

Pediatric Tuberculosis

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Pediatric tuberculosis (TB) is different than that in adults in several ways. (1) The diagnosis of TB is more difficult in children due to non-specific or complete absence of symptoms and difficulty in confirming the diagnosis microbiologically. (2) Young children suffer more extrapulmonary and disseminated TB than adults. (3) Treatment of TB in children is challenging due to the lack of pediatric drug formulations and challenges in monitoring for toxicity. Fortunately, children generally do very well with treatment and tolerate the medications well. Treatment regimens are very similar to those used in adults. Four drug treatment should be initiated for treatment of presumed active TB if there are any risks of drug resistance in the child or adult source case (including res-

istance or travel to an area where there is > 4% resistance to INH). (4) Children should be TB skin tested only if they have risks for TB infection, are likely to progress to active TB, or are suspected of having active TB. Unlike adults, all children should be treated for latent TB infection if identified because the therapy is very safe in young people, they were likely to have been infected relatively recently, and they have a long time to reactivate their latent infection. (5) Young children are not contagious with active TB and acquired their disease from shared airspace with adolescents or adults with pulmonary TB or ingestion of unpasteurized milk products (*M. bovis*).
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ALTHOUGH CHILDREN have the lowest tuberculosis (TB) case rates of any age group in the United States, the importance of pediatric TB must be stressed for several reasons. First, untreated children with latent TB infection (LTBI) serve as the pool for future TB epidemics. A percentage of children with LTBI eventually will reactivate their infection and develop active tuberculosis. This is particularly true in developing countries where 40% to 60% of the population may be infected in the first 20 years of life (2% to 3% annual rate of infection).¹ Identification and treatment of children and their families with TB infection and disease are therefore the key to TB elimination. Second, TB disease and skin test conversion in young children represent recent acquisition and therefore ongoing transmission from adolescents and adults in the community. The recognition of new infection and disease in young children serves as an indicator of the need for additional public health intervention. Because an untreated adult with active TB infects 10 to 15 new people each year, the identification of the child's source case is very important. Third, the presentation of TB in children is often distinctly different than that in adults. Children frequently have more

subtle and modest symptoms when diagnosed with TB. Unless these differences are recognized, children at risk for or suspected of having tuberculosis will receive suboptimal care. Finally, young children are especially vulnerable because if infected, they are more likely than adults to develop active and disseminated TB.² These forms need to be recognized and treated early to avoid significant morbidity and mortality.

In 2001, the state of California incurred an increased number of TB cases for the first time in 8 years. Although the increase in cases was only 1% overall, the increase among 0 to 4 year olds was 15%. Case rates increased for African American and Hispanic children by 33% and 41%, respectively. This suggests that there was an increase in ongoing TB transmission in California and not merely immigration of high-risk individuals. This observation should be of concern to all U.S. jurisdictions.

TRANSMISSION TO CHILDREN

In most cases, a child is infected with *Mycobacterium tuberculosis* (Mtb) after an adolescent or adult with active tuberculosis expels bacilli into the shared air. Several other modes of infection occur more rarely: ingestion of the organism (usually *M. bovis*), vertical transmission (congenital tuberculosis), or direct inoculation of the skin or other tissue. In the case of aerosolized transmission, the likelihood of infection depends on the symptomatic status and personal habits of the active case, the bacillary load in their sputum (as evidenced by smear positivity), the volume of air in the shared space, and the amount of time and intimacy of the

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interaction. When an individual with active TB expels their secretions into the air, the smallest mucus particles will dehydrate around just a few Mtb organisms. The particles, which are less than 10 μm , are particularly aerodynamic and small enough to reach the alveoli of their next host. These infectious particles are termed the *dreaded* droplet nuclei.

It frequently is quoted that 30% to 50% of household contacts of an active source case will become infected. The ability of public health efforts to identify the adult responsible for infecting the child (the source case) varies greatly based on the age of the child, U.S. versus foreign birth, and other factors. Published studies have quoted rates of identified source cases as 15% to 90%.³⁻⁹ Very young children, African American and U.S. born children and children screened during a contact investigation of an active case are more likely to have a source case identified.

In 2 series with intermediate numbers of source cases identified (37% and 58%), 25% of children with active TB were infected by their mothers, 15% to 25% by their fathers, 24% to 30% by aunts and uncles, and 7% to 22% by grandparents or other relatives.^{3,8} In one of these series, 84% of source cases lived in the home with the child, 10% were family friends, and 3% were child-care providers.³ Because many of the source cases were not identified, it is presumed that there are significant numbers of active cases who have more distant or transient relationships with the children.

