Evidence Guiding the Treatment of Children with Mycobacterial Diseases

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(See the article by Lindeboom et al. on pages 1057–64)

The global burden of childhood mycobacterial diseases (mostly caused by Mycobacterium tuberculosis) is very great. Because of differences in notification practice, it is difficult to assign the precise number of persons affected, but in areas of high transmission, children constitute up to 25% of total persons with tuberculosis [1]. Because of the well-recognized difficulty in making a diagnosis of tuberculosis in children and the rapid progression of the disease, it can reasonably be estimated that several hundreds of thousands of the 1.6 million deaths due to tuberculosis in 2001 [2] were among children.

Nevertheless, the diagnosis and treatment of mycobacterial disease in children is a neglected area of research. In particular, there is a paucity of randomized clinical trial data involving children to provide an evidence base for the therapy of both tuberculous and nontuberculous mycobacterial infections. In this issue, Lindeboom et al. [3] report the findings of a randomized trial of surgical excision, compared with antibiotic treatment, for nontuberculous mycobacterial cervicofacial lymphadenitis in children. Historically, surgical excision has been recommended for these infections; however, complications (particularly facial paralysis) may arise. Because antibiotic therapy has been used with variable success for other forms of nontuberculous mycobacterial infection, such as pulmonary Mycobacterium avium complex disease, the authors considered trial evidence to be desirable.

In this well-conducted trial, 100 children with culture- or PCR-confirmed infection were randomized to undergo surgical excision or receive at least 12 weeks of therapy with clarithromycin and rifabutin. The majority of the infections were due to M. avium (n = 71) and Mycobacterium haemophilum (n = 22). Surgery was clearly more effective than antibiotic therapy, with cure rates of 96% and 66%, respectively. Adverse events were common in both groups. Surgery was frequently complicated by staphylococcal wound infection and transient facial nerve palsy (permanent palsy occurred in 1 patient), and antibiotic therapy frequently caused adverse effects (most were mild; however, 4 patients had to discontinue treatment). There was no association between the mycobacterial species or in vitro resistance to antibiotic therapy and treatment failure.

The findings of this study are not completely surprising. M. avium complex infection is difficult to eradicate, with pulmonary infections frequently requiring prolonged antibiotic therapy (18–24 months) [4]. Lack of response to 3 months of antibiotic therapy (with no change of pretreatment status or worsening of swelling) was considered an indication for surgery. The choice of antibiotics was based on previous successful case reports. It is possible that the inclusion of ethambutol as a third agent might have improved the success rate; however, the authors were concerned about the possibility of ocular toxicity, which is more complicated to evaluate in children than adults.

The study has a number of important strengths, including the confirmation of nonmycobacterial infection in all patients by culture or PCR and the standardization of surgery in a single center. The outcome provides a rare—but clear—guide for the therapy of this manifestation of nonmycobacterial illness in children and, thereby, confirms existing clinical guidelines.

A search of the PubMed database (search terms, child and [tuberculosis or mycobacterium]) on 29 December 2006 for randomized, controlled clinical trials evaluating therapeutic interventions in...
childhood mycobacterial infections other than leprosy revealed only 62 articles. Of these, 12 evaluated tuberculosis of the spine. Of the remainder, only 18 specifically evaluated children (9 of these were studies of tuberculous meningitis). An evaluation of the Cochrane Library of Systematic Reviews database revealed only 2 reviews that independently report on children in assessments of therapeutic trials of mycobacterial disease [5, 6].

The multicenter contributions to the study by Lindeboom et al. [3] also suggest a useful approach for the evaluation of interventions in children with mycobacterial infection. For HIV infection, the Paediatric AIDS Clinical Trial Group provides valuable data that informs treatment, but there is no equivalent for mycobacterial diseases. Should we not adopt a similar model for evaluating therapy for other common and important infections in children? In 2006, ∼36,000 children were born with HIV infection in South Africa alone. Because of the very high incidence of tuberculosis in South Africa, many of these children will develop tuberculosis. How should it be prevented? What is the optimum duration of therapy? What is the evidence base for coprescribing and dosing of antiretroviral and antituberculosis agents in this group? How common is disease due to bacille Calmette-Guérin vaccine in this and other groups, and how should it be managed? How should multidrug-resistant tuberculosis be managed in children? How can it be prevented after documented exposure?

Isolated attempts have been made to resolve some of these questions, such as recent data that suggest a significant reduction in mortality among HIV-infected children receiving isoniazid preventive therapy [7]. A mortality benefit has never been shown in several similar trials of isoniazid preventive therapy among HIV-infected adults [8] and underscores the need to investigate potential interventions, specifically in children. We suggest that a concerted effort be made to address these issues in a coordinated manner, using the power of multicenter, randomized controlled trials.

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