Review

The use of corticosteroids in the management of bacterial meningitis in adults

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Despite the introduction of newer antimicrobial agents, bacterial meningitis continues to be associated with significant morbidity and mortality. Evidence from in-vitro studies, experimental animal models, and clinical studies indicate that the host inflammatory response is responsible for much of the deleterious consequences of this disease. Thus, there is much interest in the adjunctive use of antiinflammatory agents in the therapy of bacterial meningitis. Although there is considerable evidence from animal models and from clinical trials in children that adjunctive antiinflammatory therapy with corticosteroids is effective in reducing inflammation and in improving long-term outcomes, similar data involving adults are largely lacking. The rationale for the use of corticosteroids in the management of bacterial meningitis, and the applicability to disease in adults, are discussed, and some recommendations for their use in this setting are made.

Introduction

Bacterial meningitis is a disease characterized by the presence of bacteria within the subarachnoid space and an accompanying inflammatory response. In the last 15 years a great deal of research has been performed, both in the clinical setting and in the laboratory, on the pathophysiology of bacterial meningitis. This research has revealed that the deleterious consequences of bacterial meningitis are, in large part, not caused by the offending bacteria directly, but by the inflammatory response to the bacteria and their components generated by the host. The major constituents of this inflammatory response are activated polymorphonuclear neutrophils and soluble pro-inflammatory mediators such as cytokines, platelet-activating factor, and toxic oxygen derivatives.

The fact that bacteria are not wholly responsible directly for the pathophysiologic consequences of bacterial meningitis is reflected by the relative lack of improvement in outcomes for this disease recently. During the last fifteen years a number of advances in the management of bacterial meningitis have been made. These include the
Introduction of third-generation cephalosporins, which have excellent antimicrobial activity against the more common pathogens (Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitidis), and which penetrate into the cerebrospinal fluid in adequate concentrations in the presence of inflammation. However, in this time there have been no significant reductions in the overall mortality (Schlech et al., 1985; Wenger et al., 1990; Durand et al., 1993) or in the incidence of long-term neurological sequelae (Sell, 1983; Klein, Feigin & McCracken, 1986; Pomeroy et al., 1990) following bacterial meningitis. With the possible exception of addressing problems with emerging antimicrobial resistance, it is unlikely that improvements in the outcomes associated with bacterial meningitis will be achieved by the introduction and use of newer antimicrobial agents alone.

In light of this, there has been considerable interest in the potential adjunctive use of one or more agents directed at reducing the inflammatory response. Such an agent should be able to inhibit the synthesis of, or to antagonize the effects of, several endogenous mediators. In addition, the use of such an agent should be associated with minimal adverse effects. Finally, there should be no clinically significant interference with the activity of appropriate antimicrobial agents within the subarachnoid space.

Many different antiinflammatory agents have been studied in experimental models of bacterial meningitis, and some have been demonstrated to reduce some of the indices of inflammation observed in these models. These agents include corticosteroids, anti-cytokine antibodies (when introduced intracisternally), platelet-activating factor antagonists, free radical scavengers, and leucocyte-endothelial cell adhesion molecule antagonists. However, only one class of antiinflammatory agents, the corticosteroids, has been studied in the clinical setting. Most of the patients enrolled in the trials of corticosteroids have been in the paediatric age group.

This article reviews the rationale for use of corticosteroids as adjunctive therapy for bacterial meningitis, and the results of experimental and clinical trials of these agents. The implications of these studies as they relate to the possible use of corticosteroids for the management of bacterial meningitis in adults are examined.

