Glycerol and Bacterial Meningitis

Xavier Sáez-Llorens¹ and George H. McCracken, Jr.²

¹Department of Infectious Diseases, University of Panama School of Medicine, Hospital del Niño, Panama City, Panama; and ²Division of Pediatric Infectious Diseases, University of Texas Southwestern Medical Center, Dallas

(See the article by Peltola et al. on pages 1277–86)

Scientific efforts aimed at improving the prognosis of patients affected by severe diseases deserve to be highlighted and thoroughly evaluated for potential impact. Despite modern intensive care management and the advent of potent, broad-spectrum antimicrobial agents, bacterial meningitis is still associated with unacceptably high rates of long-term morbidity and case fatality. During the past 20 years, comprehensive experimental and clinical studies have been performed to define the molecular pathophysiologic events involved in bacterial meningitis that are responsible for clinical manifestations and adverse outcomes. These studies have demonstrated that administration of dexamethasone before the first effective parenteral antibiotic dose reduced neurologic and/or audiologic sequelae in infants and children with Haemophilus influenzae meningitis and, possibly, in those infected with Streptococcus pneumoniae [1]. Recently, the benefit of corticosteroid therapy was confirmed in adults with pneumococcal meningitis [2].

Nevertheless, the favorable effects of treatment with dexamethasone are far from ideal, and in selected situations, they can be marginal or nonexistent. Children with delayed medical attention, profound malnutrition, HIV infection, or treatment with suboptimal antibiotics (based on current bacterial drug-resistance profiles) are less likely than others to respond to adjunctive antiinflammatory therapy. These situations are commonly seen in poor regions of the world, as illustrated in a clinical trial conducted in Malawi [3]. Consequently, novel and accessible forms of adjuvant therapy are clearly needed for the unique challenges faced by countries with limited economic and technical resources.

In this issue of the journal, Peltola et al. [4] explore the potential usefulness of glycerol in the context of a pediatric population with bacterial meningitis living in the underdeveloped public sectors of several Latin American nations. These authors should be congratulated for conducting the largest bacterial meningitis trial to assess the safety and efficacy of adjuvant strategies for treatment of this devastating disease. A talented group of investigators participated in a very complicated and difficult randomized, double-blinded study with 4 management arms comprising a glycerol group, a dexamethasone group, a glycerol plus dexamethasone group, and a placebo (carboxymethylcellulose) group.

In this study [4], 654 infants and children with bacterial meningitis caused predominantly by H. influenzae type b (Hib), pneumococci, and meningococci were enrolled. Glycerol was given to 159 patients, dexamethasone was given to 166, dexamethasone and glycerol were given to 159, and placebo was given to 163. Compared with those patients who received placebo, patients receiving glycerol and patients receiving dexamethasone plus glycerol experienced fewer severe neurologic sequelae (OR, 0.31 [95% CI, 0.13–0.76] and 0.39 [95% CI, 0.17–0.93], respectively; P = .01 and P = .03, respectively). Treatment with dexamethasone prevented only deafness in patients with Hib meningitis when subjects were divided into dexamethasone recipients and nonrecipients (OR, 0.27; 95% CI, 0.09–0.77; P = .014). The authors concluded that glycerol prevents severe neurologic sequelae in childhood meningitis and, because of its safety, wide availability, low cost, and oral administration, it should be particularly useful in resource-limited settings.

Although these are exciting and welcome results, the study has several methodologic problems that compromise reliable interpretation of the data. Our main concerns are the following:

1. Use of placebo, instead of adjuvant therapy, for the treatment of meningitis in countries where Hib disease predominated in the years of the trial (Hib was found to be the causative bacteria in 221 [46%] of 484 cases) raises ethical con-
cerns. Evidence derived from animal studies and from pediatric trials conducted in single centers [5, 6], from a multicenter trial [7], and from 2 meta-analyses [8, 9] support the significant neurologic and/or audiologic salutary effects of early dexamethasone administration for Hib meningitis. Analysis of the data from table 2 in Peltola et al. [4], which stratifies Hib disease outcome into dexamethasone recipients versus nonrecipients, indicates that many children were subjected to an unnecessary risk for sequelae. Severe neurologic sequelae were observed in 4 (4.5%) of 88 patients who received dexamethasone and 9 (9.4%) of 95 patients who did not (a nonsignificant difference), whereas profound hearing loss was detected in 5 (5.5%) of 91 and 16 (17.6%) of 90 patients, respectively (P = .01). If moderate or more-severe sequelae had been included as the outcome variable, as was the case in most other trials, it is possible that differences could have been even greater. Because some of the adverse outcomes detected at hospital discharge improve with time [10], especially in children who are treated with steroids, longer periods of follow-up could have resulted in the detection of even larger differences between treatment groups for Hib meningitis.

3. Hearing was assessed by brainstem evoked response or traditional audiometry. These techniques are not comparable, especially among different institutions and countries, and there is no information on how many patients were evaluated by one or the other method.

4. The authors state that dexamethasone and/or glycerol was administered (if possible) ~15 min before the first dose of parenterally administered ceftriaxone at the time of diagnosis, but there is lack of specific data regarding the number of patients or the outcomes of those who did not receive timely administration of adjunctive therapies. Peltola et al. [4] reassure the reader that the investigators at every institution followed assiduously the protocol and that timing of the first dexamethasone dose was not a factor in outcome; however, we are not provided the data to confirm this. In traditional drug trials, independent monitors rigorously audit protocol activities for potential deviations or violations that can jeopardize data validity.

5. The authors excluded patients when >1 parenteral antibiotic dose was administered before diagnosis. Orally administered antibiotics were allowed before study enrollment, but we are not told which drugs were used. Drugs like chloramphenicol, rifampin, or high-dose amoxicillin (90 mg/kg used for treatment of acute otitis media) could affect bacterial concentrations in the CSF compartment. In Latin America, intramuscular penicillin is frequently used (ceftriaxone is expensive), but Peltola et al. [4] do not reveal the number of patients in each treatment group who qualified for this exclusion, nor do they reveal the number of patients who received a dose of parenteral antibiotic that could have adversely affected the modulatory effect of dexamethasone on the secondary inflammatory response, which is the known mechanism of action in bacterial meningitis.

6. At most centers, a nasogastric tube was inserted to administer glycerol, but there is no information regarding the number of infants involved. This is important, because blinding of the treatments would be impossible unless all infants received nasogastric administration of the study drugs, including placebo. Insertion of a nasogastric tube is not common practice for infants and children with uncomplicated meningitis and adds logistic and cost concerns to disease management.

7. In contrast with the many publications on the molecular mechanisms of action of dexamethasone as an antiinflammatory agent in the treatment of bacterial meningitis in animals and humans, there is sparse information regarding the mechanism(s) of action of glycerol in this disease. Furthermore, for some outcomes, there appears to be an unexplained antagonism of action between these 2 agents.

If the results reported by Peltola et al. [4] are confirmed by additional carefully designed, controlled trials and if glycerol is proven to improve the prognosis of children with meningitis, the medical community will have an inexpensive and readily available agent to reduce adverse outcomes from disease, particularly in the poorest regions of the world. It must be emphasized, however, that the most effective strategy for managing bacterial meningitis and its associated sequelae is prevention by implementing large-scale immunization strategies against the common meningococcal pathogens. Hib meningitis has been virtually eliminated in countries where there is universal vaccination. The number of pneumococcal invasive infections caused by common circulating serotypes has been significantly reduced in the United States after incorporation of the heptavalent conjugate vaccine into the infant immunization schedule. The advent of new conjugated vaccines that include a larger number of S. pneumoniae serotypes will add broader coverage for other countries worldwide. Effective conjugate vaccines against non–group B meningococci are already available, and promising group B meningococcal vaccine candidates are currently undergoing phase III clinical trials. We urgently need a dedicated collaborative effort between vaccine manufacturers, philanthropic foundations, global health organizations, and national govern-
ments to make these vaccines available for those who need them most: the infants and children living in less advantageous areas of the world.

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References