REVIEW ARTICLE

Steroid Therapy for Bacterial Meningitis

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Routine dexamethasone therapy for bacterial meningitis in pediatric patients is controversial. Two experts debated this topic at the 1993 meeting of the Infectious Diseases Society of America. Both experts agreed that for management of *Haemophilus influenzae* meningitis, dexamethasone significantly reduced sensorineural hearing loss and probably reduced other long-term sequelae. Because relatively few patients with pneumococcal and meningococcal meningitis have been studied, no conclusions could be reached regarding the effectiveness of dexamethasone. Dr. Urs Schaad emphasized the impressive anti-inflammatory effects of dexamethasone in experimental pneumococcal meningitis and the lack of any adverse events when given to children for 2 or 4 days. He recommended routine use of dexamethasone in treating pediatric patients with bacterial meningitis. Dr. Sheldon Kaplan expressed concern regarding the effectiveness of steroids in treating pneumococcal meningitis, especially when penicillin-resistant and cephalosporin-resistant isolates are present, and he addressed the question of the long-term effects of administration of dexamethasone in children with viral meningitis. He advised against the routine use of dexamethasone for non-*H. influenzae* meningitis.

At the annual meeting of the Infectious Diseases Society of America in October 1993, one of the sessions was devoted to the controversy of whether dexamethasone should be routinely used to treat patients with bacterial meningitis. The two physicians chosen to address this issue had recently conducted multicenter, placebo-controlled, double-blind studies of dexamethasone therapy in children with meningitis. Dr. Urs B. Schaad was asked to present information supporting the routine use of dexamethasone therapy in these patients. Dr. Sheldon L. Kaplan took the opposing view—that dexamethasone should be used only in select patients with bacterial meningitis. The following paper represents a distillation of their presentations and a commentary by Dr. George H. McCracken, Jr.

Affirmative View

Bacterial meningitis remains an important cause of death and permanent neurological disability despite advances in antimicrobial therapy, rapid diagnostic techniques, and supportive care. The two main strategies for further reducing the impact of purulent meningitis are prevention of disease by active immunization against the common bacterial pathogens and reduction of CNS pathology by use of appropriate antiinflammatory measures.

Data from recent in vitro and animal experiments indicate that the bacteria causing meningitis elaborate outer membrane–active or cell wall–active components that affect monocytes, leukocytes, cerebrovascular endothelial cells, and astrocytes [1–3]. These cells, in turn, produce various proinflammatory cytokines or express specific receptors on their surface. These cytokines and receptors initiate an accelerating cascade of events, resulting in alteration of the blood-brain barrier, meningeal inflammation, increased intracranial pressure, and decreased cerebral vascular perfusion. If the interaction of these pathopysiological alterations is severe and sustained, it will produce neuronal injury and irreversible focal or diffuse brain damage.

Dexamethasone is a potent antiinflammatory agent. There is convincing in vitro and in vivo evidence that this steroid decreases the liberation of various cytokines [4–6]. Other effects of dexamethasone, some of which may be independent of its effect on cytokine release, include reduction of brain edema, intracranial pressure, blood-brain barrier permeability, and CSF lactate concentrations. These findings suggest a beneficial effect of this drug in the treatment of bacterial meningitis, especially when given before the first dose of antibiotics.

Five recent clinical studies have evaluated the use of dexamethasone as part of the initial regimen for management of

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bacterial meningitis [7–10]. All of these studies showed a reduction in neurological sequelae when patients were given dexamethasone therapy. Because of the relatively small numbers of patients enrolled in the therapeutic arms of these clinical trials, beneficial effects were statistically significant only when sequelae were unusually common because of suboptimal antibiotic treatment (i.e., cefuroxime) or because of suboptimal supportive and diagnostic management (i.e., the studies were conducted in developing countries). For these reasons, routine use of steroid therapy for bacterial meningitis remains controversial for some physicians and represented a good topic for discussion at this meeting.

To assess the effects of dexamethasone therapy on the course and outcome of bacterial meningitis in Swiss children, we conducted a prospective, placebo-controlled, double-blind, multicenter study of children who received ceftriaxone and routine supportive treatment for meningitis [11].

