

## CORRESPONDENCE



## Corticosteroids for Bacterial Meningitis

**TO THE EDITOR:** Mai et al. (Dec. 13 issue) report that dexamethasone improved survival among patients with definite bacterial meningitis.<sup>1</sup> However, dexamethasone was associated with decreased survival in the group of patients with probable meningitis, which was hypothesized to be due to delayed antituberculosis treatment in patients with presumed tuberculous meningitis. Since it is recommended that corticosteroids be given before or at the time of the initial dose of antibiotics,<sup>2</sup> do the authors recommend that only patients with positive Gram's staining of cerebrospinal fluid receive corticosteroids? Should this restriction be applied only to countries with a high incidence of tuberculous meningitis?

How long was the delay in antituberculosis therapy after dexamethasone treatment for the eight patients with presumed tuberculous meningitis in the group of patients with probable meningitis? In the nine patients with confirmed tuberculous meningitis in the alternative-diagnosis group, four patients received dexamethasone and five patients received placebo, and yet there was a trend toward increased mortality among those who received dexamethasone. In light of the authors' previous findings on the benefits of dexamethasone in patients with tuberculous meningitis,<sup>3</sup> was there a delay in the receipt of antituberculosis drugs in the four patients with confirmed tuberculous meningitis who received dexamethasone? If so, what was the difference in the delay in administering antituberculosis drugs between the eight patients with presumed tuberculous meningitis and the four patients with confirmed tuberculous meningitis who received dexamethasone?

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1. Mai NTH, Chau TTH, Thwaites G, et al. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. *N Engl J Med* 2007;357:2431-40.
2. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002;347:1549-56.
3. Thwaites GE, Bang ND, Dung NH, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004;351:1741-51.

**TO THE EDITOR:** Scarborough and coworkers (Dec. 13 issue)<sup>1</sup> conclude that there is no role for adjunctive corticosteroids for bacterial meningitis in developing countries like Malawi, where the main pathogen is pneumococcus and where there is a high prevalence of infection with the human immunodeficiency virus (HIV). This might unnecessarily deprive a subgroup of patients — those who are HIV-negative, present early, and have had no previous exposure to antibiotic therapy — from the potential benefits of adjunctive corticosteroids. In another developing country where the HIV prevalence is lower, corticosteroids given before or with antibiotics have improved the rate of survival among patients with proven bacterial meningitis.<sup>2</sup> A recent meta-analysis also concluded that corticosteroid therapy reduced the rate of mortality among adults, especially in the subgroup of patients with pneumococcal meningitis.<sup>3</sup> An appro-

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appropriate risk stratification of patients with meningitis and a judicious use of corticosteroids might prove beneficial even in resource-poor, HIV-prevalent areas.

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1. Scarborough M, Gordon SB, Whitty CJM, et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. *N Engl J Med* 2007;357:2441-50.
2. Mai NTH, Chau TTH, Thwaites G, et al. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. *N Engl J Med* 2007;357:2431-40.
3. van de Beek D, de Gans J, McIntyre P, Prasad K. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev* 2007;1:CD004405.

**TO THE EDITOR:** Local epidemiologic characteristics of bacterial meningitis may affect the therapeutic role of corticosteroids.<sup>1,2</sup> Induction of the inflammatory response is probably the crucial element in the damage from the infection. However, differences are observed among genetic lineages within the same etiologic agent of meningitis. Such conclusions were recently reported regarding *Streptococcus pneumoniae*, for which both genotype and capsular types determine the pathogenic behavior of pneumococci.<sup>3</sup> An association of fatal meningococcal disease with meningococcal isolates of the clonal complex ST-11 was observed in patients with *Neisseria meningitidis*.<sup>4</sup> These isolates induce stronger inflammation and apoptosis during meningococcal sepsis.<sup>5</sup> Host factors may also influence the induction inflammatory response. Future studies and trials should consider bacterial and host factors that are usually overlooked in addressing the issue of corticosteroids.

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1. Scarborough M, Gordon SB, Whitty CJM, et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. *N Engl J Med* 2007;357:2441-50.
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3. Sjöström K, Spindler C, Ortvist A, et al. Clonal and capsular types decide whether pneumococci will act as a primary or opportunistic pathogen. *Clin Infect Dis* 2006;42:451-9.
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5. Zarantonelli ML, Lancellotti M, Deghmane AE, et al. Hyperinvasive genotypes of *Neisseria meningitidis* in France. *Clin Microbiol Infect* (in press).