Pathophysiology of bacterial meningitis

To understand the rationale for using corticosteroids (or any other agents) as adjunctive therapy for bacterial meningitis, it is necessary to comprehend the pathophysiology of the disease. The pathophysiology of bacterial meningitis will be reviewed briefly here; for more extensive reviews the reader is referred elsewhere (Sáez-Llorens et al., 1990; Tunkel, Wispelwey & Scheld, 1990; Quagliarello & Scheld, 1992). In the usual sequence of events, bacteria establish bacteraemia and are able to survive within the intravascular space. By mechanisms which have not yet been elucidated, bacteria then cross the blood-brain barrier (BBB) or gain entry into the subarachnoid space (SAS) by routes not dependent upon the BBB. Bacterial replication proceeds because there is relatively little opsonic or bactericidal activity within the SAS, a consequence of minimal concentrations of complement and antibody. Bacterial subcapsular components such as lipopolysaccharide and lipoteichoic acids are uncovered by bacterial replication or lysis (which may be promoted by the use of bactericidal antibiotics). When exposed to these compounds, cerebral microvascular endothelial cells and other resident central nervous system (CNS) cells (e.g., macrophages and macrophage-like cells such as astrocytes and microglia) produce and release chemotactic factors, vasodilators, and inflammatory mediators.
Numerous potential mediators have been implicated in this process, including, among others, the cytokines interleukin-1 (IL-1) and tumour necrosis factor (TNF), the phospholipid derivatives prostaglandins and platelet-activating factor (PAF), and nitric oxide. Some of these molecules contribute to the activation of polymorphonuclear neutrophils (PMNs). In addition, there is increased expression of leucocyte-endothelial cell adhesion molecules on PMNs and endothelial cells, which facilitates the transendothelial migration of PMNs into the SAS. Within the SAS, activated PMNs release cytotoxic molecules (including reactive oxygen and/or nitrogen species) and inhibit cerebrospinal fluid (CSF) outflow.

Cerebral oedema results from cytotoxicity, increased BBB permeability, and vasodilation, and in turn contributes to increased intracranial pressure. These pathological effects are ultimately responsible for alterations in neuronal homeostasis, resulting in neuronal dysfunction and/or death and thus contributing to the pathophysiological consequences of bacterial meningitis.

The potential role of corticosteroids

The physiological effects of corticosteroids suggest their potential role in the adjunctive therapy of bacterial meningitis, as they have antiinflammatory effects in many steps of the pathophysiological cascade of bacterial meningitis. Among the steps which corticosteroids may inhibit are the expression of mRNA for TNF and IL-1, the production of phospholipid derivatives such as prostaglandins and PAF, complement activation, and the activity of the inducible nitric oxide synthase. Since these agents affect many of the steps proposed to occur in bacterial meningitis, it would seem that corticosteroids would have great potential as adjunctive agents in the management of this disease.

The potential antiinflammatory effects of corticosteroids on the pathophysiological effects of bacterial meningitis have been studied extensively in animal models. These studies have almost universally confirmed the proposed ability of corticosteroids to reduce many of the inflammatory indices and pathophysiological consequences of bacterial meningitis. In rabbit models of pneumococcal meningitis, the use of methylprednisolone has resulted in decreased meningeal inflammation (Nolan et al., 1978), CSF outflow resistance (Scheld et al., 1980), and cerebral oedema (Täuber, Khayam-Bashi & Sande, 1985) when compared with animals not treated with corticosteroids. Similarly, dexamethasone use in a rabbit model of pneumococcal meningitis resulted in more rapid normalizations of CSF protein concentrations (considered by some investigators to be a measure of BBB permeability), compared with untreated animals (Kadurugamuwa, Hengstler & Zak, 1989). Dexamethasone plus ceftriaxone resulted in significant reductions in CSF concentrations of TNF, and in CSF leucocyte concentrations, compared with ceftriaxone alone in a rabbit model of *H. influenzae* meningitis (Mustafa et al., 1989). Thus, the possible efficacy of corticosteroids as adjunctive agents in the management of bacterial meningitis is supported by evidence from experimental animal models.

Possible deleterious effects of corticosteroids

There has been concern that the antiinflammatory effects of corticosteroids may actually have deleterious consequences for antimicrobial therapy in the management of bacterial meningitis.
meningitis. The increased permeability of the BBB observed in bacterial meningitis, while contributing to the pathophysiological consequences of the disease, may actually facilitate therapy. Because of the 'leaky' BBB early in treatment, systemically administered antimicrobial agents can achieve CSF concentrations which would not be achieved in the presence of an intact BBB. This may be important for bacterial killing. It is possible, therefore, that corticosteroids may rapidly normalize the homeostatic derangements observed, but the decreased permeability of the BBB causes decreased penetration and CSF concentrations of antimicrobial agents.