On the basis of pathophysiological and pharmacokinetic data [1, 2, 12], and for achievement of maximum benefits and minimum complications, dexamethasone therapy was started 10 minutes before the first dose of ceftriaxone was administered, and it was given every 12 hours for only 2 days. Results from animal studies strongly indicate that the optimal time for adjunctive dexamethasone therapy is just before administration of the first dose of parenteral antibiotics [4–6]. Exacerbation of inflammation that occurred during the initial antibiotic therapy in pediatric patients with *Haemophilus influenzae* meningitis was shown by documentation of a substantial increase in cytokine concentrations in the CSF 2–6 hours after the first dose of ceftriaxone was administered [13].

All 115 pediatric study patients with acute bacterial meningitis received ceftriaxone (100 mg/kg body weight) in one single daily intravenous dose. By random assignment, 55 patients received placebo and 60 patients received four intravenous doses of dexamethasone (.4 mg/kg body weight) over 2 days; the first dose of dexamethasone was given 10 minutes before the first ceftriaxone dose was given, and the next three doses were given every 12 hours. Baseline demographic, clinical, and laboratory features of the two groups were similar.

After 24 hours of treatment, meningeal inflammation (as shown by CSF glucose concentration) was significantly increased in those given dexamethasone compared with those given placebo (mean percentage increase in glucose concentration, 63 mg/dL vs. 40 mg/dL; $P = .008$). However, at 24 hours of therapy, other indices of inflammation showed that changes were similar in both groups.

Addition of dexamethasone did not affect the rate at which CSF became sterile. Both groups showed prompt clinical responses and similar frequencies of acute complications: 12% for the dexamethasone group vs. 15% for the placebo group. Fever resolved more rapidly in patients receiving dexamethasone, but they experienced secondary fever more frequently. However, the probable causes of secondary fever did not include any complication of bacterial infection. An antipyretic action of dexamethasone that is followed by a rebound effect has been previously observed [7].

We monitored for possible adverse effects of dexamethasone and saw no abnormalities. Despite more frequent detection of occult blood in the stool of those patients treated with dexamethasone, there was neither overt gastrointestinal bleeding nor a substantial drop in the blood hemoglobin concentration in any of the study patients.

At follow-up examinations 3, 9, and 15 months after discharge from the hospital, 3 (5%) of 60 dexamethasone recipients and 9 (16%) of 55 placebo recipients had one or more neurological or audiological sequelae ($P = .066$); the relative risk of sequelae in placebo recipients was 3.27 (95% CI: .93–11.47).

The study designs of two other prospective, double-blind trials of adjunctive dexamethasone therapy for bacterial meningitis [7, 14, 15] were similar to that of our study (11); all children received ceftriaxone, and the diagnostic and supportive management of the patients in the two other studies was similar to that in ours. The results of a meta-analysis (table 1) of these three studies to determine the risk of developing any sequelae showed that the relative risk of developing persistent neurological and/or audiological sequelae for children treated with placebo was 2.29 (95% CI: 1.20–4.39).

Because only 60 (17%) of 352 patients enrolled in these three studies [7, 11, 15] had meningitis caused by *Streptococcus pneumoniae*, it was not possible to determine conclusively whether dexamethasone was as effective when used to treat infants and children with pneumococcal meningitis. We compared the data from these three studies with the results of a retrospective analysis of pediatric patients with pneumococcal meningitis treated in Dallas from 1984 to 1990 [16]. In the first three studies, adverse neurological or audiological sequelae were documented in 9 (26%) of 34 patients receiving placebo as compared with 14 (33%) of 43 non-steroid-treated and 3 (9%) of 32 dexamethasone-treated patients ($P = .025$) in the retrospective analysis. These clinical data are also consistent with results from a model for experimental pneumococcal meningitis [1–3, 5]. We need additional data on dexamethasone therapy used in conjunction with other classes of antibiotics (such as vancomycin and rifampin) to determine its effect in patients with meningitis due to penicillin-resistant and cephalosporin-resistant pneumococci.

