

## ADJUNCTIVE THERAPY IN CHILDREN WITH BACTERIAL MENINGITIS

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Over the past decade, a fuller understanding of the pathophysiology of bacterial meningitis at the molecular level has led to a greater interest in adjunctive measures in the management of this infection. The major emphasis has been on modulating the host response to infection, which itself may be contributing to tissue or other damage that results in neurologic dysfunction.<sup>1,2</sup> Dexamethasone has been the agent primarily evaluated in clinical trials, but other anti-inflammatory drugs, as well as compounds with other modes of action, have been studied in animal models and may ultimately be tested in children. These approaches have been undertaken because it is unlikely that more potent antibiotics or achieving greater concentrations of antibiotics in cerebrospinal fluid will result in any better outcome than is achieved with antibiotics currently available. This review will summarize current concepts regarding the pathophysiology of bacterial meningitis and possible ways by which this process can be modified to benefit the patient.

### Pathophysiology

The host response to bacterial invasion of the central nervous system leads to a very complex cascade of events that appears to be initiated by specific components of the bacteria. For gram-negative bacteria, endotoxin or lipopolysaccharide (LPS) is the critical component leading to the production of multiple pro-inflammatory cytokines. LPS interacts with its CD14 receptor on monocytes, macrophages, and neutrophils to stimulate cytokine synthesis.<sup>3</sup> These cells, when infiltrating into the CNS, are important sources of the pro-inflammatory cytokines TNF- $\alpha$ , IL-1, and IL-6. Furthermore, microglia and astrocytes, cells resident within the CNS, are capable of producing these cytokines locally, although they lack the CD14 receptor.<sup>4</sup> In addition, endothelial cells from microvessels of the human brain *in vitro* are stimulated by LPS in the presence of a soluble form of CD14 to produce these cytokines.<sup>5</sup> Gram-positive bacteria such as *S. pneumoniae* contain glycopeptides and teichoic acid

among cell wall components that also stimulate the inflammatory response.

The proinflammatory cytokines facilitate the recruitment of PMNs into tissues (and cerebrospinal fluid, or CSF, in the case of meningitis), where these cells release oxygen metabolites, and other enzymes. These toxic products, along with platelet-activating factor (another endogenously produced factor whose concentration is increased in the CSF of patients with bacterial meningitis), cytokines, arachidonic acid metabolites, and bacterial components affect CNS microvasculature by disrupting tight intercellular junctions mediated in part by nitric oxide, thus altering the "blood-brain barrier."<sup>2,6,7</sup> This allows leakage of proteins and water into the brain parenchyma, leading to vasogenic edema.

The inflammatory response also diminishes CSF resorption through arachnoid villi, which results in a greater volume of CSF within the cranial vault. It is thought that white blood cells, protein, and other debris actually interfere with the normal resorptive function. Vasogenic edema and the increased CSF volume are the predominant factors causing increased intracranial pressure (ICP) during bacterial meningitis. Increased ICP may combine with other factors such as vasculitis and thrombosis of intracranial vessels in altering cerebral blood flow (CBF) in some patients. Very few studies actually measuring CBF have been conducted in patients with bacterial meningitis. In the one study performed in children, 13 of 20 children had normal total CBF, although marked variability in local blood flow was noted.<sup>8</sup> These children were much more severely affected than usual in that 12 were comatose, 15 had seizures and 10 had respiratory impairment. Doppler studies in adults are consistent with a reduction in the diameter of intracranial blood vessels, but cannot determine if this is due to vasculitis, vasospasm or a combination of both.<sup>9</sup>

How the inflammatory response participates in damaging the cochlea, which results in hearing loss, is unknown. From human and animal studies, it can be shown that labyrinthitis can develop during bacterial meningitis, probably by bacteria reaching the perilymphatic channels via the cochlear aqueduct.<sup>10-12</sup> The resulting invasion may lead to destruction of the

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organ of Corti and calcification of the perilymphatic channels. Nitric oxide may contribute to mediating this injury as well.<sup>13</sup> In a model of pneumococcal meningitis in rabbits, dexamethasone added to antibiotic therapy prevented the development of profound deafness, although antibiotics alone greatly decreased the incidence and severity of hearing loss, compared with untreated rabbits.<sup>14</sup>