To complicate our understanding of transmission of TB to children, 2 recent projects have revealed that up to 25% of culture-positive pediatric TB cases had a different molecular fingerprint than their identified source case.^{10,11} In one of the series, 16 of 111 children (14%) were linked epidemiologically with more than one other case of active TB.¹⁰ Several studies have reported children and their source cases as having different drug susceptibility patterns. Susceptibility discordance between child-source pairs has been reported as 2% to 10%.^{6,8,12,13} The potential for misidentification of the source case naturally will be more frequent in high-prevalence communities.

Accurate identification of a child's source case is important for several reasons. First, identification of the source case is an opportunity to treat that adult and to avoid further transmission to other individuals (including other children) in the community. Next, confirmation of a source case diag-

nosis of TB provides supporting evidence that a child's radiographic changes or clinical disease are in fact caused by TB in children with negative cultures but who fulfill the clinical case definition for TB. Finally, culture and susceptibility testing of the source case's *M. tuberculosis* isolate provides valuable information for treatment of the child.

IMMUNOLOGY

Like adults, most children infected with *M. tuberculosis* do not progress on to active TB, but rather they have a successful immune response and the organism becomes latent. A successful immune response in adults appears to be associated with a strong TH1/CD4 lymphocyte response and high levels of interferon- γ . Very young children are at particular risk of acute hematogenous dissemination (miliary disease) and meningitis. Several elements of the immune response to TB appear to be different in children, perhaps explaining their difficulty in containing the infection or disease. Animal model and human data suggest that youngsters have fewer and/or relatively poorer functioning dendritic and CD4 cells. Young animals and humans are biased toward development of TH2 immune responses rather than the TH1 response prominent in the adult response to TB. Defective chemotaxis of monocytes and macrophages in children may delay recruitment to sites of infection; less efficient antigen presentation would slow the antigen-specific immune response; interferon- γ levels in mycobacterial infections are significantly lower (other cytokines are less depressed), which may limit macrophage activation.¹⁴

The likelihood that a child will develop active TB rather than controlling their infection in a dormant or latent state is related primarily to the child's age. Although 10% of all individuals infected with Mtb will develop active TB in their lifetime, children less than 5 years of age are much more likely to develop active TB. Babies less than 1 year of age have a 42% chance of progressing to active TB if infected and 24% of infected children 1 to 5 years of age will develop TB.¹⁵

TUBERCULIN SKIN TESTING AND SCREENING FOR TB INFECTION

The Mantoux test is the standard skin test used in the United States. The sensitivity and specificity of the test are about 90% each, leading to the possibility of false-positive and false-negative skin

tests. In the circumstance of a very low rate of TB in a community, the likelihood of a reactive tuberculin skin test (TST) being caused by *Mtb* infection (true positive) versus a false positive is low. The vast majority of reactive skin tests in this scenario will be false positives and significant resources will be diverted from more valuable efforts.¹

To increase the positive predictive value of the TST, 2 strategies have been undertaken. First, the definition of a positive TST (the break-point) depends on the likelihood that the child is exposed to TB and the risk that the child will progress on to active TB. An induration of 5 mm or greater is considered to be positive if the child is immunocompromised, if the child has clinical or radiographic evidence of active TB, or if the child has been exposed to a known or suspected case of active TB. An induration of 10 mm or greater is considered positive if the child is exposed to individuals at high risk for active TB, has other medical conditions that may put the child at risk for progression of infection to disease, or if the child is less than 4 years of age. An induration of 15 mm or greater is considered positive if the child has none of the earlier-described risks.¹⁶

The other strategy used to improve the value of the TST is relatively new, but very exciting. Instead of applying the TST to large groups of people who have little risk of TB exposures (and in which case, the positive predictive value of the test is low), the test is now recommended only for individuals identified as having risk of TB exposure. In this way, the same 90% sensitivity of the test leads to a much higher positive predictive value. The goal of targeted screening and treatment of LTBI has now been embraced by the American Academy of Pediatrics (AAP), Centers for Disease Control and Prevention, and the American Thoracic Society.^{16,17} Targeted screening and treatment of children is different than that in adults. Children should be skin tested if risks for TB exposure are identified. Any child diagnosed with LTBI should be treated as described later. Adults should be screened for risks of recent exposure and for other risks for progression to active TB if infected. Only adults at increased risk for progression to active TB should be treated for LTBI. For both children and adults, only individuals who would be treated for LTBI if identified should be skin tested. A decision to test is a decision to treat.