Factors other than antibacterial and anti-inflammatory therapies can affect the outcome for patients with meningitis; for example, type and virulence of the causative etiologic agent (especially *S. pneumoniae*), initial severity of disease, time to sterilization of CSF, and the rate of complications during hospital stay all affect outcome. Our results except for delayed sterilization of CSF confirmed these relationships. Knowledge of these prognostic factors is essential for adequate management of patients with bacterial meningitis, but

Table 1. Meta-analysis of persistent sequelae reported in three studies of children treated for bacterial meningitis with ceftriaxone plus dexamethasone or placebo.

Study location [reference]	No. of patients with any neurological or audiological sequelae		*P* value*	Relative risk (95% CI)†
	Placebo	Dexamethasone		
Dallas [7, 14]	9/46 (20)	3/49 (6)	.065	3.20 (0.92–11.08)
United States [15]	10/74 (14)	6/68 (9)	.434	1.53 (0.59–3.99)
Switzerland [11]	9/55 (16)	3/60 (5)	.066	3.27 (0.93–11.47)
Total‡	28/175 (16)	12/177 (7)	NA	2.29 (1.20–4.39)

NOTE. CI = confidence interval; NA = not applicable.

* Significance is based on the comparison of the two treatment groups.

† The relative risks presented are for a patient in the placebo group as compared with a patient in the dexamethasone group.

‡ Results of all three studies combined.

does not help in the determination of initial antimicrobial and anti-inflammatory therapy, which needs to be started as soon as a diagnosis of meningitis is suspected. The results of our study and of the meta-analysis convince me that adjunctive dexamethasone therapy improves the outcome for infants and children with bacterial meningitis. Thus, I recommend the use of adjunctive dexamethasone therapy in these patients, preferably at the dose regimen used in our study.

Final recommendations regarding the use of dexamathosone in the treatment of bacterial meningitis in neonatal and adult patients can not be made until the results of ongoing studies are known.

Opposing View

Although I was asked to present the opposing view regarding the use of adjunctive dexamethasone therapy in the treatment of bacterial meningitis, I am not completely opposed to the administration of dexamethasone for this infection. In fact, there is convincing evidence that dexamethasone reduces neurological sequelae, especially hearing loss, associated with meningitis due to *Haemophilus influenzae* type b [7, 9, 11]. This was also the conclusion of three influential groups that put forth guidelines for treatment of meningitis [17–19]. Several well-conducted, placebo-controlled, double blind studies in which optimal antibiotics were used have found fewer total neurological sequelae at discharge and at the time of short-term follow-up in children who received adjunctive dexamethasone therapy compared with those who received placebo [7, 9, 11]. However, the majority of the children in these studies had meningitis due to *H. influenzae* type b; thus, the findings cannot necessarily be applied to cases where meningitis is caused by *S. pneumoniae*, *Neisseria meningitidis*, or other bacteria.

Since the licensure of the polysaccharide vaccine and the subsequent licensure of *H. influenzae* type b protein conjugate vaccines, the incidence of *H. influenzae* type b meningitis has dramatically declined [20]. If we assume that this decline will continue and will also be documented in other countries, then the type of meningitis for which dexamethasone has been shown to be beneficial will be encountered infrequently.

The etiologies of bacterial meningitis for seven recent randomized studies on the use of adjunctive dexamethasone therapy in four countries are shown in table 2 [7–9, 11, 15, 21, 22]. The studies were conducted between 1984 and 1992. Although each study had exclusion criteria related to underlying illness, prior parenteral antibiotics, or initial CSF findings, the overall distribution of etiologies probably represents fairly the relative frequencies of the causes of bacterial

Table 2. Distribution of organisms isolated from patients in studies in which dexamethasone was used in therapy for meningitis.

Variable	No. (%) isolated	Percent of organisms isolated if *H. influenzae* type b organisms are excluded
Haemophilus influenzae type b	534 (58)	...
Neisseria meningitidis	146 (16)	38
Streptococcus pneumoniae	107 (11.7)	28
Other organism	11 (1.2)	2.9
No isolate*	39 (4.3)	10.2
Aseptic meningitis	52 (5.7)	13.5
Excluded (other reasons)	29 (3.2)	7.5
Total no. of organisms isolated	915 (...)	...

NOTE. Seven prospective studies were reviewed [7–9, 11, 15, 21, 22].

