Dexamethasone in adults with bacterial meningitis - Reply (letter)
de Gans, J.; van de Beek, D.

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sad when fears about vaccination begin to spread because of statements in the scientific literature that are hypothetical and unproven. The large, careful study by Madsen et al. found absolutely no evidence to support the hypothesis that MMR vaccination is responsible for the development of autism.

Edward W. Campion, M.D.

Dexamethasone in Adults with Bacterial Meningitis

TO THE EDITOR: The study by de Gans and van de Beek and their colleagues (Nov. 14 issue) demonstrates the benefits of dexamethasone in adults with bacterial meningitis. The authors conclude by recommending dexamethasone for all adults with acute bacterial meningitis. How to operationalize this recommendation poses a problem. In addition to having suspected meningitis, patients in this study had to have cloudy cerebrospinal fluid, bacteria on Gram’s staining, or a cerebrospinal fluid white-cell count of more than 1000. Thus, these patients were very likely to have acute bacterial meningitis. Most patients seeking medical attention with suspected meningitis, however, are unlikely to have a bacterial cause, and they typically receive empirical therapy pending complete evaluation. Is it clinically justifiable to wait for the confirmatory data before administering an antibiotic when waiting may constitute a delay in therapy? To avoid this pitfall, the clinical threshold for administering antibiotics is likely to be set much lower than that used in this study.

It is likely that the majority of potential candidates for dexamethasone will not have bacterial meningitis. As the target group becomes diluted by patients without bacterial meningitis, the benefit from dexamethasone will be correspondingly reduced, and the frequency of adverse outcomes may increase. Before recommending the routine use of adjunctive dexamethasone therapy for most adults with suspected bacterial meningitis, we must determine whether the benefits extend to initial empirical therapy.

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TO THE EDITOR: Because delaying treatment is associated with worse outcomes, the standard of emergency care in the United States is to administer antibiotics immediately to patients with suspected bacterial meningitis. The results of a culture of cerebrospinal fluid from a subsequent lumbar puncture should not be affected for several hours after the administration of antibiotics.

Given that the interval between the arrival of the patient and the beginning of treatment probably varied and that the time to treatment may affect the outcome, it is disturbing that de Gans and van de Beek did not provide a record of time to treatment. In the absence of such data, one is left to wonder whether statistically significant differences in the time to treatment between the dexamethasone group and the placebo group might help to account for differences in outcome between the groups. Evidence of unusual delay would raise questions about the conclusions of the study.

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TO THE EDITOR: The study by de Gans and van de Beek and their colleagues provides important data on the use of dexamethasone in patients with acute bacterial meningitis. All pneumococci isolated in this study were sensitive to penicillin, although in many areas of the world, the reality is unfortunately different. A big issue of concern is the possibility of a negative interaction between dexamethasone and vancomycin in patients who require treatment with the latter drug. Thus, we might see more therapeutic failures with broader use of dexamethasone therapy. Vancomycin has been considered to be the best treatment for meningitis caused by pneumococci with reduced sensibility to cephalosporins. In spite of the widespread recommendation for its use, there is relatively little clinical research on vancomycin for
the treatment of meningitis, and it has poor penetration in cerebrospinal fluid, where it often reaches only subtherapeutic concentrations.

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TO THE EDITOR: De Gans and van de Beek clearly show a beneficial effect of dexamethasone on outcome in adults with bacterial meningitis, particularly that due to penicillin-susceptible pneumococci. Could most of this effect be attributable to the beneficial effects of corticosteroids on mortality and hemodynamic stability in patients with septic shock? Hypotension was a predictor of an unfavorable outcome in this study (P=0.03). In addition, patients in the dexamethasone group were significantly less likely to have cardiorespiratory failure (10 percent vs. 20 percent, P=0.02). Moreover, from Table 3 of the article, it appears that most of the reduction in the risk of an unfavorable outcome can be accounted for by the difference in mortality between the groups. There was no reported difference in the frequency of neurologic sequelae, including hearing loss. Are there data on the cause of death — particularly, data differentiating refractory shock and multiple-organ dysfunction syndrome, which are typical of septic shock, from neurologic causes (e.g., brain death or withdrawal of care because of poor neurologic prognosis) suggesting sequelae of meningitis?