The possible effects of corticosteroids on antimicrobial penetration have been investigated in several experiments using animal models. In a rabbit model, concomitant administration of methylprednisolone resulted in reduced CSF concentrations and percent CSF penetration (100 × CSF concentration/serum concentration) of ampicillin during pneumococcal meningitis, and of gentamicin during Escherichia coli meningitis. However, for both species CSF concentrations of the respective antibiotics exceeded the minimum bactericidal concentrations (MBCs), and bacterial killing in vivo was not affected (Scheld & Brodeur, 1983). Dexamethasone did not affect CSF concentrations or percent CSF penetration of ampicillin, cefotaxime, or cefuroxime in an infant rat model of H. influenzae meningitis (Rodriguez et al., 1991).

In an experimental model of pneumococcal meningitis, however, concomitant administration of dexamethasone has been demonstrated to reduce entry of vancomycin into CSF. Importantly, the rate of bactericidal activity achieved (i.e., rate of bacterial killing in CSF per hour) was also significantly reduced. Neither ceftriaxone nor rifampin was affected by dexamethasone administration in this model. Dexamethasone also adversely affected the rate of bactericidal activity of the combination of vancomycin and ceftriaxone in experimental meningitis induced by a highly penicillin-resistant strain of S. pneumoniae (Paris et al., 1994).

There has been a limited study of the possible effect of dexamethasone on the penetration of antibiotics across the BBB in the clinical setting. In a single study of 11 children with bacterial meningitis treated with ceftriaxone and dexamethasone, the CSF concentrations of ceftriaxone were comparable to those reported earlier for children not treated with dexamethasone (Gaillard et al., 1994).

Thus, while there is some evidence to support the theoretical contention that corticosteroids could reduce penetration of antibiotics into the CNS, this phenomenon, if it occurs at all, does not occur universally or is not of general clinical significance. If corticosteroids do reduce CSF concentrations of antibiotics, the resulting CSF concentrations may still be sufficient to achieve adequate bacterial killing. A possible exception to this may be the use of vancomycin for the therapy of pneumococcal meningitis. The potential influence of high-dose corticosteroids on the entry of antibiotics into the CSF, and upon bactericidal activity in the CSF, has not been well studied for all drugs or combinations of drugs relevant to current clinical practice.

Clinical trials of corticosteroids

The potential adjunctive role of corticosteroids in the management of bacterial meningitis predated knowledge of the specific antiinflammatory effects noted above. The original clinical trials were performed based upon knowledge of the ability of corticosteroids to reduce cerebral oedema in patients with intracranial neoplasms or in the postoperative state. Although the first studies using corticosteroids as adjunctive
therapy were published in the 1950s, the first double-blinded, placebo-controlled trials were performed in the 1960s.

In the first controlled trial, hydrocortisone 300 mg/day was compared with placebo in a group of 56 adult patients with pneumococcal meningitis. There was no reduction in mortality in the patients in the hydrocortisone arm, and the incidence of long-term neurologic sequelae was not evaluated (Cooperative Study Group, 1963).

The results of two trials were published in 1969. In one study, methylprednisolone 40 mg or placebo was administered to 117 children with bacterial meningitis. There was no reduction in mortality or in long-term neurological sequelae noted in the methylprednisolone arm (de Lemos & Haggerty, 1969). In the other study, the use of dexamethasone 1.2 mg/m² every 6 h for 4 days was associated with fewer neurological complications during hospitalization and at the time of discharge. However, the authors noted that despite randomization, there was a disproportionate number of children with poor prognostic factors in the placebo arm than in the dexamethasone arm, and attributed the differences in outcome to this selection bias (Belsey, Hoffpauir & Smith, 1969).