* Meningitis was due to a virus.

meningitis in children. *H. influenzae* type b accounted for 60% of the cases. If these cases are now excluded, *N. meningitidis* accounted for 38% of the other case, *S. pneumoniae* accounted for 28% of the cases, and no isolates were recovered from 10.2% of the patients (table 2). Almost 14% of the children who were initially thought to have bacterial meningitis when enrolled in these studies were later found to have viral or aseptic meningitis.

I would like to focus on three basic questions regarding the efficacy and safety of routine adjunctive dexamethasone therapy in children with suspected bacterial meningitis, taking into consideration the decline in *H. influenzae* type b meningitis: (1) What is the evidence that adjunctive therapy with dexamethasone is efficacious for the treatment of *S. pneumoniae* or *N. meningitidis* meningitis? (2) What effects, if any, does dexamethasone have on the treatment of meningitis due to *S. pneumoniae* that is resistant to penicillin or third-generation cephalosporins? (3) Does dexamethasone have any adverse effects on children with viral meningitis?

The studies referred to previously did not enroll enough children with meningitis due to *S. pneumoniae* or *N. meningitidis* to establish the efficacy of dexamethasone in treating cases with these etiologies. Even when the data from selected studies are combined to obtain some estimate of the efficacy of dexamethasone for treating pneumococcal meningitis, a significant difference in outcome for the dexamethasone-treated children is not seen.

A large, open, prospective study conducted in Egypt [10] compared therapy that included dexamethasone to that with no adjunctive measure for children and adults who were treated for bacterial meningitis with intramuscular ampicillin and chloramphenicol [10]. The dramatic finding was that the case-fatality rate for pneumococcal meningitis was reduced from 40.7% (22 of 54) among the controls to 13.5% (7 of 52) in the dexamethasone group ($P < .002$). Furthermore, none of 45 patients receiving dexamethasone became deaf due to *S. pneumoniae* meningitis ($P < .05$), whereas 4 of 32 in the control group did; however, hearing could not be evaluated in children <4 years old. The application of the results from this Egyptian study to the use of dexamethasone in the treatment of pneumococcal meningitis in the United States is problematic for the following reasons: the ampicillin dose was low (160 mg/[kg · d]) when compared with the standard recommended dose [23]; a high percentage of patients with pneumococcal meningitis were comatose on admission (79% in dexamethasone group and 69% in the control group) and had suboptimal supportive care; and it was not clear if chloramphenicol therapy was discontinued once *S. pneumoniae* was identified (prolonged combination therapy with ampicillin and chloramphenicol might be antagonistic for pneumococcal meningitis [24]. It should also be noted that no benefit was found when dexamethasone therapy was used to treat meningitis due to *N. meningitidis*, the organism most commonly isolated in this study.

In a retrospective study, Kennedy et al. [16] reviewed the records of 97 children with pneumococcal meningitis who were treated at Parkland Memorial Hospital or Childrens Medical Center in Dallas between 1984 and 1990. Forty-one patients received dexamethasone and 56 did not. Although the ages, duration of illness, and several other clinical features were similar between the groups, important differences were present in other areas. In the dexamethasone group 51% of children were white, whereas in the group not treated with dexamethasone, 39% were white. Although this is a not significant difference, it shows there were differences based on the racial makeup of the groups. There was a significant difference ($P < .001$) in the number of children in the years 1984–1987 who were not treated with dexamethasone (44 of 56) compared with the number who were treated with dexamethasone (10 of 41) during that period. The main concern is that the children treated in the earlier years received different antibiotics (including cefuroxime) than did the children seen after 1987, at which time cefotaxime or ceftriaxone was administered more frequently. This may be an important factor since there is some evidence that cefuroxime is inferior to ceftriaxone for treating bacterial meningitis. In one prospective evaluation, two of six children treated with cefuroxime vs. none of seven children receiving ceftriaxone for pneumococcal meningitis developed a hearing impairment [25].

Overall, 4 of 35 children who received dexamethasone compared with 14 of 43 children who did not receive dexamethasone had an adverse neurological and/or audiological outcome ($P = .033$). A bilateral hearing loss (moderate or greater) occurred in 3 (9%) of 35 steroid-treated and 10 (21%) of 47 nonsteroid-treated patients ($P = .14$). However, if more children in the nonsteroid group than were in the steroid group were treated with cefuroxime, the interpretation of these results on hearing loss might be altered.