Since 1994, the AAP has recommended targeted

Table 1. Risk Factors for TB Exposure or Progression to Active TB

Clinical or radiographic findings suggesting TB
Exposure to an individual with known or suspected active TB
Foreign birth
Travel or exposure to individuals from high TB prevalence areas
Incarceration
Exposure to other high-risk adults
HIV infected
Illicit drug users
Residents of congregate settings
Migrant workers
Homeless
HIV infection
Malnourishment
Diabetes
Renal failure

TB skin testing. A schedule of recommended skin testing was devised based on risk factors known to be associated with TB transmission or progression of TB. Families should be questioned about TB risks at each health care encounter. Table 1 lists the risk factors identified by the AAP. The recommended skin testing frequency is based on the degree of risk conferred. For example, exposure to a case of active TB is known to cause infection in 30% to 50% of household contacts and therefore skin testing should be undertaken immediately.¹⁶

A number of efforts have been made to evaluate the usefulness of the risk factor questions and the questionnaire process. Their conclusions have been uniform. Implementation of screening and targeted skin testing can greatly decrease the number of skin tests performed and increase the positive predictive value of the test. This decreases the number of false-positive tests that lead to unnecessary chest radiographs, evaluation of close contacts, treatment with potentially toxic drugs, and (not inconsequential) great anxiety on the part of the family.

In one study, the parents of more than 30,000 children in Northern California were asked to fill out an 11-item questionnaire at the time of a visit requiring a routine TST. The following risks were associated with a positive TST: foreign birth, prior receipt of bacille Calmette-Guérin (BCG) vaccine, residence outside the United States, Asian or Hispanic race/ethnicity, and a household member with TB or a positive TST. Other factors were not independently significant predictors of TST positivity.¹⁸ Only 1% (mean age, 8.1 y) of children

screened by TST had a positive result using the 10-mm cut-off standard in California. An abbreviated 5-question survey based on the earlier-described significant risks would result in a questionnaire with a 47.5% sensitivity. Application of this method of screening would have averted 15,000 skin tests, but would have failed to identify 19 of 159 children with a TST of 15 mm or greater induration. Other series have found that birth in or travel to a TB endemic area, having a family member with a positive TST, being over 11 years of age, and consumption of raw milk products increased the likelihood that a child would have a positive TST.¹⁹⁻²³ Some of these risk factors were universal across the study populations, but some were specific to individual locales and groups of people. Therefore, targeted screening will need to be customized based on local epidemiology. Additionally, each screening provider or agency will need to consider its willingness to accept false-negative tests and its magnitude of resources for identifying, evaluating, and treating children with a positive TST.

Rate of return for Reading, Misreading, and Improving TST Reading in Children

The Mantoux skin test methodology requires that the patient return to the health care professional for skin test reading 48 to 72 hours after placement. Many studies have shown that individuals cannot reliably read their own skin tests. Families in the Northern California screening study incorrectly interpreted 10- to 15-mm skin test induration as having no induration 9.9% of the time.¹⁸ Caregivers of human immunodeficiency virus (HIV)-infected children misinterpreted 24% of the candida controls and 41% of the tetanus controls as negative.²⁴

Unfortunately, many families do not return for TST reading. Several interventions have been studied to improve the return rate for skin test reading. In one setting with a baseline return rate for reading of 45%, verbal and written instructions increased the rate to 58%, a reminder phone call resulted in a 70% return rate, and a transportation token/toy brought 67% back. The intervention that improved return most impressively was the withholding of required school forms, which resulted in 84% return.²⁵ The simple intervention of calling the family if they had not returned for reading by midday the second day after the test increased the return rate from 59% to 91% in one Bronx clinic.²⁶

Another study evaluated a collaboration with the school nurse for skin test reading. The clinic had a 43% historic skin test reading rate. After educating and communicating with the nurses, skin test results were reported to the provider by the school nurse for 92% of children in the study group.²⁷ This method seems ideal for school-aged children and in schools with a school nurse. Another school-based program placed and read the skin tests at school and achieved a 98% reading rate.²⁸

CONTRIBUTION OF BCG VACCINATION IN INTERPRETATION OF THE TST

The most extensively used vaccine in the world is the BCG. The vaccine was developed after serial passage of *M. bovis* in tissue culture until a non-virulent mutant was isolated. Since then, serial passage has led to numerous different vaccine strains that are used in different parts of the world. These various strains appear to have different efficacy and produce different degrees of reactivity to the TST. Unfortunately, there appears to be no correlation between TST reaction after BCG administration and protection from disease. The effect of receipt of BCG on TST reaction is an ongoing challenge for clinicians. The Centers for Disease Control and the AAP advise the clinician to ignore the history of receipt of BCG when interpreting the TST. This is easier said than done for children with small reactions (<15 mm) to TST and a family who is adamant that the skin test response is caused by BCG and not to TB infection. The following factors make it less likely that the skin test reaction is caused by BCG: receipt of a single rather than multiple BCGs, BCG given in the first month of life, a long period since the BCG dose, receipt of no other TST in the past year, and large TST induration.²⁹ Although many studies support the notion that BCG does not have a long-standing impact on TST size,^{21,22,30} some reports conclude that it does increase TST reactivity.^{23,31} New blood tests may clarify further the impact of BCG on TST reactions and allow for more accurate TST cut-off points in individuals who have received BCG.^{32,33}