These three early trials did not provide evidence for the possible benefit of corticosteroids in the management of bacterial meningitis. However, in evaluating these results several points should be noted. In the first trial (Cooperative Study Group, 1963), there may have been a bias against the possible benefit of corticosteroids because the hydrocortisone arm included a greater number of elderly patients, who generally have a poorer prognosis than do younger patients. The corticosteroid used in the second trial (de Lemos & Haggerty, 1969), methylprednisolone, has been demonstrated in animal models of bacterial meningitis to have decreased efficacy in reducing the pathophysiological consequences in comparison with dexamethasone (Täuber et al., 1985). Finally, the dose of dexamethasone used in the third trial (Belsey et al., 1969) was lower than has been used in more recent trials. Thus, the potential efficacy of corticosteroids as adjunctive therapy may not have been properly evaluated in these three early trials. However, almost two decades elapsed before further trials were conducted.

The results of several well-designed, randomized, double-blinded, placebo-controlled trials have been published on the use of dexamethasone for bacterial meningitis since 1988 (Lebel et al., 1988; Girgis et al., 1989; Odio et al., 1991; Schaad et al., 1993; Kanra et al., 1995; Kilpi et al., 1995). The results of these trials are summarized in the Table showing considerable variation in the effects of dexamethasone on inflammatory indices and on clinical outcomes. However, a reduction in bilateral hearing loss and in long-term neurological sequelae associated with the use of dexamethasone was demonstrated in a meta-analysis of data from four of these reports (Lebel et al., 1988; Girgis et al., 1989; Odio et al., 1991) and from one of the trials reported in 1969 (Belsey et al., 1969). Thus, there is evidence from clinical trials that the adjunctive use of dexamethasone improves outcomes in the management of bacterial meningitis, at least in children.

A major consideration in the evaluation of any new treatment is the potential for serious adverse effects. The administration of dexamethasone at the doses used in these studies appears to be quite safe. Although there were two episodes of gastrointestinal bleeding associated with dexamethasone use reported in one study (Lebel et al., 1988), this has not been reported in the other studies. In fact an increased risk of any adverse effects has not been reported in any of the other studies.
<table>
<thead>
<tr>
<th>Author/year</th>
<th>No of children/ adults</th>
<th>Dexamethasone dose</th>
<th>% of isolates*</th>
<th>Antibiotic(s)</th>
<th>Changes* at 24 h in CSF concentrations</th>
<th>Effects* on incidence of long-term clinical parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lebel et al. (1988)</td>
<td>100/0</td>
<td>0.15 mg/kg q6 h x 4 days</td>
<td>77</td>
<td>Cefuroxime</td>
<td>(\uparrow) (\uparrow) (\downarrow) (\downarrow)</td>
<td>(\downarrow) (\downarrow) (\downarrow) (\downarrow)</td>
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<td>Lebel et al. (1988)</td>
<td>100/0</td>
<td>0.15 mg/kg q6 h x 4 days</td>
<td>77</td>
<td>Ceftriaxone</td>
<td>(\uparrow) (\uparrow) (\downarrow) NA</td>
<td>(\downarrow) (\downarrow) (\downarrow) (\downarrow)</td>
</tr>
<tr>
<td>Lebel et al. (1989)</td>
<td>60/0</td>
<td>0.15 mg/kg q6 h x 4 days</td>
<td>75</td>
<td>Cefuroxime</td>
<td>(\uparrow) (\uparrow) (\downarrow) NA</td>
<td>(\downarrow) (\downarrow) (\downarrow) (\downarrow)</td>
</tr>
<tr>
<td>Girgis et al. (1989)</td>
<td>282,147</td>
<td>8 12 mg q12 h x 3 days</td>
<td>13</td>
<td>Ampicillin + chloramphenicol</td>
<td>(\uparrow) (\uparrow) (\downarrow) NA</td>
<td>(\downarrow) (\downarrow) (\downarrow) (\downarrow)</td>
</tr>
<tr>
<td>Odio et al. (1991)</td>
<td>101/0</td>
<td>0.15 mg/kg q6 h x 4 days</td>
<td>8</td>
<td>Cefotaxime</td>
<td>(\uparrow) (\uparrow) (\downarrow) (\downarrow)</td>
<td>(\downarrow) (\downarrow) (\downarrow) (\downarrow)</td>
</tr>
<tr>
<td>Schaad et al. (1993)</td>
<td>115/0</td>
<td>0.4 mg/kg q12 h x 2 days</td>
<td>58</td>
<td>Ceftriaxone</td>
<td>(\uparrow) (\uparrow) (\downarrow) (\downarrow)</td>
<td>(\downarrow) (\downarrow) (\downarrow) (\downarrow)</td>
</tr>
<tr>
<td>Kilpi et al. (1995)</td>
<td>122/0</td>
<td>0.5 mg/kg q8 h x 3 days</td>
<td>10</td>
<td>Ceftriaxone</td>
<td>NA NA NA NA</td>
<td>(\downarrow) (\downarrow) (\downarrow) (\downarrow)</td>
</tr>
<tr>
<td>Kanra et al. (1995)</td>
<td>56/0</td>
<td>0.15 mg/kg q6 h x 4 days</td>
<td>100</td>
<td>Ampicillin + sulbactam</td>
<td>NA NA NA NA</td>
<td>(\downarrow) (\downarrow) (\downarrow) (\downarrow)</td>
</tr>
</tbody>
</table>

