EDITORIAL

Corticosteroids for Acute Bacterial Meningitis

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Death and long-term disabilities are common outcomes of acute bacterial meningitis, especially in developing countries, even when highly effective antibiotic therapy is given. Therefore, improvement in the outcomes of acute bacterial meningitis is unlikely to come from developments in chemotherapy but rather from measures that alleviate the damage done before the causative bacteria are killed. Some of this damage is caused by bacterial toxins, but experiments in animals suggest that host inflammatory responses induced by bacterial products are also involved.[1] Thus, there are strong theoretical grounds for believing that antiinflammatory drugs should improve the outcomes of acute bacterial meningitis. Establishing whether this is the case has taken more than 25 years,[2] and the situation is still not entirely clear.

Many of the early trials of corticosteroid therapy in acute bacterial meningitis were underpowered and had flaws in their designs. However, there is now a consensus, based largely on the results of meta-analyses rather than on individual, definitive trials, that in industrialized countries, the administration of dexamethasone to children with acute *Haemophilus influenzae* type b meningitis before the start of antibiotic therapy reduces the incidence of sequelae, especially deafness.[3] The increasing use of the *H. influenzae* type b conjugate vaccines is reducing the burden of disease caused by this pathogen. The effect of dexamethasone on meningitis caused by other bacteria is less certain. Nevertheless, the administration of dexamethasone is now widely accepted as standard practice in the management of acute bacterial meningitis in children in the industrialized world. There is evidence, based largely on the results of a large multicenter trial in Europe, that dexamethasone also improves outcomes in adults in industrialized countries.[4,5] Can these findings be translated to the developing world, where acute bacterial meningitis is many times more prevalent than it is in wealthy countries?

The results of some early studies of corticosteroid therapy for the management of acute bacterial meningitis in children in less developed countries were encouraging.[6-8] However, a trial involving 598 Malawian children, about one third of whom were positive for the human immunodeficiency virus (HIV), provided convincing evidence of a lack of any benefit.[9] The negative outcome of this large, well-conducted trial has persuaded most pediatricians practicing in Africa that the routine administration of corticosteroids to children with acute bacterial meningitis is not indicated. Results from another Malawian trial suggest that, in this part of Africa, the same may be true for adults.

In this issue of the *Journal*, Scarborough et al.[10] report the results of a trial of dexamethasone in 465 Malawian patients 16 years of age or older with acute bacterial meningitis. Dexamethasone was given at a dose of 16 mg twice daily for 4 days in conjunction with ceftriaxone (given intravenously or intramuscularly in a nested, factorial trial). Overall mortality at 40 days after enrollment was high (54%) and did not differ significantly between patients who received dexamethasone (56%) and those who received placebo (53%) (odds ratio, 1.14; 95% confidence interval [CI], 0.79 to 1.64). The rates of disability or death or clinically detectable hearing loss 1 month after enrollment or of death 6 months after enrollment were not different between the groups. Multiple subanalyses, including one subanalysis

restricted to patients with proven bacterial meningitis, showed no evidence of a protective effect of dexamethasone in any patient subgroup.

In contrast to these findings in Malawi, a study conducted in Vietnam by Mai et al.,[11] also reported in this issue of the *Journal*, came to a different conclusion. This trial randomly assigned 435 subjects older than 14 years of age to receive dexamethasone at a dose of 0.4 mg per kilogram of body weight every 12 hours for 4 days or placebo before the administration of ceftriaxone. More than half of the patients had received antibiotics before enrollment in the trial. Overall, there were no significant differences in outcomes between the two treatment groups, although there was a trend in favor of patients who had received dexamethasone. One month after enrollment, overall mortality in the patient group was 11%: 10% in the dexamethasone group and 12% in the placebo group (relative risk of death, 0.79; 95% CI, 0.45 to 1.39). However, when the analysis was restricted to patients with proven bacterial infection, differences in mortality between the groups were seen at 1 month after enrollment (relative risk of death, 0.43; 95% CI, 0.20 to 0.94) and in the rate of disability or death at 6 months (odds ratio, 0.56; 95% CI, 0.32 to 0.98). Deafness was reduced significantly in the dexamethasone group. Surprisingly, the patients with probable meningitis who received dexamethasone had a higher mortality rate (although not significantly so) at 1 and 6 months after enrollment than the controls. The authors suggest that this result may have been due to the inclusion of patients with tuberculous meningitis in this group in whom corticosteroid therapy without concomitant antituberculosis therapy was harmful.

How can the difference in results between these two trials be explained? Both trials were well designed, included sufficient numbers of patients to show a moderately large protective effect, and were conducted by experienced investigators in hospitals with reasonable resources. Both studies used an effective antibiotic (ceftriaxone) and a similar dose of dexamethasone. In Malawi, the predominant pathogen was *Streptococcus pneumoniae*; in Vietnam, the predominant pathogen was *S. suis*, which is similar in many ways to *S. pneumoniae.* The most striking difference between the two studies is the much higher overall mortality in Malawi than in Vietnam (54% vs. 11%). This high rate of death may have been due in part to the very high HIV prevalence among the Malawian patients (90%), although a rate of death of approximately 50% among African patients with pneumococcal meningitis in areas where HIV is not prevalent has been described frequently. The HIV positivity rate was 1% in the Vietnamese study. Perhaps pathogenic changes were too far advanced in the African patients to be influenced by adjuvant therapy.

What are the practical messages provided by the results of these two important studies for clinicians who care for patients with acute bacterial meningitis in the developing world? In Africa, there seems to be little justification for giving dexamethasone, which may present a considerable drain on limited budgets, to children in any country or to adults in areas where the prevalence of HIV is high. Evidence is lacking for the treatment of adults in areas with a low incidence of HIV infection and for the treatment of patients with meningococcal meningitis, an important cause of deafness in sub-Saharan Africa, in areas where this infection is epidemic.[12] A case could be made for undertaking further trials in these groups. In Vietnam, there is now good evidence that, as in Europe, where mortality associated with acute bacterial meningitis is also relatively low, dexamethasone helps adults with proven acute bacterial meningitis, and this finding may be applicable to other parts of Southeast Asia. However, the trend toward a higher rate of death among patients with probable bacterial meningitis suggests that corticosteroids should be given only when a diagnosis can be made promptly by means of Gram's stain or a rapid diagnostic test before the start of treatment. In other parts of the developing world, such as the Indian subcontinent, there is insufficient evidence on which to base a decision. In South America, results of a recent multicenter study suggest that dexamethasone is ineffective in children with acute bacterial meningitis but that glycerol, given alone or with dexamethasone, protects against severe neurologic sequelae.[13]

The debate about the value of corticosteroids in acute bacterial meningitis will continue. However, it seems likely that in the developing world, the use of corticosteroids or other adjunctive therapies will have only a marginal effect on survival. The goal should be to prevent most forms of these devastating infections, which are associated with a high morbidity, through the widespread

use of the conjugate vaccines that are becoming increasingly available.

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