Editorials

Corticosteroids for Everyone with Meningitis?

In 1988, a landmark study was reported on the use of adjunctive treatment with dexamethasone in infants and children who had bacterial meningitis.[1] The rationale for this study was based on studies involving animal models of bacterial meningitis, which demonstrated that the subarachnoid-space inflammatory response was a major factor contributing to morbidity and mortality among patients with this disorder. This inflammatory response is generated through local release by the central nervous system of proinflammatory mediators such as interleukin-1 and tumor necrosis factor in response to lysis of meningeal pathogens induced by antimicrobial agents. The consequences of this inflammatory response were attenuated with adjunctive dexamethasone therapy.[2,3] In the double-blind, placebo-controlled study reported in 1988, which involved 200 infants and older children with bacterial meningitis,[1] those randomly assigned to receive adjunctive treatment with dexamethasone were less likely to have moderate or more severe bilateral sensorineural hearing loss than were those who received placebo (3.3 percent vs. 15.5 percent, $P<0.01$). In two subsequent trials involving infants and children, dexamethasone was administered before the first dose of an antimicrobial agent in order to attain maximal attenuation of the subarachnoid-space inflammatory response.[4,5] The patients treated with adjunctive dexamethasone therapy were significantly less likely to have one or more neurologic sequelae at a mean interval of 15 months than were the patients who received placebo, findings that support the use of adjunctive dexamethasone therapy in infants and children with bacterial meningitis.

Other clinical trials of adjunctive dexamethasone therapy for bacterial meningitis in children and adults have produced conflicting results.[2,6,7] Some studies demonstrated a benefit with the use of dexamethasone, whereas others revealed no difference or a worse outcome. These studies differed in design (some were retrospective and some prospective), enrollment criteria, the socioeconomic status of the study population, the severity of the illness, case definition, the timing of the administration of dexamethasone in relation to the first dose of an antimicrobial agent, and the antimicrobial agents used. Despite these issues, a meta-analysis of clinical studies reported between 1988 and 1996 confirmed the benefit of adjunctive treatment with dexamethasone (0.15 mg per kilogram of body weight every six hours for two to four days) in children who had meningitis caused by *Haemophilus influenzae* type b and suggested a benefit, if the treatment was initiated with or before parenteral antimicrobial therapy, in children with *Streptococcus pneumoniae* meningitis.[8]

The question remains, however, whether adjunctive dexamethasone therapy can be of benefit in all patients with bacterial meningitis, regardless of their age or of the causative microorganism. In most reported studies of adjunctive dexamethasone therapy for bacterial meningitis, the majority of the patients had *H. influenzae* type b meningitis, a disease that has been virtually eliminated in countries where immunization with the *H. influenzae* type b conjugate vaccine is performed routinely. In the United States, *S. pneumoniae* is now the most common cause of bacterial meningitis.[9] A randomized but unblinded trial involving 429 children and adults with bacterial meningitis[10] showed that in the subgroup with pneumococcal meningitis, the mortality rate was lower among the patients who received corticosteroids than among those who did not (13.5 percent vs. 40.7 percent, $P<0.01$), as was the incidence of hearing loss (0 vs. 12.5 percent, $P<0.05$). However, 60 percent of the patients were in a comatose state at the time of enrollment, most patients received inadequate therapy for three to five days before hospitalization, and there was no documentation of possible adverse effects of dexamethasone. In a subsequent, placebo-controlled study involving adults with bacterial meningitis,[11] the rate of cure without any neurologic sequelae did not differ significantly between the dexamethasone and placebo groups (74.2 percent vs. 51.7 percent, $P=0.07$). However, amoxicillin was the antimicrobial agent most commonly used, and it may have been inadequate for the treatment of meningitis caused by resistant pneumococci. In addition, dexamethasone was administered within three hours after the first antimicrobial dose (which may have been too late for a benefit), and the patients in the dexamethasone group were significantly younger and less ill than those in the placebo group.