### Clinical Trials

In experimental animals infected with *H. influenzae* type b or *S. pneumoniae* or injected intracisternally with lipopolysaccharide or pneumococcal cell wall components, dexamethasone treatment is associated with decreased brain edema, CSF pressure and CSF lactate concentrations. Presumably, this action of dexamethasone is mediated through inhibiting the production of TNF and IL-1 by macrophages, as well as astrocytes and microglia among other cells. Cytokine activity in the CSF is diminished in the animals receiving dexamethasone. It was further shown that the activity of dexamethasone was more beneficial in *H. influenzae* type b meningitis if it was administered prior to antibiotics, which induces bacterial lysis, leading to increases in CSF concentrations of endotoxin and cytokines compared with untreated animals. Therefore, clinical trials employing dexamethasone were initiated in children with bacterial meningitis.

Four randomized placebo-controlled studies of dexamethasone for adjunctive therapy of bacterial meningitis due to any organism in children have been conducted with optimal antibiotic therapy. In three of these studies, measures of CSF inflammation were repeated at 12 to 24 hours after therapy was initiated. Improvements in these parameters for dexamethasone treatment were not consistent among the studies. These four studies are outlined in Table 1. When taken together, these studies indicate that dexamethasone appears beneficial in decreasing neurologic sequelae. However, the only neurologic sequelae that is convincingly diminished is deafness. The duration of fever is shorter in the dexamethasone groups, but this is not a critical outcome measure. Furthermore, once dexamethasone was discontinued, there was a tendency for patients to develop secondary fevers more often. Gastrointestinal bleeding or guaiac-positive stools tended to be more common in the steroid groups.<sup>19</sup> A fifth study compared two with four days of dexamethasone without a placebo group and found outcomes were similar, but there was less gross gastrointestinal bleeding with two days of dexamethasone.<sup>20</sup>

Over 70% of the patients in the four placebo-controlled studies had meningitis due to *H. influenzae* type b meningitis. Thus, the results may be most readily applied to children with *H. influenzae* type b meningitis. Too few

TABLE 1. Selected aspects of placebo-controlled trials of dexamethasone in children with bacterial meningitis due to any organism.

	Dallas, TX <sup>15</sup>		Costa Rica <sup>16</sup>		Switzerland <sup>7</sup>		US multi-center <sup>18</sup>	
	Ceftriaxone	Cefotaxime	Ceftriaxone	Ceftriaxone	Ceftriaxone	Ceftriaxone	Ceftriaxone	Ceftriaxone
Timing*	Not stated	15-20 min. prior to <sup>†</sup>	15-20 min. prior to <sup>†</sup>	10 min. prior to <sup>‡</sup>	10 min. prior to <sup>‡</sup>	10 min. prior to <sup>‡</sup>	10 min. prior to <sup>‡</sup>	Within 4 hr <sup>†</sup>
	P**	D	P	D	P	D	P	D
Number	49	51	49	52	55	60	74	69
Mean age (months)	17.8	15.2	19	16.2	36	36	11.3	9.8
Etiology								
<i>H. influenzae</i> type b	40	39	40	39	30	37	39	44
<i>S. pneumoniae</i>	3	4	4	4	6	5	20	13
<i>N. meningitidis</i>	4	6	2	0	12	16	13	11
Other	4	2	5	7	7	2	2	1
Outcome								
Neurologic sequelae (%)	22	19	31	10	9	5	8	6
Deafness (%)	11	2	16	6	15	5	9	4

\*Dexamethasone and first IV dose of antibiotic; \*\*P=placebo, D=dexamethasone; <sup>†</sup>dexamethasone dose=0.15 mg/kg q 6h x 16 doses; <sup>‡</sup>dexamethasone dose=0.4 mg/kg q 12h x 4 doses.

children with other forms of meningitis were enrolled to make strong conclusions regarding the efficacy of dexamethasone for pneumococcal meningitis, in particular. Several advisory groups have recommended dexamethasone as adjunctive therapy in *H. influenzae* type b meningitis, but do not unequivocally endorse it for meningitis due to other bacteria.<sup>21-23</sup>

The Committee on Infectious Diseases of the American Academy of Pediatrics recommends dexamethasone for treatment of infants and children with *H. influenzae* meningitis.<sup>21</sup> The dose of dexamethasone is 0.15 mg/kg/dose every six hours intravenously for 16 doses and it should be administered at the time of, or shortly after, the first dose of parenteral antibiotics.