*HI, *H. influenzae*; SP, *S. pneumoniae*; NM, *N. meningitidis*.

*Statistically significant changes \((P < 0.05)\) compared with placebo: \(\uparrow\) = increase, \(\downarrow\) = decrease, \(\leftrightarrow\) = no difference; NA = results not available

*Patients < 12 years were given 8 mg, and patients \(\geq 12\) years were given 12 mg, q12 h

*Hearing loss and other neurological sequelae were considered together in this study.

*In this study, 32 patients received dexamethasone alone. 30 patients received glycerol alone. 34 patients received dexamethasone and glycerol, and 26 patients received placebo.
Another concern is the possible deleterious effect of empirical treatment with dexamethasone upon the course of children with CNS infections caused by organisms such as viruses, when T-cell immunity may be particularly important. In a retrospective analysis of 32 children with suspected bacterial meningitis treated with dexamethasone some were found to have nonbacterial infections; viral cultures were positive for enterovirus in seven of these cases. There were no adverse effects associated with the use of dexamethasone among these patients (Waagner et al., 1990). The results of this small study suggest that the empirical use of dexamethasone with antibiotics for suspected bacterial meningitis is safe for patients with aseptic meningitis.

Several very important points must be considered when evaluating the results of these trials. The design of the trials has not been entirely consistent, which may make accurate comparison and compiling of data difficult. For example, in one trial, the timing of the dose of dexamethasone is not noted (Lebel et al., 1988), and in another trial the first dose of dexamethasone was given within 12 h of the first dose of antibiotics (Lebel et al., 1989). This may have biased against a treatment effect for dexamethasone, because inhibition of synthesis of cytokines IL-1 and TNF by corticosteroids is limited after genes for these cytokines have been expressed. Since increased synthesis of IL-1 and TNF occur after antibiotic-induced lysis of bacteria and exposure of cell surface components, for optimal effect corticosteroids should be given before or at the same time as the initiation of antimicrobial therapy. While this has been the case for some studies, it is possible that many of the patients in the two trials noted above were given corticosteroids much later, and thus may not have benefited fully from corticosteroid therapy.

Another possible confounding factor is the choice of antibiotics in one of the studies. The earliest of the recent reports actually compiled the results of two separate studies; in one the antibiotic used was cefuroxime, and in the other it was ceftriaxone. Statistically significant reductions associated with the use of dexamethasone in the incidence of short-term neurologic abnormalities and moderate to severe bilateral hearing loss were observed only in the cefuroxime arm; there were no significant differences in outcomes in the ceftriaxone arm (Lebel et al., 1988). In another trial the only antibiotic used was cefuroxime (Lebel et al., 1989). The significance of this is that cefuroxime, in comparison with ceftriaxone, has been associated with delayed sterilization of the CSF and increased hearing loss, at least for the therapy of disease in the paediatric age group and caused by H. influenzae (Schaad et al., 1990). Thus cefuroxime is regarded as suboptimal therapy for bacterial meningitis, and it may not be appropriate to base decisions regarding the adjunctive use of corticosteroids on such therapy.

