Childhood Tuberculosis

A Diagnostic Dilemma

It is estimated that each year throughout the world there are 1.3 million cases of tuberculosis in children less than 15 years of age, resulting in 450,000 deaths annually.\(^1\) A large proportion of cases go unrecognized because of the poor sensitivity of currently available diagnostic methods in children.\(^2\) While an acid-fast stain of sputum identifies up to 75 percent of adults with pulmonary tuberculosis,\(^3,4\) fewer than 20 percent of children with tuberculosis have a positive acid-fast smear of sputum or gastric contents. Even optimal sputum or gastric aspirate cultures from children with pulmonary tuberculosis yield *Mycobacterium tuberculosis* in fewer than 50 percent of cases.\(^5\)

In technologically advanced countries, the diagnosis is usually established clinically, based upon an abnormal chest radiograph, a positive tuberculin skin test, and documented exposure to an adult with infectious tuberculosis.\(^6\)

Although a new diagnostic test for tuberculosis in adults must have a sensitivity greater than 75 percent to be considered a major advancement, a simple and inexpensive test with a lower sensitivity would be valuable for diagnosing tuberculosis in children. It is imperative that this test maintain a very high specificity—approaching 100 percent—in high- and low-prevalence populations, since a positive result would lead to treatment with antituberculosis chemotherapy, and in many cases might end the diagnostic evaluation.\(^7\) This test also must be able to distinguish tuberculous infection from disease, since this distinction determines the number of antituberculosis drugs given to the child.

Little is known about the humoral response to *M tuberculosis* in infants and children; previous attempts to develop enzyme-linked immunosorbent assay (ELISA) serodiagnostic tests for children have had mixed results. One ELISA study of South African children with tuberculosis using adsorbed mycobacterial sonicates as the antigen yielded a sensitivity of only 21 percent with a low specificity of 40 percent.\(^8\)

A study of Argentinean children with culture-confirmed tuberculosis using purified protein derivative (PPD) antigen yielded a sensitivity of 51 percent with a specificity of 98 percent.\(^9\) A third study, also from Argentina, which used the more specific *M tuberculosis* antigen 5, yielded a sensitivity of 86 percent with a specificity of 100 percent.\(^10\) Unfortunately, there have been no published studies verifying these results in other populations.

The study in this issue of Chest by Delacourt et al (see page 393) used an ELISA to detect IgG and IgM antibodies against antigen 60 (a purified polymer from the cytoplasm of *Mycobacterium bovis* that is also found in PPD\(^11\)) in children with tuberculosis and control subjects. While the IgM results were not helpful, measurement of anti-antigen 60 IgG yielded a diagnostic sensitivity of 68 percent at a predetermined specificity of 98 percent. In the same patients, the sensitivities for culture and acid-fast smear compared with the clinical diagnosis were 45 percent and 26 percent, respectively. The small number of children with tuberculous infection but no clinical or radiographic disease all had negative results in the ELISA study.

In order to achieve these results, the authors had to separate control patients by age and history of prior bacillus Calmette-Guérin (BCG) vaccination and then compare study patients with the appropriate control group. Control children less than 2 years of age who had received BCG had significantly higher IgG titers than children of similar age who had not received BCG. This is not surprising since antigen 60 is derived from *M bovis*. Unfortunately, this study had only 1 control subject older than 2 years of age who had not received BCG, so it was not possible to determine whether the effect of prior BCG vaccination on anti-antigen 60 titers wanes over time. It is unclear whether the different strains of BCG used throughout the world would have varying effects on subsequent antigen 60 antibody titers in children.

This study also found that anti-antigen 60 IgG titers increased with age among control children. The authors' suggestion that this trend was due to repeated exposure to environmental mycobacteria is plausible but would be very difficult to prove. In addition, since PPD contains antigen 60, the placing of a skin test on a child previously sensitized by BCG, exposure to environmental mycobacteria, or infection with *M tuberculosis* could increase subsequent anti-antigen 60 titers; this study did not address this issue.

The potential influence of age, prior BCG vaccination, and exposure to environmental mycobacteria on production of antigen 60 antibody in children means that "normal values" must be established locally; results cannot be generalized among populations, and titers from children with suspected tuberculosis must be compared with those from narrow, well-matched...
control groups. The practical limitations of this approach are enormous, especially in the areas of the world that need a simple diagnostic test the most.

The study by Delacourt et al is thoughtful and expands our knowledge about humoral responses to mycobacterial antigens in children. Unfortunately, it also reveals the shortcomings of the serodiagnosis of tuberculosis that have precluded its wide acceptance and application. Accurate diagnostic techniques for tuberculosis in children remain elusive, and serodiagnosis will not be a panacea in the near future.

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REFERENCES
8 Daniel TM, Debanne SM. The serodiagnosis of tuberculosis and other mycobacterial diseases by enzyme-linked immunosorbent assay. Am Rev Respir Dis 1987; 135:1137-51
12 Cocito CC. Properties of the mycobacterial antigen complex A60 and its applications to the diagnosis and prognosis of tuberculosis. Chest 1989; 100:1687-93

Role of Pulse Oximetry in the ICU

In this issue of Chest (see page 542), Inman et al report the impact of pulse oximetry on the utilization of arterial blood gas (ABG) analysis in an ICU. By means of a combined prospective and retrospective study, they tested their hypothesis that pulse oximetry would have little effect on the frequency of ABG analysis unless there were specific guidelines for the latter. The study is well designed and appears to accomplish its goal, within the limitations of a study that compares prospective and retrospective data. Some investigations have reached different conclusions on ABG utilization; one ICU study predicted a 48 percent reduction in the number of ABG analyses used for ventilator management.1

This article raises important issues regarding both the effectiveness of pulse oximetry and the ethics of clinical studies. From the scientific viewpoint, the study would have been more rigorous if it had been entirely prospective, comparing simultaneous matched patient groups with and without pulse oximetry. Despite the fact that "no published investigation has demonstrated that pulse oximetry makes a difference in morbidity or mortality,"2 the authors chose to use a retrospective control group. Thus, they acknowledge the importance of pulse oximetry in the ICU by stating that "it was . . . deemed unethical to randomly assign patients to not receive this mode of monitoring." Let us consider the purpose of pulse oximetry and some of the evidence of how effectively it accomplishes its goals.

One purpose of pulse oximetry may be that stated by Rutledge et al: to reduce the required number of ABG analyses. A more important purpose is to improve safety by providing continuous arterial oxygenation data in patients who are at risk for hypoxia. Is there evidence that it does this? In the operating room, clinical studies have shown that the use of pulse oximetry reduces the number of "hypoxic events," which are arbitrarily defined as SpO2 values below a critical threshold (eg, 75 percent).3 This result clearly does not prove that pulse oximetry improves patient safety. However, it is strongly suggestive when coupled with retrospective studies showing a decrease in unexpected admissions to the ICU and closed-claim studies showing that many injuries and deaths may have been preventable if pulse oximetry had been used.5 For these reasons, and because it is inexpensive and nearly risk-free, pulse oximetry has become a minimum standard of care in US operating rooms and recovery rooms (according to a resolution passed by the House of Delegates of the American Society of Anesthesiologists in 1991).

If pulse oximetry is a minimum standard in both the operating room and the recovery room, can we justify not using it in the ICU? Admittedly, there are no clinical studies showing decreased morbidity or mortality in the ICU setting, but neither are there any such studies in the operating room. Some forms