

Dissenting views on dexamethasone therapy for bacterial meningitis

BACTERIAL MENINGITIS REMAINS A DREADED INFECTION, both for its potential to threaten life acutely and to cause permanent central nervous system (CNS) damage in survivors. While it is heartening to observe the stunning decline in cases of *Haemophilus influenzae* type b infection following the introduction of vaccination programs, cases of group B streptococcus, meningococcus, pneumococcus and other pathogens remain all too familiar.

The fundamental frustration for meningitis therapists is the lack of a consistent correlation between prompt bacteriological cure and a favourable clinical outcome. With currently available antibiotics, most cases have sterile cerebrospinal fluid (CSF) within 24 h of starting therapy. For children with meningitis, treatment with drugs such as ceftriaxone results in bacteriological cure (sterile CSF) within 24 h in approximately 93%, with the remaining cases 'cured' by 48 h (1). Equally impressive results were achieved with ampicillin or chloramphenicol in earlier series. Despite prompt eradication of bacteria the risk of CNS sequelae remains high.

In the past decade much effort has gone into improving understanding of the pathophysiology of bacterial meningitis, using animal models of infection. Detailed information is now available (2) about the specific components of bacteria that trigger inflammation in CSF; the inflammation-enhancing effects of antibiotic-induced bacterial killing; and the mediators of CSF inflammation and cerebral injury. While the crude results are similar, the detailed mechanisms of injury vary remarkably among common pathogens. The model studies suggest that control of meningeal inflammation during bacterial eradication will reduce CNS injury, but they also warn that effective control therapies may differ by pathogen (3,4). In the case of models using *H influenzae* type b organisms, corticosteroids administered with the initial antibiotic therapy significantly reduced CSF inflammation and brain edema (3), prompting clinical trials to be undertaken in children with meningitis.

The modern studies of corticosteroid adjunctive therapy began in Dallas, using dexamethasone. While these were randomized, placebo controlled, blinded

studies (5), their design was exploratory in nature, ie, without specified primary outcome measures. The initial report from Dallas, combining two studies involving different cephalosporin antibiotics, involved more than two dozen comparisons, encompassing clinical signs, changes in CSF composition, auditory tests and measures of persistent CNS injury. While the expected effects of treatment on fever and some CSF parameters were observed, the only complication ameliorated was sensorineural hearing loss. Subsequent studies of similar design produced conflicting results. A noteworthy Swiss study (1) that emphasized administration of dexamethasone just before commencement of antibiotic therapy (the strategy with greatest impact in animal models of meningitis) demonstrated marginal benefits. After 24 h, five of six indices of CSF inflammation had changed to similar extents in both treatment groups, with only glucose concentrations improving faster with dexamethasone. The duration of fever was not significantly shorter in dexamethasone-treated children, nor were the rates of persistent neurological or audiological sequelae reduced significantly.

The study by King et al in this issue of the *Journal* (pages 210-215) demonstrated no improvement in the outcome of childhood meningitis associated with use of dexamethasone, although the necessity to obtain informed consent delayed its use by a median of 11 h after antibiotics. With well balanced treatment groups hearing loss occurred in 10 and 11% of the dexamethasone and placebo groups, respectively, and neurological deficits occurred in 20 and 18%, respectively. One dexamethasone-treated child had a duodenal perforation, a poignant reminder that the use of this drug is not without risk.

A multicentre study in the United States (6), in which children were treated with dexamethasone within 4 h of starting antibiotic therapy, also reported lack of efficacy. That study is noteworthy for its emphasis on hearing damage as a primary outcome measure. Most children had audiometric tests performed within 24 h of admission, by which time most instances of sensorineural hearing impairment were already detectable. This is not a new insight because others (7,8) had

previously demonstrated the early onset of hearing damage in meningitis cases and the potential for a proportion of cases to improve or recover. From a study design perspective, it would have been ideal (but admittedly impractical) in all of these studies to randomize separately patients who presented with hearing impairment, as the question is then whether dexamethasone treatment improves recovery. Failure to distribute patients randomly with early onset deafness may explain the inconsistent results of the recent studies, most of which were not large enough to ensure equal distribution of such patients by chance alone. In the American multicentre study (6), dexamethasone treatment did

not improve the outcome of early onset hearing impairment compared with placebo treatment.

In short, the promise of corticosteroid therapy summarized in studies of rabbits with meningitis has not been realized in afflicted children. Inconsistent study results indicate that the benefits of such therapy, if real, must be limited in situations where parents have good access to medical care. With the disappearance of cases caused by *H influenzae* type b, which were the majority in recent studies of adjunctive therapy, the effects of dexamethasone are even more uncertain. Clinicians should not feel compelled to use this strategy, and King et al question its value appropriately.

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