The selection of antimicrobials used in the trials has been somewhat variable. The antibiotics used have included cefuroxime, ceftriaxone, cefotaxime, ampicillin-sulbactam, and the combination of intramuscular ampicillin and chloramphenicol; some of these regimes would not be considered appropriate in many industrialized areas today.

The doses used for dexamethasone have also been inconstant among the various trials. In most of the trials, dexamethasone was used at a dose of 0.15 mg/kg intravenously every 6 h for 4 days. However, in one trial, dexamethasone was given intramuscularly at a dose of 8 mg for patients younger than 12 years, and 12 mg for patients 12 years and older, every 12 h for 3 days (Girgis et al., 1989). Dexamethasone has also been given intravenously at 0.4 mg/kg every 12 h for 2 days (Schaad et al.,
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1993), and at 0.5 mg/kg every 8 h for 3 days (Kilpi et al., 1995). The optimal dose of dexamethasone has not been established; a recent comparison of the most commonly used regimen (0.15 mg/kg intravenously every 6 h) given for 2 days versus 4 days in 118 children (with disease due primarily to *H. influenzae* or *N. meningitidis*) suggested that the two-day schedule was as effective as the four-day schedule (Syrogiannopoulos et al., 1994).

Of overriding importance in evaluation of the utility of corticosteroids as adjunctive therapy for bacterial meningitis in adults, is the nature of the patient populations and the microbiology observed in these trials. Adults were enrolled in only one of the recent trials, and in that trial patients ages 13 years and older represented only about one-third of the total number of patients (Girgis et al., 1989); the remainder of the trials enrolled only children between the ages of 6 weeks and 16 years. Because *H. influenzae* type b has traditionally been the most common cause of bacterial meningitis in the paediatric age group, the vast majority (approximately 50–75%) of cases of meningitis in the trials restricted to children were caused by this organism; overall, approximately 43% of the total number of cases reported in all of the trials were caused by *H. influenzae*. It is difficult, then, to apply the results of these trials to the management of bacterial meningitis in adults, in whom the organisms most commonly responsible are *S. pneumoniae* and *N. meningitidis*. It is worthwhile to analyze the results of the trial which did involve adults separately.

As noted above, of the 429 cases reported in the lone trial that involved adults (Girgis et al., 1989), only 147 (approximately 34%) were 13 years old or older. Approximately 62% of cases were due to *N. meningitidis*, 25% due to *S. pneumoniae*, and 13% (all in children less than 6 years old) due to *H. influenzae*. There was a trend toward reduction in long-term neurological sequelae (severe hearing loss, hemiparesis) in the dexamethasone-treated group (2.1%) compared with the group given placebo (4.5%), but this difference was not statistically significant. The difference in hearing loss in the subgroup of 106 patients with pneumococcal meningitis (0% vs 12.5%) was considered significant (*P* < 0.05). Dexamethasone therapy was associated with reduced overall mortality compared with placebo (9.5% versus 19.2%, *P* < 0.01). In the subgroup of patients with pneumococcal meningitis, the difference in mortality was even more pronounced (13.5% in the dexamethasone group versus 40.7% in the placebo group, *P* < 0.002). The effects (if any) of dexamethasone on mortality and long-term neurological sequelae were not stratified according to age group.

Again, several points should be considered when interpreting the results of this trial. Sixty per cent of patients were comatose on admission, and thus may represent a population of patients more severely ill than is ordinarily encountered. The incidence of possible adverse effects is not well documented, making evaluation of the safety of dexamethasone in the adult population difficult. Finally, antibiotics and dexamethasone were administered intramuscularly, and thus the treatment given may not be adequately representative of the management practices in most western countries at present.