In this issue of the *Journal,* de Gans and van de Beek[12] report the results of a prospective, randomized, double-blind trial of adjunctive dexamethasone therapy for bacterial meningitis in 301 adults (defined as persons 17 years of age or older) in five European countries over a period of nine years. Dexamethasone was administered 15 to 20 minutes before the first dose of an antimicrobial agent and was given every 6 hours for four days. The base-line characteristics of the two study groups were similar, although seizures were twice as frequent in the dexamethasone group as in the placebo group. Adjunctive treatment with dexamethasone was associated with a reduction in the proportion of patients who had unfavorable outcomes (15 percent vs. 25 percent, $P=0.03$) and in the proportion of patients who died (7 percent vs. 15 percent,

P=0.04) as assessed at eight weeks. The benefits were most striking in the patients with pneumococcal meningitis (proportion with an unfavorable outcome, 26 percent, vs. 52 percent in the placebo group [P=0.006]; proportion of patients who died, 14 percent vs. 34 percent [P=0.02]), as well as in those with moderate-to-severe disease as assessed by the score on the Glasgow Coma Scale on admission. In addition, during the hospital stay, impairment of consciousness, seizures, and cardiorespiratory failure developed less frequently in the dexamethasone group than in the placebo group, and the risk of other adverse events did not differ significantly between the two groups.

One concern, however, is whether adjunctive dexamethasone therapy is detrimental in patients with meningitis caused by *S. pneumoniae* strains that are highly resistant to penicillin or cephalosporins, because these patients may require antimicrobial therapy with vancomycin or other agents in combination regimens.[2] A diminished cerebrospinal fluid inflammatory response after the administration of dexamethasone may substantially reduce vancomycin concentrations in cerebrospinal fluid and delay cerebrospinal fluid sterilization, as shown in animal models of meningitis caused by pneumococcal isolates that are highly resistant to penicillin or cephalosporins. However, vancomycin concentrations in cerebrospinal fluid were not reduced by dexamethasone in a study of children with acute meningitis. In the study by de Gans and van de Beek, only 78 of the 108 cerebrospinal fluid cultures that were positive for *S. pneumoniae* (72 percent) were submitted for susceptibility testing; all the isolates were susceptible to penicillin, a finding that is unusual in many areas of the world.

On the basis of the data that are now available, what should the recommendations be for the use of adjunctive dexamethasone therapy in adults with bacterial meningitis? Given the results of the trial by de Gans and van de Beek and the apparent absence of serious adverse outcomes in the patients who received dexamethasone, we believe that routine use of adjunctive dexamethasone therapy is warranted in most adults with suspected pneumococcal meningitis. The dexamethasone can be given with or just before the first dose of an antimicrobial agent. We do not recommend the use of adjunctive dexamethasone therapy in patients who have already received antimicrobial therapy, nor do we recommend its use in patients with septic shock, because corticosteroid therapy may be detrimental in patients with septic shock if they have an adequate adrenal reserve.[13,14] If the meningitis is found not to be caused by *S. pneumoniae,* dexamethasone therapy should be discontinued.

In patients with pneumococcal meningitis caused by strains that are highly resistant to penicillin or cephalosporins, careful observation and follow-up are critical in order to determine whether dexamethasone therapy is associated with adverse clinical outcomes. Cerebrospinal fluid analysis should be repeated in a patient receiving adjunctive dexamethasone whose condition is not improving as expected. Vancomycin should not be used as the sole antimicrobial agent in a patient with suspected or confirmed pneumococcal meningitis who is receiving concomitant dexamethasone therapy and should be administered in doses that ensure vancomycin concentrations in cerebrospinal fluid that are adequate for appropriate bactericidal activity. Furthermore, given the difficulty of enrolling a sufficient number of patients in a study of adjunctive dexamethasone therapy for pneumococcal meningitis caused by highly penicillin- or cephalosporin-resistant strains, we may need to rely on small case series or case reports to determine whether adjunctive dexamethasone therapy may be harmful in such patients.

