Glycerol and Bacterial Meningitis: A Response to the Editorial Commentary by Sáez-Llorens and McCracken

To the Editor—In addition to well summarizing the main findings of our study of glycerol for the treatment of childhood bacterial meningitis [1], Sáez-Llorens and McCracken raised concerns in their editorial commentary [2]. On behalf of the entire Latin America meningitis study group, we wish to address some of those concerns.

First, a shadow is cast over the entire study by hinting that it was unethical. The authors deem the use of dexamethasone so beneficial (especially for treatment of *Haemophilus influenzae* type b meningitis) that a group of patients receiving no adjunctive therapy should not have been allowed. Accusing serious investigators of unethical research is very serious, and we strongly object.

The authors list “evidence” of the benefits of dexamethasone use, but how reliable is the information with regard to the treatment of children? Except for one small (n = 100) study [3] in which statistical significance was achieved when using a suboptimal antimicrobial treatment (cefuroxime), no randomized, double-blind study has shown great clinical benefits. Even that study [3] supporting the use of dexamethasone raised strong counterargument [4].

All other evidence for the use of dexamethasone is presented in underpowered prospective and retrospective studies in which outcomes with dissimilar definitions were lumped together or in meta-analyses comparing profoundly different populations and conditions. This is not justified for a disease as diverse as bacterial meningitis. Furthermore, all of those meta-analyses neglected the presenting conditions of the patients who they studied. This is a drawback that may seriously distort the interpretations [5]. The only sufficiently powered study prior to ours, which also did not support the use of dexamethasone, was from Malawi [6]. This trial and ours, comprising 1252 children, agree well with regard to results for dexamethasone.

As opposed to being unethical, we followed our conscience in trying to settle the open question of bacterial meningitis treatment with a large-enough trial. Furthermore, our protocol was accepted by all relevant ethics committees. Portraying our study as unethical, Sáez-Llorens and McCracken, cast doubt on the ethics of those prestigious committees as well.

Second, most data could not be presented by center or country, simply because we were near the 3000-word limit for major articles in *Clinical Infectious Diseases*. In addition to the text, we presented 5 tables and 1 figure. We were unable to describe less relevant details, such as the fact that almost all patients from Argentina presented with meningococcal meningitis (which has low mortality and sequelae rates); the exact timing of ceftriaxone, adjuvant treatment, or pretreatment antimicrobial administration; or which patients required insertion of a nasogastric tube. As is generally the case in modern scientific literature, only the numbers relevant to the subject were presented in publication.

Third, results of the brainstem evoked response (BERA) and traditional audiometry are not directly comparable. However, being experienced clinicians, Sáez-Llorens and McCracken should have realized that the vast majority of our patients were <3 years of age, necessitating the use of BERA.

Fourth, we agree that all mechanisms of glycerol activity are not known. The same can be said for dexamethasone. We described the most recent understanding and provided references. We also performed another randomized, double-blind trial examining the mechanisms of glycerol [7]. Are the commentators of the opinion that a safe, encouraging drug should not be used to treat a devastating disease until all its mechanisms are dis-
closed? Is it unethical to use gold to treat rheumatoid arthritis?

By no means do we claim that our study was without shortcomings—is any study? Nevertheless, we examined a large group of no less than 654 patients; this, for the first time in history, allowed an examination of the effects of dexamethasone and glycerol on bacterial meningitis without lumping nonsimilar outcomes together. We are proud of our achievement and feel that the information we provided serves children better than most previous dexamethasone trials—and not only children in developing nations, but also those in Finland, Panama, and the United States of America.

Acknowledgments


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References


Regression of HIV-Associated Mucosa-Associated Lymphoid Tissue Lymphoma during Highly Active Anti-Retroviral Therapy

To the Editor—Growing evidence indicates that marginal-zone B cell lymphoma is associated with chronic antigen stimulation by microbial pathogens. The list of microbial species associated with marginal zone lymphoproliferations now comprises at least 5 distinct members: Helicobacter pylori, Campylobacter jejuni, Borrelia burgdorferi, Chlamydia psittaci, and hepatitis C virus [1]. We describe a patient with HIV-associated mucosa-associated lymphoid tissue (MALT) lymphoma, whose pulmonary lesions dramatically regressed during receipt of HAART. A 56-year-old man developed cough, increased sputum production, and low-grade fever. A nonsteroid anti-inflammatory medication caused brief improvement of his symptoms. Subsequently, he presented to a community hospital, and CT of the chest revealed an abnormal bilateral shadow (figure 1).

The patient was referred to our hospital, and a transbronchial lung biopsy of the lesion revealed a non-Hodgkin lymphoma, MALT lymphoma. Completion of the staging evaluation showed enlargement of the right salivary gland and borderline swelling of bilateral submandibular and pulmonary hilar lymph nodes. Excisional biopsy of the salivary gland revealed no evidence of involvement of MALT. Diagnosis of H. pylori infection was excluded. The patient tested positive for HIV antibodies by ELISA with Western blot confirmation. The CD4 cell count was 146 cells/μL, and the HIV load was 28,000 copies/mL. With informed consent, the patient commenced a regimen of HAART with efavirenz and lamivudine-abacavir, and chemotherapy was scheduled thereafter. He experienced no major toxic effects, and the HIV RNA level decreased to <400 copies/mL after 1 month.

Surprisingly, follow-up chest CT demonstrated regression of the pulmonary lesions. After 3 months, they had almost disappeared, as shown in figure 1, and the patient’s CD4 cell count reached 215 cells/μL, and his HIV RNA level was <50 copies/mL. Although HIV-associated indolent lymphoma is rare, compared with aggressive lymphoma [2], our case and an earlier report [3] suggest that HAART should be the first-line treatment for HIV-associated MALT lymphoma, as is the case for H. pylori eradication in gastric lymphoma.

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Increased Detection of Meningococcal Infections in California Using a Polymerase Chain Reaction Assay

To the Editor—By detecting small