. Convincing trial data are still needed, however, and hopefully can be supplied by the Netherlands study.

**TUBERCULOUS MENINGITIS**

**Basic Features**

Tuberculous meningitis is the major infectious cause of the chronic meningitis syndrome. In untreated patients, the mortality rate is 20% to 30%. Morbidity in both adult and pediatric survivors can run as high as 50%, with neurologic deficits in up to 25%. Mortality is related to severity of infection. The severity of TB meningitis has been staged by the British Research Council. Patients with stage I (mild) disease have a normal level of consciousness, no focal deficits, and a mortality rate less than 10%. Patients with stage II (moderate) disease have lethargy or altered behavior; minor deficits, such as cranial nerve palsies; and a mortality rate ranging from 4% to 55%. Stage III patients with severe disease are in stupor or coma; have seizures and severe focal deficits, such as hemiparesis; and have a mortality rate of 37% to 87%. Clinical experience with TB meningitis indicates that the response to antituberculous therapy is often delayed, and that patients may even paradoxically worsen when bactericidal agents are started. The pathologic mechanism of TB meningitis involves an exudative reaction that is especially prominent within the basilar meninges. This inflammatory response can involve blood vessels, particularly those at the base of the brain. These pathologic features lead to parenchymal damage and abnormal neuroimaging. Complications of TB meningitis include hydrocephalus, stroke, seizures, and spinal block.

There are experimental and clinical data that glucocorticoids are useful adjunctive therapy. In a rabbit model, cortisone added to isoniazid decreased meningeal inflammation and cleared exudative subarachnoid block. Anecdotal clinical data suggest that the institution of corticosteroid therapy is often associated with dramatic clinical improvement within days. This association is strengthened by the observation that abnormalities return once glucocorticoids are stopped. In addition to producing clinical improvement, corticosteroid use lowers CSF pressure, protein content, and cell count, and these objective measures can increase when corticosteroids are discontinued. The theoretic concern, that there might be lower antituberculous drug penetration into CSF, has been shown not to occur.

**Evidence-Based Data**

There have been 9 controlled trials, published from 1955 to 1997, that have looked at glucocorticoid treatment of TB meningitis. They have different study designs, entry criteria, corticosteroid regimens, outcomes, and randomization schemes. All but 1 study noted more favorable end points with adjunctive glucocorticoids, but results were not always statistically significant. Studies that treated for 4 or more weeks tended to have better results than shorter-term studies. The evidence-based data are strongly suggestive, but not conclusive, that adjunctive glucocorticoids decrease morbidity and mortality in TB meningitis. The most recent study, from South Africa, is one of the largest to date. It evaluated data from 141 consecutive children. Mortality was significantly decreased with the addition of corticosteroids, from 24% (13/54) in controls to 6% (4/63) in treated patients (P = .02). Most of the children who died had stage III disease. At a 6-month follow-up children who received corticosteroids were significantly more likely to have an IQ greater than 75, although there was no significant difference in motor, visual, or hearing deficits. On serial computed to-
mographic scanning (performed at baseline and at 1 and 3 months), corticosteroids produced a significant decrease in meningeal enhancement at 1 month (20% vs 45%) compared with controls. Tuberculomas developed in 9 (17%) of the control group children compared with only 2 (3%) of the children who received corticosteroids. However, no difference was found in the frequency of increased intracranial pressure or basal ganglia infarction. Another small trial from India examined 47 patients ranging in age from 12 to 78 years (mean, 27 years). In this study, 6 patients were unavailable for follow-up. A poor outcome was noted in 5 (25%) of 20 corticosteroid-treated patients compared with 8 (38%) of 21 control patients. Among the survivors who had more severe disease, corticosteroid treatment was associated with a more rapid improvement in level of consciousness, fever, and headache. Corticosteroid-treated patients also showed greater improvement in mental function and daily activities, but none of these differences was statistically significant. The largest study to date is an Egyptian study of 160 patients with culture-positive CSF collected during a 5-year period. Corticosteroid treatment significantly decreased the mortality rate (43% vs 59%; P<.05). This was particularly true for patients who were drowsy (15% vs 40%; P<.04), and in patients who survived long enough to be treated for 10 or more days (14% vs 33%; P<.02). Neurologic complications (4 vs 10) and permanent sequelae (6 vs 13) occurred significantly less often in the corticosteroid-treated group.