Of note, although most children develop a local ulceration and subsequent scar after the BCG vaccination, recent studies show that not all children with a record of receipt of BCG have a scar. In a series of internationally adopted children, 27% of children with a vaccine record of BCG receipt did not have a scar.²⁰ In Northern Brazil, 89% of

children who reportedly had received BCG had a scar.³⁰ Thus, the presence or absence of a scar cannot be relied on for purposes of inferring BCG history.

EVALUATION OF A CHILD WITH A POSITIVE TST

Once a tuberculin skin test is determined to be positive based on the size of the induration, risk factors for exposure, and likelihood of progression to active tuberculosis, the child must be evaluated to determine whether or not they have active TB. A normal history and physical examination and normal frontal and lateral chest radiograph essentially rule out active TB. Ideally the history should include information regarding a possible source case, risk for resistance in the source case or child (previous treatment for TB, residence in areas with high rates of resistance), symptoms of active TB (both pulmonary and extrapulmonary), other medications the child takes, and underlying diseases including liver disease, HIV, and so forth. It must be emphasized that at least half of children diagnosed with active TB in the United States have no identifiable symptoms at the time of initial screening.⁶

The physical examination can be quite focused and brief once the clinician is comfortable evaluating for extrapulmonary TB in children. The following elements should be evaluated to assess for forms of active TB or risks for drug toxicity: general appearance and growth, color of the conjunctiva, neck (including flexion and nodes) and axilla, lungs and heart, abdomen and flank, spine, and skin. Poor weight gain may be the only finding of active TB. Similar to the history, the examination in children with TB can be deceptively normal. Even children with markedly abnormal radiographs frequently have no abnormal lung findings.

The child should be in full inspiration and not rotated for the best quality radiograph. Both the frontal and lateral views should be obtained.³⁴ The lateral view is particularly helpful in distinguishing other central shadows from lymph nodes, which are spheric and can be seen frequently on both views.³⁵ Some nodes are only visible on the lateral view and paratracheal nodes are only discernible on a frontal view. Ideally, the films should be interpreted by a clinician or radiologist very experienced in pediatric TB. For children less than 5 years of age the radiograph should be performed no more than 3 months before institution of LTBI

therapy. For children at increased risk for progression to active TB (**LESS THAN** 1 year of age, immunocompromised, recent exposure to a contagious case of TB) the radiograph should be performed no more than 1 month before institution of LTBI therapy (young children can progress to active TB in a matter of weeks to months). Computed tomography (CT) is not indicated in the evaluation of an asymptomatic child with a normal chest radiograph and a positive TST. A CT scan can be very helpful when the radiograph is equivocal or when required to evaluate for other causes of disease.

TREATMENT OF LATENT TB INFECTION IN CHILDREN

Evaluation of treatment of latent TB infection began shortly after the usefulness of isoniazid (INH) for treatment of TB was identified in the 1950s. At that time, the treatment was called *preventive* or *prophylactic* therapy. Almost 3,000 asymptomatic young children with positive TST and either normal or abnormal radiographs were enrolled between 1955 and 1957 in a United States Public Health Service (USPHS) trial. There was an 8.4-fold reduction in morbidity in the treatment group who were treated with INH for 12 months.³⁶

Intermittent therapy has been studied for treatment of active TB but not for treatment of LTBI. Expert opinion based on indirect evidence has led to the use of 2 or 3 times weekly therapy for LTBI. Intermittent TB therapy should be given only under directly observed therapy (DOT).¹⁷

Rifampin alone has had some limited evaluation in treatment of LTBI.¹⁷ A 6-month regimen of rifampin was used to treat 157 adolescents with probable INH-resistant LTBI and none of these developed active TB during the 2-year follow-up period. Eight of the students discontinued rifampin therapy, only one for transaminase level increase. The minimum protective value of the regimen was calculated at 56%.³⁷

The use of isoniazid and rifampin together for treatment of LTBI in children has been reported from the Blackburn Health District in England. The investigators observed a marked decrease in pediatric TB notifications, initially using a 9-month regimen, then a 6-month regimen, then a 4-month regimen, and, finally, a 3-month regimen. They examined and could not find any reason besides the use of the LTBI regimen for the decrease in pediatric TB cases. The children tolerated the regimen

well and the investigators recommended no liver function monitoring in the absence of symptoms.³⁸ This regimen deserves further study in a more controlled setting.