I believe that these two studies do not provide sufficient evidence that dexamethasone is beneficial for the treatment of pneumococcal meningitis. The question then becomes: is there a disadvantage in administering dexamethasone to such children? Gastrointestinal bleeding may occur more commonly in children receiving dexamethasone, but serious hemorrhaging rarely develops.

A problem of growing concern is the increasing number of reports of the isolation of *S. pneumoniae* strains that are resistant to penicillin and/or third-generation cephalosporins. In many cases, vancomycin is the agent chosen to treat such infections. How or whether dexamethasone affects the treatment of bacterial meningitis in these patients is unknown. To date, three of eight patients in whom cefotaxime or ceftriaxone treatment for pneumococcal meningitis failed had received adjunctive therapy with dexamethasone [26]. In other cases, prolonged dexamethasone administration has been associated with CSF cultures that remain persistently positive for *S. pneumoniae* in otherwise healthy children who have been appropriately treated for meningitis [27]. In the

study by Kennedy et al. [16], 2 (7%) of 30 dexamethasone-treated and none of 35 nondexamethasone-treated patients had a positive CSF culture 24–48 hours after therapy was begun ($P = .21$).

Administration of dexamethasone is associated with a more rapid decrease in fever and could result in an inaccurate clinical appraisal of the patient's response (the clinician might assume that the child is responding favorably to the antibiotic administered but defervescence is due to dexamethasone therapy). On the other hand, the recurrence of fever in these patients may alert the physician to a possible poor response to antibiotic therapy; however, this can also simply be due to the discontinuation of dexamethasone therapy. An example of this problem is seen in the report by Viladrich et al. [28] in which vancomycin therapy for pneumococcal meningitis in adults was evaluated. The authors reported that vancomycin therapy failed in 4 of 11 adults, and they defined treatment failure as a recrudescence of a patient's illness based on a rise in temperature and recurrence of meningeal signs and symptoms after clear, initial clinical improvement. However, all patients in that study had also received dexamethasone for four days, and clinical relapse had occurred on days 4 (2 patients), 7 (1 patient), and 8 (1 patient) of therapy; certainly in two of these patients (those who relapsed on day 7 and 8), dexamethasone therapy had been discontinued before the fever recurred. Unfortunately, because a suboptimal dose of vancomycin and because a repeated CSF analysis was not performed, it is not clear whether treatment truly failed or if the reappearance of fever and symptoms was related to the inadequate dose or to the discontinuation of dexamethasone therapy.

Because of the decline in the incidence of *H. influenzae* type b meningitis, a greater proportion of patients who will receive dexamethasone for suspected bacterial meningitis will be children with viral meningitis. In real-life situations, children with viral or aseptic meningitis may make up an even greater proportion of patients treated with dexamethasone; the discrepancy in numbers is due to the fact that investigators involved in the various studies are probably more selective in considering which children to enroll, whereas a physician not involved in a study does not have to make such considerations when encountering a child whose CSF shows pleocytosis. Many children with viral meningitis initially have a predominance of polymorphonuclear leukocytes in the CSF, which may make it difficult to distinguish readily between viral and bacterial meningitis at the time of presentation. Such children are sometimes given dexamethasone empirically until the etiology of the meningitis is clarified; thus, we must be certain that dexamethasone will not have adverse effects on the outcome of aseptic meningitis. The report by Waggner et al. [29] is the only one that addresses this issue. They reviewed the clinical course of 32 hospitalized children with aseptic meningitis who received dexamethasone after being enrolled in Dallas study protocols. The clinical course of these children during the hospital stay and condition at discharge were unusual for children with aseptic meningitis. After discharge, follow-up conducted by a phone interview with parents indicated that the children had returned to their usual activity levels and behavior. No long-term follow-up examinations were performed, and the records of those children with aseptic meningitis who did not receive dexamethasone were not reviewed. Certainly, additional studies are required before we can be certain that dexamethasone therapy is not detrimental to children with viral meningitis, including long-term subtle effects on behavior or intellect that may be seen at follow-up.