In areas of the world where the *H. influenzae* type b conjugate vaccines are administered routinely to infants at two months of age, the incidence of *H. influenzae* type b meningitis has declined precipitously. Thus, the one organism for which there is the most agreement regarding the benefits of steroids has essentially been eliminated as an etiologic agent of meningitis. Unfortunately, it cannot be assumed that if dexamethasone is beneficial for *H. influenzae* meningitis, it should be efficacious for other pathogens. The host response to gram-positive or gram-negative bacteria may be different. For example, in experimental models, modifying the inflammatory response (by deleting TNF receptors<sup>24</sup> or intercellular adhesion molecule-1<sup>25</sup>) appears to be an advantage for gram-negative bacteria, but detrimental for gram-positive organisms.

The clinical data regarding the safety and efficacy of

dexamethasone for pneumococcal meningitis are minimal. A retrospective analysis of cases from Dallas between 1984 and 1990 found that four of 35 (11%) children who received dexamethasone compared with 14 of 43 (33%) of children without steroid treatment had an adverse neurologic or audiologic outcome.<sup>26</sup> However, the antibiotic therapy many of these patients received may not have been optimal, since cefuroxime was administered to more no-steroid than steroid-treated patients. Subsequent studies have shown that cefuroxime is inferior to ceftriaxone for treating bacterial meningitis and is associated with higher rates of neurologic sequelae.<sup>27</sup>

A randomized placebo-controlled trial of dexamethasone was conducted in Egypt and included children and adults.<sup>28</sup> Ampicillin and chloramphenicol were administered intramuscularly and the dose of dexamethasone in children was 8 mg q 12 hours for three days. Two-thirds of the patients were comatose on admission. Overall mortality in the patients with pneumococcal meningitis was dramatically reduced in the dexamethasone group (7/52, 15.5%) compared with the placebo group (22/54, 40.7%). For children up to 12 years, deaths occurred in five of 33 (15%) steroid-treated versus 10 of 34 (29%) nonsteroid-treated patients. For patients over four years old, deafness due to *S. pneumoniae* meningitis also was decreased by dexamethasone. How these results can be applied to countries with more sophisticated medical structures is unclear.

The US Multicenter trial had the largest number of patients with pneumococcal meningitis (n=33) of the previously described studies.<sup>18</sup> There was no difference between the study groups in outcome for this small number of children.

Most recently, Kanra and associates reported a study of dexamethasone in pneumococcal meningitis for children two to 16 years of age in Turkey.<sup>29</sup> All patients were treated with ampicillin (200 mg/kg/day) plus sulbactam (Unasyn®). Dexamethasone (0.15 mg/kg q 6h x 4 days) or placebo was administered 15 minutes prior to the first dose of antibiotic. Selected aspects of this study are shown in Table 2. There was a tendency for patients receiving dexamethasone to have fewer adverse audiologic sequelae. No details regarding any adverse reactions to study medications were provided. Thus, there still is no truly convincing data that dexamethasone is beneficial for pneumococcal meningitis and this area remains controversial.<sup>30,31</sup>

This issue is further complicated by the increasing prevalence of *S. pneumoniae* isolates resistant to penicillin and extended-spectrum cephalosporins.<sup>32-34</sup> Multiple-drug-resistant *S. pneumoniae* have emerged worldwide and clearly have impacted the antibiotic treatment of pneumococcal meningitis. Currently, cefotaxime or

ceftriaxone is considered the agent of choice for treating pneumococcal meningitis due to isolates intermediate (MIC 0.1-1.0 µg/mL) or resistant (MIC ≥2.0 µg/mL) to penicillin.<sup>35</sup> Chloramphenicol is not considered first-line therapy in this case due to excessive treatment failures.<sup>36</sup> Some authorities now recommend using cefotaxime at doses up to 300 mg/kg/day (maximum dose 24 g) for isolates with a cephalosporin MIC=1-2 µg/mL.<sup>37</sup> However, several reports have documented treatment failure with cefotaxime or ceftriaxone as well. In these cases, the pneumococcal isolates are typically considered resistant (MIC ≥2.0 µg/mL), but some have had intermediate (MIC=1.0 µg/mL) susceptibility for these two antibiotics.<sup>38</sup> A regimen containing vancomycin appears optimal when an isolate resistant to the extended-spectrum cephalosporins is responsible for the meningitis.<sup>35</sup>