Based on clinical trials, observational studies, and extrapolation from adult data, the following regimens are recommended by the AAP for treatment of latent TB infection in children: (1) 9 months of INH daily (or if necessary, twice weekly by DOT, preferably after 1 mo of daily therapy) at a dose of 10 to 15 mg/kg/d for daily treatment up to 300 mg/d or 20 to 30 mg/kg/dose for twice-weekly therapy up to 900 mg per dose; (2) 6 months of rifampin daily at 10 to 20 mg/kg/d up to 600 mg for known infection with INH-resistant strains.¹⁶ INH alone should be used unless there is strong evidence of drug resistance in the source case (not merely acquisition in a high-resistance area).

Analysis of early INH preventive trials revealed that short breaks in therapy were not particularly detrimental to successful outcomes. For this reason, the American Thoracic Society recommends that instead of counting the months of therapy, 270 doses of INH should be the goal of LTBI treatment. These 270 doses should be ingested within a 12-month period. When there is a prolonged break after a short initial period, it is probably prudent to restart therapy, but short lapses are tolerated, especially if the regimen is well underway.¹⁷

Routine liver function testing is not indicated for asymptomatic children who do not have underlying liver disease and are not taking other hepatotoxic drugs. INH rarely causes hepatotoxicity in children. Many series of children receiving INH report no hepatotoxicity, but it has been reported in as many as 1% of cases in 2 series and even has been fatal very rarely.¹ There appears to be an increased risk in adolescent girls, especially African Americans and Latinas.³⁹

Families should be educated thoroughly to watch for the symptoms of hepatotoxicity (anorexia, malaise, abdominal pain, and vomiting) and to stop the therapy and return to the clinic if the symptoms are consistent with drug toxicity. Lack of association with other viral symptoms and lack of improvement after a few days should suggest the possibility of hepatotoxicity rather than an intercurrent illness. Children should be seen in the clinic monthly and questioned about toxicity symptoms as well as the symptoms of active TB, adherence to

Table 2. Improving Adherence and Completion Rates for TB Therapy

Use crushed tablets into semisoft vehicles to avoid stomach upset from the liquid preparation
Warn the family that the first couple of weeks of therapy will be challenging
See the patients monthly and supply only 1 month of medication at a time
Provide written education regarding reasons for therapy and symptoms of TB and toxicity
Develop a small, dedicated, and enthusiastic team of staff providers, nurses, and interpreters
Develop systems to encourage compliance such as having the child put a sticker on the calendar for each dose taken
Have convenient clinic hours and short waiting times
Develop a system of following-up patients who have missed appointments
Praise the family and child for good adherence and clinic attendance

therapy, and results of skin testing of their family members and other contacts.

Children taking anti-epileptic drugs should be monitored closely because INH affects the drug levels of some of these medications.

Historically, the completion rate for a 9- to 12-month regimen of LTBI is between 20% and 60%.⁴⁰ Because we are now targeting our tuberculin screening to high-risk individuals, every effort should be made to maximize the efficacy of LTBI treatment by helping patients complete the prescribed course of therapy. Ideally, all children should receive DOT for LTBI (formerly referred to as directly observed preventive therapy). Because few jurisdictions have the resources for universal DOT for LTBI, most focus on those young children at highest risk for progression: those exposed to an active source case. DOT can be administered at home, in school, at daycare, or in the clinic. One school-based program in Brooklyn achieved a 54% completion rate after one attempt and a 71% completion rate after 2 attempts at LTBI DOT at school (compared with 26% for traditional therapy).²⁸

Table 2 lists some elements that may be helpful for improving adherence to therapy completion rates for LTBI.

PREVENTION OF TB IN CHILDREN

The most efficient way to prevent pediatric TB is to evaluate and treat those children exposed to a contagious adult source case. Ideally all exposed children should be evaluated promptly by TST, and for children less than 5 years of age by physical examination and chest radiograph. Children with a