Dexamethasone for management of bacterial meningitis in adults

Given the dearth of information regarding the utility of adjunctive dexamethasone in the management of adults with bacterial meningitis, it is not possible to make definitive recommendations in this setting. Some arguments which may be made either for or
against the use of dexamethasone in adults with bacterial meningitis are presented below.

Since the inflammatory processes thought to occur in children with bacterial meningitis are likely to occur in adults as well, it would be reasonable to assume that antiinflammatory therapy with corticosteroids would be similarly effective in each age group. Thus, since clinical trials suggest strongly that dexamethasone reduces the incidence of long-term neurological sequelae in children, the same should hold true for adults. Animals models of pneumococcal meningitis, the most common cause of bacterial meningitis in adults in many countries, suggest that dexamethasone is effective in reducing the pathophysiological consequences of subarachnoid space inflammation elicited by this organism. As noted earlier, the single clinical trial which involved adults demonstrated statistically significant reductions in the incidence of long-term neurological sequelae and in mortality caused by *S. pneumoniae* associated with dexamethasone use; indeed, this was the only trial to demonstrate an overall reduction in mortality among recipients of dexamethasone (Girgis et al., 1989). In addition, one paediatric trial was restricted to children with pneumococcal meningitis, and in this trial there was a reduction in long-term hearing loss (Kanra et al., 1995).

Dexamethasone appears to be reasonably safe, at least in children. It does not appear from animal models or from limited data in children that dexamethasone administration has a deleterious effect on antimicrobial activity within the CSF. An important possible exception to this is the potential reduction in vancomycin entry into the CSF; because of this, it may be unwise to use dexamethasone for the management of bacterial meningitis in adults in areas in which there is a high incidence of highly penicillin-resistant *S. pneumoniae*.

The strongest argument against the use of corticosteroids as adjunctive therapy for bacterial meningitis in adults is that there is insufficient data to support routine use of these agents. Because of marked differences between adults and children in microbial aetiology and in possible comorbid illness (and thus potential adverse effects), it would be inappropriate to apply without careful consideration the results of the trials performed to date involving only or predominantly children to the management of disease in adults. Without more extensive data in the adult population, it is not possible to make general recommendations.

In the absence of firm data from clinical trials, some recommendations may be made based upon prognostic indicators of potentially severe disease. It may be reasonable to consider the use of dexamethasone in the management of adult patients with organisms present in CSF stained with Gram's stain, as this finding suggests a high concentration of organisms in the CSF. The administration of bactericidal antibiotics in such a setting would be expected to result in the exposure and release of high concentrations of bacterial cell surface components, thereby eliciting an amplified inflammatory host response. It may also be reasonable to administer dexamethasone to adults with poor prognostic factors as marked alterations in consciousness (e.g., coma or stupor), or increased intracranial pressure; the latter may be documented by clinical evaluation (e.g., cranial nerve VI palsy), laboratory parameters (e.g., markedly elevated opening pressure), or radiological techniques (e.g., oedema on CT or MRI scan of the brain). It is important to monitor the patient for the occurrence of potential adverse effects, particularly gastrointestinal bleeding.

In summary, evidence from animal models of bacterial meningitis indicate that the host inflammatory response is largely responsible for the pathophysiological
consequences of this disease, and that antiinflammatory agents may reduce the indices of inflammation. Corticosteroids have a number of antiinflammatory effects, and clinical trials with dexamethasone, primarily involving children, indicate that these agents may be effective in reducing long-term neurological sequelae and possibly mortality. However, there is insufficient information on the use of corticosteroids in adults with bacterial meningitis to allow for reasonable analysis of the efficacy and safety of such therapy in this setting. Thus, it is not possible to make general recommendations on therapy in the adult population at this time. Until large well-designed clinical trials are performed, and the results of these trials are subjected to critical analysis, decisions regarding the use of corticosteroids in the management of bacterial meningitis in adults must be individualized, with careful consideration of the potential benefits and risks.

References


Corticosteroids for bacterial meningitis in adults


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