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TO THE EDITOR: The results of the study by de Gans and van de Beek and their colleagues are intriguing. We believe, however, that the recommendations in the accompanying editorial by Tunkel and Scheld regarding the use of dexamethasone in suspected pneumococcal meningitis are premature. A recent study in Malawi evaluated the use of corticosteroids in children with bacterial meningitis but came to different conclusions. In addition to possible differences between the pathogenesis of pneumococcal meningitis in the developing brains of children and that in adults, other differences between the studies include the rates of antimicrobial resistance and immunocompetence. These differences may modify the effect of corticosteroids.

In Malawi, 34 percent of the 459 patients tested for human immunodeficiency virus (HIV) were positive. In the report by de Gans and van de Beek, there was no reference to the immune status of the subjects. The increasing incidence of HIV and the fact that the HIV-infected population has a high incidence of invasive pneumococcal disease make representation of this group in any such efficacy studies vital.

Clearly, with such conflicting results, more studies are needed. Corticosteroids may have a role in treating bacterial meningitis, but exactly what that role is needs to be further elucidated.

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DRS. DE GANS AND VAN DE BEEK REPLY: Tabas and Chambers ask whether it is clinically justifiable to wait for confirmatory data before administering antibiotics. Although prospective data are lacking on the relation between the timing of administration of antimicrobial agents and the clinical outcome in adults with suspected bacterial meningitis,2 in our opinion, dexamethasone and antibiotics should be administered as soon as possible. However, in some patients, waiting for confirmatory data seems to be justifiable, especially in patients with a low level of clinical severity (53 percent of our study population).2 In addition, “dilution” of the target group is not relevant to the effect of dexamethasone in patients with bacterial meningitis; it is analogous to the dilution of the effect of antibiotic therapy in this group. The rate of side effects will be minimal with the administration of 10 mg of dexamethasone, and therapy should be discontinued if the patient is found not to have bacterial meningitis.

N ENGL J MED 348;10 WWW.NEJM.ORG MARCH 6, 2003 955
Tancredi and Binder ask about the absence of data concerning the time of treatment. Although we did not record the duration of the delay, the treatment groups were similar in terms of all baseline characteristics. Therefore, it is unlikely that the results are confounded.

We agree with Abril and Ortega that decreased cerebrospinal fluid vancomycin levels are a matter of concern. Therefore, patients receiving dexamethasone should not be treated with vancomycin as the sole antimicrobial agent and should be observed carefully.3

Joffe would like us to provide more data on the cause of death. At this time, we are analyzing these data and will present them when we have finished doing so.

Poshkus and Obaro state that consideration of persons with HIV, a population that is growing and is at increased risk for pneumococcal disease, is crucial to any evaluation of adjunctive dexamethasone in bacterial meningitis. According to our prospective data from a nationwide cohort of adults with bacterial meningitis (1998 through 2002), however, only 5 of 336 patients with pneumococcal meningitis (1.5 percent) were HIV-positive. We disagree that only 5 of 336 patients with pneumococcal meningitis (1998 through 2002), however, only 5 of 336 patients with pneumococcal meningitis (1.5 percent) were HIV-positive. We disagree that the results of the Malawian trial preclude a recommendation for adults with bacterial meningitis.4 The Malawian study included mainly children in whom treatment began late, HIV-positive children, and children receiving inappropriate antibiotic therapy. Therefore, the results are not representative for patients with bacterial meningitis in developed countries. Moreover, results of our meta-analysis are pending. Four randomized trials are included, so that we summarize the results in 508 adults with bacterial meningitis. Relative risks of death reported in various studies have been consistent, ranging from 0.32 to 0.56, with an overall relative risk of 0.43 (95 percent confidence interval, 0.26 to 0.70). The results of our randomized, controlled trial and this meta-analysis support routine use of dexamethasone in adults with acute bacterial meningitis.5