I have highlighted my concerns regarding the evidence that dexamethasone is safe and efficacious for the adjunctive treatment of bacterial meningitis, taking into consideration the fact that the one type of meningitis for which it is proven beneficial (*H. influenzae* type b) has markedly diminished in incidence due to the development of remarkable vaccines. It is hoped that well-designed, prospective studies of adjunctive dexamethasone therapy for pneumococcal meningitis will be conducted or that an effective pneumococcal conjugate vaccine will be developed, ending this debate.

Comment

There was general agreement among the speakers and the large audience that the etiology of bacterial meningitis in infants and children has dramatically changed in countries where conjugate *H. influenzae* vaccines are routinely used. As pointed out by Drs. Schaad and Kaplan, the efficacy of dexamethasone therapy in humans has only been proven for *H. influenzae* meningitis. In several studies of experimental pneumococcal meningitis, dexamethasone was effective in modulating meningeal inflammation, including cerebral edema and intracranial pressure [1, 2]. In the two clinical trials of pneumococcal meningitis mentioned previously [10, 16], there was evidence suggesting that steroid therapy improved outcome. There is no information on the efficacy of dexamethasone in treating meningococcal meningitis; because sequelae occur in $<10\%$ of these patients, a very large number of patients would need to be studied to establish its efficacy.

At present, physicians must base their decision to use dexamethasone therapy in patients with pneumococcal or meningococcal meningitis on the evidence presented and on personal experience. Additional data are needed to determine the optimal treatment for meningitis caused by penicillin-resistant and cephalosporin-resistant pneumococci. The effect of dexamethasone therapy on the activity of the cephalosporins and vancomycin and their penetration into the CSF of these patients is required before definitive recommendations can be made. Data derived from studies of experimental pneumococcal meningitis clearly indicate that dexamethasone reduces the CSF penetration of ceftriaxone and vanco-

mycin sufficiently to alter the clearance of resistant organisms from CSF cultures [30]. Penetration of rifampin into the CSF appears to be unaffected by concomitant dexamethasone therapy.