negative TST and no evidence of active TB by examination or radiograph should be considered for window prophylaxis to prevent the development of TB. There are 3 reasons to start this empiric therapy: (1) it can take as long as 3 months for the TST to turn positive after infection with Mtb; (2) young children can develop disseminated (as well as pulmonary) forms of active TB shortly after infection and before the TST becomes positive; and (3) it is easier to treat all the household members at the same time. If one member starts treatment 3 months later, it is much more difficult to maintain momentum. Many health jurisdictions treat all children in a household regardless of age if the source case is smear positive (suggesting high bacillary load and risk for transmission) and children less than 5 years of age with significant contact with any case of active TB. Additionally, many experts recommend that treatment of young children exposed to contagious adults receive window prophylaxis and treatment of LTBI by DOT. Isoniazid can be used to treat children whose sources cases have sensitive TB isolates. The INH should be continued until a repeat TST is found to be negative 3 months after the source case is deemed to be noncontagious or contact between the source case and the child was broken. If the child is an infant who may be too young to mount the delayed-type hypersensitivity reaction required to document a positive skin test, the treatment should be prolonged past the 3-month period. Some providers wait until the child is at least 6 months of age⁴¹ to stop window prophylaxis and others continue until the child is 1 year of age before repeating the skin test. If the repeat TST is positive, the child should complete a 9-month course of INH. If the child is asymptomatic and there has been no concern for nonadherence, a repeat radiograph is not necessary.¹⁶

Children evaluated during a contact investigation whose initial TST is positive should be evaluated and treated as with all other children with positive TST (see earlier).

Several studies have detailed the development of pediatric TB during suboptimal public health interventions.^{3,5,42,43} Various missed opportunities to prevent cases of pediatric TB included delayed reporting of a source case to the local health jurisdiction, failure to identify a child during the contact investigation, failure to treat the source case with DOT despite indications of nonadherence, failure to document sterilization of cultures, failure

to start the child on INH prophylaxis or LTBI treatment, and failure to ensure that the child took the treatment. These studies suggest that as many as 20% of pediatric cases probably were preventable and as many as 40% possibly were preventable.

EPIDEMIOLOGY OF ACTIVE TB DISEASE IN CHILDREN

In the United States in 2000, among children less than 5 years of age reported with TB, 32% were African American, 40% were Hispanic, and 12% were Asian/Pacific Islander. The epidemiology of active TB in children differs somewhat from that in adults. Compared with 47% of all U.S. TB cases, only 18% of young children with TB were foreign born.⁴⁴ In California more than 70% of pediatric TB is in Hispanic children, whereas only one third of the total cases are Hispanic.

Pediatric TB is concentrated in very young children, 60% are less than 5 and 26% are less than 2 years of age.⁴⁵ The school-aged years have been called the *golden-age* or *favored-age* because these children have the lowest case rates of any age group (1.0 case per 100,000 in 2000 compared with 4.1 for 15 to 24 year olds and 9.9 for 65 years and over).⁴⁴ Unlike adults, in whom TB is more common in men, both sexes of children are represented equally in pediatric TB.⁴⁴

For epidemiology to be helpful when caring for an individual patient, one must know the local epidemiology, but must also realize that TB can occur in any child regardless of age, race, ethnicity, or socioeconomic class.

DIAGNOSIS OF ACTIVE TB

The diagnosis of active TB in a child frequently is challenging. Ideally, all children with active TB would have a positive TST, a known exposure to active TB, fever, cough, and the classic radiographic findings of hilar lymphadenopathy and air-space consolidation. In this idealized scenario, there also would be highly sensitive and specific tests to distinguish LTBI from active TB. But alas, life of the TB clinician is not so easy. The diagnosis of TB in children is as much art as it is science.

Approximately 10% to 15% of children with active TB have a negative TST at the time of initial diagnosis.^{7,43,45,46} Most, but not all of these, developed a positive TST over time. Some children have

a negative initial TST because they are diagnosed with active TB in the first few months after infection, before the delayed-type hypersensitivity responsible for the TST reaction has developed. Other children have disseminated or advanced pulmonary disease, which are known to be associated with anergy even in adults. The anergy to skin testing can be specific to the TB antigen or can be universal. For this reason, anergy panels are not particularly helpful in clarifying the diagnosis. Hence the rule: a negative TST never excludes disease. The converse also is true, not all children with abnormal skin tests and radiographs have active TB. The diagnosis always needs to be made in the context of demographics, exposure, and the clinical presentation.