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C-Reactive Protein — To Screen or Not to Screen?

Prediction is very difficult, especially about the future.
— Niels Bohr

MORE than 20 years ago, 246 risk factors for coronary heart disease (CHD) had already been identified, and the number continues to grow.[1] Advances in genomics and proteomics will provide even more candidate markers to consider for routine assessment in practice. Risk stratification is important because information about the probability of a cardiovascular event in the future can help target therapy and resources to those most likely to benefit. Of the several hundred known correlates of CHD, only a handful have had the staying power to be recommended for routine screening. The question of which new risk factors, if any, should be added to conventional risk assessment with regard to CHD is important for clinicians and policymakers, especially because the disease continues to be a major public health problem.

The impetus to pursue new predictors of CHD arises from the discovery that traditional risk factors do not fully account for the occurrence of disease. For example, only about half of patients with CHD have hypercholesterolemia.[2] This finding may indicate that average levels of cholesterol in the population are not normal from a pathobiologic perspective, but it also underscores the multifactorial pathogenesis of CHD.

Important advances in understanding the pathophysiology of atherosclerosis have been made in recent years, and inflammatory mechanisms are now believed to play a central part in the origins and complications of CHD.[3] C-reactive protein is an acute-phase reactant that markedly increases during an inflammatory response. C-reactive protein levels have been helpful for decades in monitoring many diseases. A new use for this old test has gained momentum in recent years as a result of observations that minor elevations of C-reactive protein are predictive of cardiovascular events in patients with CHD.[4] High-sensitivity tests for C-reactive protein now make possible the measurement of C-reactive protein levels within the normal range.[5] C-reactive protein not only may be a marker of low-grade chronic systemic inflammation but also may be directly involved in atherosclerosis; it can amplify the inflammatory response through complement activation, tissue damage, and activation of endothelial cells.[6] The possibility that the high-sensitivity assay for C-reactive protein may enhance our prognostic and therapeutic capabilities is of considerable interest, but its value has not been fully established.

In this issue of the *Journal*, Ridker et al. add to the growing body of evidence that C-reactive protein is an independent predictor of cardiovascular disease.[7] The authors previously used data from the Women's Health Study to conduct a small case–control analysis with three years of follow-up. The results showed that C-reactive protein levels predicted the risk of cardiovascular disease.[8] The current study, which extends the previous results, includes data from the entire study cohort of nearly 28,000 women with data on base-line levels of C-reactive protein, who were followed for a mean of eight years, and uses a composite cardiovascular end point.

The crude data showed that C-reactive protein levels predicted subsequent cardiovascular disease more strongly than did the levels of low-density lipoprotein (LDL) cholesterol. When adjusted for a variety of traditional risk factors, C-reactive protein and LDL cholesterol were equivalent in their ability to discriminate women who later had an event from those who did not, on the basis of the area under the receiver-operating-characteristic curve, but C-reactive protein was found to be a better predictor when a likelihood test was performed. Statistical significance can be inflated with large sample sizes, of course, whereas the clinical importance of a difference may be minimal. This fact should be taken into consideration as statistics are translated into clinical strategy. In the study by Ridker et al., the association between C-reactive protein and cardiovascular disease was independent of traditional risk factors, but no information is provided from a formal test to determine whether there was added value over the information provided by the global Framingham risk score. The data lend support to the inflammatory hypothesis of the pathogenesis of coronary heart disease and also raise a number of important issues about statistical predictors of coronary heart disease and their clinical relevance. The findings of Ridker et al. from this study of healthy women are consistent with published reports in diverse populations.[9] These data raise the question of whether it is time to begin more widespread assessment of C-reactive protein.

In 1968, Wilson and Jungner outlined criteria for screening programs and suggested that if there is no generally accepted treatment, it is premature to embark on routine screening.[10] The landscape of prevention has changed dramatically since that time, and there is growing recognition that levels of one risk factor can modify treatment plans aimed at ameliorating another risk factor. A more contemporary set of questions to consider before implementing routine