Dexamethasone probably does not affect the penetration of cefotaxime or ceftriaxone into the CSF to any important degree. It is unclear how vancomycin penetration might be affected. In the rabbit model, vancomycin levels in CSF were reduced in the presence of dexamethasone and this was associated with a delay in CSF sterilization of penicillin-susceptible or penicillin- and cephalosporin-resistant isolates.<sup>39,40</sup>

Relatively little is known about the pharmacology of vancomycin entrance into CSF in patients also receiving dexamethasone. In one study from Spain, 11 adults received vancomycin along with dexamethasone (0.25 mg/kg q 6 hours x 4 days) for pneumococcal meningitis.<sup>41</sup> Four developed recrudescence of their illness on days four through eight and were considered therapeutic failures. Whether this was related to the relatively low dose of vancomycin (7.5 mg/kg q 6 hours) administered, dexamethasone use, or some other factor was unknown.

Klugman et al. have measured vancomycin penetration into the CSF of nine children with bacterial meningitis.<sup>42</sup> All received vancomycin at a dose of 15 mg/kg q 6 hours plus dexamethasone (0.15 mg/kg q 6 hours). The mean concentration of vancomycin two to three hours after doses at 24 to 48 hours after admission was 3.3 ± 1.1 µg/mL

TABLE 2. Characteristics and outcome of patients in Turkish study of dexamethasone in pneumococcal meningitis.

Characteristics	Dexamethasone (n=27)	Placebo (n=26)
Age (years)	7.4±3.6*	6.8±3.4
Duration of illness prior to admission (hours)	49±37	49±44
Seizures prior to admission	4	4

Outcome		
Bilateral moderate or greater hearing loss at six weeks	0	2
Neurologic abnormality at 1 year	1	1
Neurologic or audiologic adverse outcome at 1 year	2	7
Deaths	2	1

\*Mean  $\pm$  standard deviation.

TABLE 3. *Experimental adjunctive agents for bacterial meningitis.*

Pentoxifylline <sup>44</sup>
Antibody to CD18 <sup>45,46</sup>
Antibody to ICAM-1 (CD54) <sup>47</sup>
N-methyl-D-aspartate antagonist <sup>48</sup>
Nitric oxide synthase inhibitor <sup>7,49</sup>
Kynurenic acid <sup>50</sup>

(range 2-5.9  $\mu$ g/mL), a level considered reliable to treat pneumococcal meningitis. However, since there were no children who did not receive dexamethasone as a comparison group, it remains unknown from this study if dexamethasone alters vancomycin penetration into CSF during meningitis.

The only other adjunctive measure formally evaluated in bacterial meningitis is the administration of glycerol, a hyperosmolar agent presumably effective in counteracting cerebral edema and increased ICP. In a multicenter study, Finnish investigators randomized children to one of four adjunctive treatment groups for three days:<sup>43</sup> 1) dexamethasone alone (0.5 mg/kg per dose q 8 hours), n=32; 2) glycerol by mouth or nasogastric tube (1.5g/kg per dose q 8 hours), n=30; 3) dexamethasone plus glycerol, n=34; 4) neither of these drugs, n=26.

All children received ceftriaxone at 100 mg/kg in one daily dose with the first dose given concomitantly with the study drug.

The average ages of the patients were 3.1 to 3.8 years and 53% had *H. influenzae* type b meningitis. No child receiving glycerol alone or with dexamethasone had neurologic or audiologic abnormalities, whereas in the nonglycerol group, 9% had neurologic and 7% had severe to profound bilateral hearing losses ( $P<.05$ ). The mechanism by which glycerol might protect from hearing loss is unclear. Confirmation of these findings is required before widespread use of adjunctive glycerol can be considered.

Other anti-inflammatory agents have been studied in experimental models of meningitis (Table 3). Only time will tell if any of these drugs can be proven efficacious for decreasing the morbidity and mortality of bacterial meningitis in children. However, it is possible that vaccines effective for preventing pneumococcal or meningococcal meningitis will reduce the incidence of bacterial meningitis to the point that clinical trials to test these agents will never be performed.

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