References

1. Sáez-Llorens X, Ramilo O, Mustafa MM, Mertsola J, McCracken GH Jr. Molecular pathophysiology of bacterial meningitis; current concepts and therapeutic implications. J Pediatr **1990**;116:671–84.
2. Tunkel AR, Wispelwey B, Scheld WM. Bacterial meningitis: recent advances in pathophysiology and treatment. Ann Intern Med **1990**;112:610–23.
3. Quagliarello V, Scheld WM. Bacterial meningitis: pathogenesis, pathophysiology, and progress. N Engl J Med **1992**;327:864–72.
4. Täuber MG, Shibl AM, Hackbarth CJ, Larrick JW, Sande MA. Antibiotic therapy, endotoxin concentration in cerebrospinal fluid, and brain edema in experimental Escherichia coli meningitis in rabbits. J Infect Dis **1987**;156:456–62.
5. Tuomanen E, Hengstler B, Rich R, Bray M, Zak O, Tomasz A. Nonsteroidal anti-inflammatory agents in the therapy of experimental pneumococcal meningitis. J Infect Dis **1987**;155:985–90.
6. Mustafa MM, Ramilo O, Mertsola J, et al. Modulation of inflammation and cachectin activity in relation to treatment of experimental *Haemophilus influenzae* type b meningitis. J Infect Dis **1989**;160:818–25.
7. Lebel MH, Freij BJ, Syrogiannopoulos GA, et al. Dexamethasone therapy for bacterial meningitis: results of two double-blind, placebo-controlled trials. N Engl J Med **1988**;319:964–71.
8. Lebel MH, Hoyt MJ, Waagner DC, Rollins NK, Finitzo T, McCracken GH Jr. Magnetic resonance imaging and dexamethasone therapy for bacterial meningitis. Am J Dis Child **1989**;143:301–6.
9. Odio CM, Faingezicht I, Paris M, et al. The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. N Engl J Med **1991**;324:1525–31.
10. Girgis NI, Farid Z, Mikhail IA, Farrag I, Sultan Y, Kilpatrick ME. Dexamethasone treatment for bacterial meningitis in children and adults. Pediatr Infect Dis J **1989**;8:848–51.
11. Schaad UB, Lips U, Gnehm HE, Blumberg A, Heinzer I, Wedgwood J, for the Swiss Meningitis Study Group. Dexamethasone therapy for bacterial meningitis in children. Lancet **1993**;342:457–61.
12. Richter O, Ern B, Reinhardt D, Becker B. Pharmacokinetics of dexamethasone in children. Pediatr Pharmacol **1983**;3:329–37.
13. Arditi M, Ables L, Yogev R. Cerebrospinal fluid endotoxin levels in children with H. influenzae meningitis before and after administration of intravenous ceftriaxone. J Infect Dis **1989**;160:1005–11.
14. McCracken GH Jr, Lebel MH. Dexamethasone therapy for bacterial meningitis in infants and children [editorial]. Am J Dis Child **1989**;143:287–9.
15. Wald E, and U.S. Meningitis Study Group. Dexamethasone for children with meningitis [abstract no. 73]. In: Program and abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy (Anaheim, CA). Washington, DC: American Society for Microbiology, **1992**:123.
16. Kennedy WA, Hoyt MJ, McCracken GH Jr. The role of corticosteroid therapy in children with pneumococcal meningitis. Am J Dis Child **1991**;145:1374–8.
17. Committee on Infectious Diseases. Dexamethasone therapy for bacterial meningitis in infants and children. In: Report from the American Academy of Pediatrics. 22nd ed. Elk Grove Village, IL: American Academy of Pediatrics, **1991**:566–70.
18. McGowan JE Jr, Chesney PJ, Crossley KB, LaForce FM. Guidelines for the use of systemic glucocorticosteroids in the management of selected infections. J Infect Dis **1992**;165:1–13.
19. The Meningitis Working Party of the British Paediatric Immunology and Infectious Diseases Group. Should we use dexamethasone in meningitis? Arch Dis Child **1992**;67:1398–401.
20. Adams WG, Deaver KA, Cochi SL, et al. Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era. JAMA **1993**;269:221–6.
21. King SM, Law B, Langley J, et al. A randomized controlled trial of dexamethasone versus placebo in children with bacterial meningitis [abstract no. 72]. 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy (Anaheim, CA). Washington, DC: American Society for Microbiology. **1992**:122.
22. Syrogiannopoulos GA, Theodoridou MN, Lourida AN, et al. Two versus four days of dexamethasone therapy for bacterial meningitis [abstract no. 74]. 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy (Anaheim, CA). Washington, DC: American Society for Microbiology, **1992**:123.
23. Feigin RD, McCracken GH, Jr., Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J **1992**;11:785–814.
24. Wallace JF, Smith RH, Garcia M, Petersdorf RG. Studies on the pathogenesis of meningitis VI. Antagonism between penicillin and chloramphenicol in experimental pneumococcal meningitis. J Lab Clin Med **1967**;70:408–18.
25. Schaad UB, Suter S, Gianella-Borradori A, et al. A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. N Engl J Med **1990**;322:141–7.
26. Kleiman MB, Weinberg GA, Reynolds JK, Allen SD. Meningitis with beta-lactam-resistant *Streptococcus pneumoniae:* the need for early repeat lumbar puncture. Pediatr Infect Dis J **1993**;12:782–4.
27. Brady MT, Kaplan SL, Taber LH. Association between persistence of pneumococcal meningitis and dexamethasone administration. J Pediatr **1981**;99:924–6.
28. Viladrich PF, Gudiol F, Liñares J, et al. Evaluation of vancomycin for therapy of adult pneumococcal meningitis. Antimicrob Agents Chemother **1991**;35:2467–72.
29. Waagner DC, Kennedy WA, Hoyt MJ, McCracken GH, Jr. Lack of adverse effects of dexamethasone therapy in aseptic meningitis. Pediatr Infect Dis J **1990**;9:922–3.
30. Paris MM, Hickey SM, Uscher MI, Shelton S, Olsen KD, McCracken GH Jr. Effect of dexamethasone on therapy of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis. Antimicrob Agents Chemother. **1994**;38:1320–4.