An additional study of 445 adult Chinese patients also reported that adjunctive corticosteroids caused a significant reduction in mortality, particularly for more severe (stage II and III) disease. Details of this study, published in the Chinese literature, are somewhat sketchy.

Theoretic concerns have been voiced that corticosteroids might activate extraneural tuberculosis, increase morbidity at the expense of mortality, and cause iatrogenic complications. These concerns have not been borne out in the studies that have used adjunctive glucocorticoid therapy.

In summary, many experts advocate the use of glucocorticoids in selected patients with TB meningitis (Table 5). Although the data to support these guidelines are not overwhelming, they are consistent with recent series that find that corticosteroids are of benefit in TB meningitis.

Next Studies

The studies to date do not allow definitive recommendations because they are not always truly comparable, do not involve sufficient numbers of patients, do not use anti-tuberculosis therapy optimally, and do not evaluate standardized glucocorticoid protocols. It is probably important to separate TB meningitis in children from that in adults, and that in immunocompetent vs immunocompromised hosts. Further studies are needed to define the role of adjunctive glucocorticoids for TB meningitis. To obtain sufficient numbers of patients, third-world countries will have to be used; it will be important to ensure that optimal medical care is provided to allow generalizability of the results.

CONCLUSIONS

Current evidence-based data provide different levels of certainty about the benefit of adjunctive glucocorticoid therapy for CNS bacterial infections, based on the causal pathogen and age of the host (Table 6). The data range from conclusive to supportive to suggestive only. Future studies are needed to determine optimal duration of treatment, as well as to document morbidity and mortality effects across a broad range of pathogens and hosts.

Table 5. Recommendations for Use of Glucocorticoids in Tuberculous Meningitis

<table>
<thead>
<tr>
<th>Indications</th>
<th>Protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td>More severe (stage II, III) disease</td>
<td>Adults: prednisone, 1 mg/kg per day, or dexamethasone, 8-16 mg/d</td>
</tr>
<tr>
<td>Increase in intracranial pressure or herniation syndrome</td>
<td>Children: prednisone, 1-4 mg/kg per day, or dexamethasone, 8 mg/d (0.3-0.6 mg/kg per day)</td>
</tr>
<tr>
<td>Spinal block</td>
<td>Dosage maintained for 3-6 wk, then tapered over 2-4 wk</td>
</tr>
</tbody>
</table>

Table 6. Summary of Current Evidence-Based Data on Use of Glucocorticoids in Central Nervous System Bacterial Infection

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Infant</th>
<th>Host</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilus influenzae</td>
<td>Conclusive data for reduction in hearing loss</td>
<td>Conclusive data for reduction in hearing loss</td>
<td>No data available</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Supportive data for reduction in neurologic morbidity</td>
<td>Supportive data for reduction in neurologic morbidity</td>
<td>Supportive data for reduction in morbidity, hearing loss, neurologic morbidity</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Suggestive data for reduction in neurologic morbidity</td>
<td>Suggestive data for reduction in neurologic morbidity</td>
<td>Supportive data for reduction in neurologic morbidity (moderate or severe infection)</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>No data available</td>
<td>Supportive data for reduction in morbidity, neurologic morbidity (moderate or severe infection)</td>
<td>No data available</td>
</tr>
</tbody>
</table>

*Supportive data consists of at least 2 controlled trials; suggestive data, at least 1 trial.*
These studies will need to enter hundreds of patients to detect significant differences with a reasonable level of certainty. Finally, there are clear instances in which glucocorticoids should not be used. They should not be used in neonates, in whom there are no available data. Glucocorticoids should also not be used in individuals who are at high risk for drug-induced complications, such as gastrointestinal tract bleeding.

Accepted for publication November 23, 1998.

Corresponding author: P. K. Coyle, MD, Department of Neurology, HSC T12, 020, State University of New York at Stony Brook, Stony Brook, NY 11794 (e-mail: pcoyle@neuro.som.sunysb.edu).

REFERENCES