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THE EDITORIALISTS REPLY: Tabas and Chambers raise the question of how to operationalize the recommendation to administer adjunctive dexamethasone to adults with bacterial meningitis, given the importance of prompt administration of antimicrobial therapy when the diagnosis is suspected. Although the study by de Gans et al. did not specifically address this issue, their results support the administration of adjunctive dexamethasone concomitant with or just before the first dose of empirical antimicrobial therapy. This approach may result in the unnecessary treatment of some patients who do not have bacterial meningitis, but the potential benefits (reduction in the rate of unfavorable outcomes and lower mortality) for patients with pneumococcal meningitis outweigh any potential risks associated with dexamethasone therapy. Previous prospective studies of adjunctive dexamethasone in bacterial meningitis, with the exception of one study involving 200 infants and children in which gastrointestinal hemorrhages requiring blood transfusion developed in 2 patients,1 have failed to demonstrate any serious adverse effects from the administration of dexamethasone.

Poshkus and Obaro cite an important study from Malawi that did not show a benefit of adjunctive dexamethasone in children with bacterial meningitis.2 However, many patients in that study had severe disease associated with malnutrition and concomitant HIV infection, and delays in presentation for medical care were common.3 In these patients, it is unlikely that adjunctive dexamethasone would have ameliorated the central nervous system damage that had already resulted from the consequences of bacterial meningitis (e.g., cerebral edema, increased intracranial pressure, and vascular thrombosis). Furthermore, more than one third of the children in that study received antimicrobial therapy before admission, and more than 30 percent were given second-line antimicrobial therapy because of an inadequate clinical or microbiologic response. No adverse effects were related to the administration of adjunctive dexamethasone in this trial.
We acknowledge that there are inadequate data regarding the use of adjunctive dexamethasone in HIV-infected patients and in patients with meningitis caused by pneumococcal strains that are highly resistant to penicillin or cephalosporins; careful monitoring is essential if these patients are treated with dexamethasone.

The study by de Gans et al. supports the use of adjunctive dexamethasone in adults with pneumococcal meningitis. Although more studies are desirable, it took almost nine years to complete this trial, which suggests that new information on the use of adjunctive dexamethasone will most likely not be available in the near future. Dexamethasone will not benefit all patients with bacterial meningitis, but there is the potential for improvement in outcome in selected patients without evidence of substantial harm from this adjunctive treatment.

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Editor’s note: Dr. Scheld reports having served on an advisory board for Pfizer and having received speaking fees from Pfizer, Abbott, Bristol-Myers Squibb, Hoffmann-LaRoche, and GlaxoSmithKline.


Treatment of Asymptomatic Bacteriuria in Diabetic Women

TO THE EDITOR: Harding et al. (Nov. 14 issue) conclude that treatment of asymptomatic bacteriuria in women with diabetes does not appear to reduce complications and that screening and treatment are therefore not needed. However, Table 3 of their article shows that the women in the placebo group received significantly more antibiotics for symptomatic urinary tract infections than the women in the antimicrobial-therapy group. In addition, in our opinion, it is the effect of asymptomatic bacteriuria on renal function, and not symptomatic urinary tract infection, that is the most important variable. In citing our study, Harding et al. do not mention that we reported that women with type 1 diabetes and asymptomatic bacteriuria had a tendency toward a decline in renal function over a short follow-up period. Since type 1 and type 2 diabetes are considered different diseases, separate analyses are warranted. In the study by Harding et al., all the patients were analyzed together, and only 21 (20 percent) had type 1 diabetes.

The conclusion of this interesting study should be that it is difficult to keep these patients free of bacteriuria. Furthermore, we believe it is premature to conclude that screening and treatment of asymptomatic bacteriuria in diabetic women are not needed. We are awaiting the results of our five-year follow-up study of nearly 200 women with type 1 diabetes, in which renal-function decline is the primary outcome variable.

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THE AUTHORS REPLY: Geerlings et al. suggest that the results of our study may not support the conclusion that treatment of asymptomatic bacteriuria in diabetic women had no benefit. The number of days an antibiotic was used for symptomatic urinary tract infection was 30 percent greater in the placebo group than in the antimicrobial-therapy group, and the number of days an antibiotic was used for all non–urinary tract infections was 20 percent higher in the placebo group. However, the rate of the primary outcome variable, symptomatic urinary tract infection, was similar in the two groups, and the total

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