Between 17% and 59% of children come to be diagnosed with TB because of symptoms.^{3-6,8,42,43} Approximately 30% to 60% of children diagnosed with active TB in the United States have no symptoms reported by the parent at the time of diagnosis.^{6,47} This is in large part owing to the fact that a significant number of children are diagnosed during a contact investigation of a contagious adult. In a series from North Carolina, only 17% of children presented because of symptoms because 80% were identified during a contact investigation.⁵ These children were diagnosed early in their disease and had not yet developed symptoms. On the other extreme, 59% of children in San Diego, CA, presented for symptoms and only 15% had confirmed source cases identified.⁴³ Additionally, we consider asymptomatic children with isolated intrathoracic lymphadenopathy or primary complex disease (a small air-space focus with associated proximal lymphadenopathy) to have active TB. We know that many of these children would involute their infections without treatment, but we treat aggressively to avoid the progression of disease and dissemination in a few patients. Finally, we have the luxury of obtaining a chest radiograph on any child we are concerned may have TB. In developing countries, radiology often is not available and active case finding, including contact investigations, frequently are not given high priority. In these situations, a child must become symptomatic before the diagnosis of TB can be made. Various scoring systems or score cards have been used to diagnose TB in these settings. Prolonged symptoms (cough and fever), weight loss, TST positivity, and exposure to a smear-positive case of TB increase the likelihood of diagnosis.^{48,49}

Interestingly, some children who are described as being asymptomatic at the time of presentation eat better, play harder, and generally are perkier after initiation of TB treatment. A clinical rule of thumb: the more modest the symptoms compared with the radiographic findings, the more likely the diagnosis is TB.

In children less than 5 years of age in New York City, 44% had cough and 44% had fever.⁵ Among culture-positive children in another series, 78% had some symptoms on presentation: 62% had cough, 55% had fever, and 32% had weight loss or failure to thrive.⁵ Because symptomatic children are known to have higher culture yield, this finding is not surprising.^{12,43} Infants are much more likely to be symptomatic. In children less than 1 year of age, 79% had cough and 64% had fever.⁵⁰ Adolescents are also more likely to be symptomatic because their disease is frequently the adult-type reactivation disease with prominent air-space consolidation and frequent cavitation.

Among recent U.S. series, 19% to 64% of children were diagnosed with active TB on clinical and epidemiologic grounds and no culture confirmation was sought.^{9,45,51,52} When the diagnosis is clear-cut and susceptibilities of the source case are available, it is appropriate to spare the child the discomfort of culture collection. A positive culture, however, confirms the diagnosis of TB and provides specific susceptibility information. Specimens for culture include morning gastric aspirates, induced sputum and bronchoalveolar lavage fluid, blood, urine, cerebrospinal fluid, biopsy materials (frequently lymph node), pleural fluid, and others. The yield for these various tests depends on the clinical presentation, age of the patient, and quality of the specimen.

Gastric aspirates are obtained with the goal of collecting mucus that has been swept up by the mucociliary system of the respiratory tract and swallowed. If the gastric contents are collected before the stomach empties in the morning, the mucus may be found and mycobacteria may be cultured. Unlike sputum in adults with active TB, gastric aspirates do not have a particularly good yield despite the common practice of collecting 3 sequential morning samples. Most investigators report yields of 40% to 50%, with much higher yields for young infants.^{6,12,43,51} In one series, 75% of babies less than 1 year of age with pulmonary TB had positive gastric aspirate cultures.⁵⁰

Some details of gastric aspirate collection de-

serve comment. The child needs to have had nothing to eat or drink for at least 6 hours (very young infants sometimes will not be able to fast so long and should be sampled after several long naps) before the test. The first gastric aspirate collected has the best yield (88% to 93% of positive cultures are obtained on the first attempt).^{12,53} Therefore, significant effort should be made to collect and process the first day's specimen very well. The child should be immobilized well and the nasogastric tube should be kept away from the nasal septum and aimed straight at the bed for the least traumatic procedure. The health care provider should puff in the child's face as the tube enters the throat to elicit a swallow reflex. Once the child swallows, the provider should quickly advance the tube into the esophagus. If the tube coils in the mouth, it is very difficult to proceed. The provider should be prepared to collect any emesis and any yield from the tube immediately. Sometimes these are the best specimens. If irrigation is required, 20 to 30 cc of sterile water rather than saline should be instilled. If the mucus pool is not found readily, the provider should try to advance or withdraw the tube or roll the child on the side (while continuously aspirating with the syringe) to maximize the yield. The specimen should be transported promptly to the laboratory (within 30 min) or neutralized at the bedside with bicarbonate.³⁵ Smears only rarely are positive because 10^5 to 10^6 organisms per mL are required to be visualized and children have paucibacillary TB disease. The youngest children are more likely to yield gastric aspirate specimens with positive smears.⁴⁵ The family should be warned that the results take many weeks and that the test is less than 50% sensitive. Only a positive test is helpful. A negative result alone does not change clinical management.