**TO THE EDITOR:** In his editorial (Dec. 13 issue), Greenwood asserts that “the administration of dexamethasone is now widely accepted as standard practice in the management of acute bacterial meningitis in children in the industrialized world.”<sup>1</sup> We agree that it is a common practice but do not believe that it is widely accepted as standard practice in the United States.

The American Academy of Pediatrics (AAP)<sup>2</sup> acknowledges that dexamethasone may be beneficial for the treatment of *Haemophilus influenzae* meningitis, but it also advises that “adjunctive therapy with dexamethasone may be considered [for pneumococcal meningitis] after weighing the potential benefits and possible risks. Experts do not agree on a recommendation to use corticosteroids in pneumococcal meningitis; data are not sufficient to demonstrate a clear benefit in children.” Similarly, the 2004 Practice Guidelines for the Management of Bacterial Meningitis<sup>3</sup> of the Infectious Diseases Society of America acknowledge the lack of consensus and refer to the AAP statement.

We agree with Greenwood that “the debate about the value of corticosteroids in acute bacterial meningitis will continue,” but we believe the debate will continue for children in the United States as well.

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3. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004;39:1267-84.

**DR. MAI AND COLLEAGUES REPLY:** Chan is right to highlight the problem of how to select patients with bacterial meningitis who are most likely to benefit from adjunctive corticosteroids, when diagnostic confirmation of the disease may take hours (with Gram’s stain of cerebrospinal fluid) or days (with cerebrospinal fluid culture), or may

not be possible (as is true throughout most of the developing world). However, we do not recommend restricting dexamethasone to patients with a positive Gram's stain, because the modest sensitivity of this test would mean a significant proportion of patients with disease subsequently confirmed by culture would miss the potential benefits of dexamethasone treatment. Instead, we suggest that physicians — especially those working in settings with a high prevalence of tuberculosis — not administer adjunctive corticosteroids if there are clinical features suggestive of tuberculous meningitis. We recommend identifying these features with the aid of a simple, clinical diagnostic algorithm.<sup>1</sup> Unfortunately, the time delay between entry into our study and the start of treatment with antituberculosis drugs was not recorded, but in most patients it was between 2 and 5 days. The delay was unlikely to have been influenced by the findings of our previous study of tuberculous meningitis, which showed that dexamethasone improved the outcome among patients treated with antituberculosis drugs.<sup>2</sup>

Determining which patients with bacterial meningitis receive the most benefit from adjunctive dexamethasone is an ongoing challenge. It remains uncertain how the treatment effect varies across subgroups defined by age, sex, bacterial pathogen, and HIV status. Taha and Alonso suggest that host and bacterial factors may also influence disease severity and response to corticosteroids. There are plausible biologic reasons for a significant effect of all these variables on treatment outcome, but proving their importance will require further very large, controlled trials.

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**DR. SCARBOROUGH AND COLLEAGUES REPLY:** Two letters suggest that it might be possible to identify subgroups of patients in whom adjuvant corticosteroid therapy is likely to be beneficial. Ong et al. propose stratification according to clinical

criteria. To be of use in directing therapy, such criteria must be available at the time of admission; this is unlikely in the case of the causative organism and, in our experience, in the case of HIV serostatus. Given that caveat, our study failed to show that the length of history, organism, previous exposure to antibiotic therapy, or HIV status influenced the effect of adjuvant corticosteroid therapy. Of the 45 HIV-negative patients, 8 of 22 corticosteroid-treated patients, as compared with 10 of 23 patients who received placebo, died by day 40. A pediatric study in Malawi, in which 302 of 459 patients were HIV-negative, also showed no benefit from adjunctive corticosteroids in this subgroup.<sup>1</sup>

Taha and Alonso suggest that patient selection on the basis of host and pathogen genotype may improve the outcome. This is an attractive proposition, and we acknowledge the need for more detailed data collection. However, we question the feasibility of determining host and pathogen genotype in a manner sufficiently timely to direct therapy for individual patients, and we think it unlikely that the technology will become available in resource-poor settings in the foreseeable future, especially given that the annual health care spending in such settings is frequently less than \$10 per person.<sup>2</sup> A dramatic improvement in outcome could perhaps be achieved by promoting public awareness of the symptoms and signs of meningitis, by improving access to health care, and by ensuring the availability of effective antibiotics. Certain patient subgroups may indeed benefit from adjuvant corticosteroid therapy, and we share the concerns of others that we have been unable to determine satisfactorily the factors that predict a benefit.

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