Traditionally, gastric aspirates are collected during hospitalization. Stomach emptying is more likely to have occurred already if the child is transported from home the morning of the specimen collection. Unfortunately, some insurance companies will no longer pay for hospitalizations of relatively asymptomatic children for culture collection. Additionally, some families whose children are being diagnosed with TB are more comfortable coming to a dedicated pediatric TB clinic than being submitted to isolation and negative stereotypes in the hospital. In my practice, 39% of children sampled as outpatients had at least one positive culture compared with 56% of inpatients

($P = .5$).¹² The hospitalized children were more likely to be symptomatic and younger, which are factors associated with improved yield for gastric aspirates.

Several series have reported positive gastric aspirate cultures in children with normal chest radiographs^{46,53,54} and gastric aspirates sometimes are positive in children with central nervous system or disseminated TB. It is unclear what the natural history of infection or disease would be for an asymptomatic child with a normal chest radiograph and a positive gastric aspirate for Mtb.

Sputum induction using nebulized 3% hypertonic saline is used frequently for sputum collection from adults. In 29 Malawian children aged 3 to 15, sputum induction confirmed the TB diagnosis in 28%.⁵⁵ A recent abstract from South Africa reported comparison of sputum induction with gastric aspiration. Mtb was cultured from induced sputum from 25% compared with 19% by gastric aspiration.⁵⁶

One report described the combination of these 2 procedures with great success. Children were exposed to 20 minutes of superheated nebulized saline after a fast in the late afternoon, immediately followed by gastric aspiration. The following morning another gastric aspirate was collected. This was performed for 3 days for a total of 6 gastric aspirates per child. Some specimens were pooled so it was not clear whether the afternoon or morning specimen provided the best culture results. At least one positive culture was obtained from 12 of 13 children (92%).⁵⁷ These and other strategies to improve culture confirmation of TB in children deserve study.

Bronchoalveolar lavage (BAL) and bronchoscopy are important tools for diagnosing pediatric lung diseases but are somewhat invasive. Several series have compared BAL with gastric aspiration for the culture confirmation of pediatric TB. Two series showed superior yields for gastric aspirates versus BAL: 50% versus 10% in one series and 32% versus 12% in the other series.^{58,59} Only one child in those 2 series ($n = 100$) grew Mtb from a BAL and not from gastric aspiration. Two other series concluded that BAL resulted in more positive cultures than gastric aspiration: 21% versus 12% in one series and 22% versus 12% in the other.^{60,61} Of note, the latter 2 studies, which showed a better yield for BAL, had unusually low yields for gastric aspirates (12%).

Mycobacterial blood and urine cultures are rel-

atively noninvasive and sometimes grow Mtb, especially in cases of disseminated or advanced disease.

Polymerase chain reaction is a molecular amplification technique that is used with good sensitivity and specificity in adults with smear-positive pulmonary TB. The application of polymerase chain reaction technology to gastric aspirates from children suspected of having TB has been disappointing. In addition to limited improvement of sensitivity compared with culture or clinical diagnosis, a significant number of false-positive results are seen (mostly in children with LTBI).⁶²⁻⁶⁵

In summary, unless the child is able to produce induced sputum for mycobacterial culture, gastric aspiration provides the best clinical specimen and is fairly noninvasive. Although the mycobacterial culture of gastric aspirates have suboptimal yield, susceptibility information is very valuable, especially when these results are not available for the source case or when risks for resistance are present. Bronchoscopy generally should be reserved for situations in which TB is considered as part of a broader differential diagnosis.

Radiology

Frontal and lateral chest radiographs are recommended by experts for the evaluation of children suspected of having intrathoracic TB.³⁴ The lateral view complements the frontal view in visualization and confirmation of hilar lymph nodes, which are noted in 63% to 95% of pediatric TB cases.^{6,34,66} Adjacent air-space disease sometimes makes the lymph nodes difficult to discern initially and they may be appreciated better on subsequent radiographs.

Findings on chest radiographs of children with TB are a combination of the effects of the organism, immune response, and secondary mechanical effects. The organism and the immune response are responsible for a small air-space focus and the proximal lymph node. An infiltrate may be seen in any lung field⁶ and is seen in multiple lobes in 25% of children. Adenopathy is seen more frequently in the young child and is reported to be present in 85% of children less than 3 years of age.³⁴ There is a right-sided predilection for nodes as the right hilar and right paratracheal nodes drain the right lung and lower half of the left lung.^{34,66} Lymph nodes may have distinct edges with lobulations or may have hazy borders. They tend to be slightly more dense than other hilar structures and usually

(but not always) are asymmetric and unilateral. Their compression or complete obstruction of airways, splaying of the carina, and disruption of the normal angle of the right pulmonary vessels are sometimes clues to their presence. Lymph nodes may calcify within several months of their infection. Paratracheal lymph nodes sometimes are difficult to distinguish from other superior mediastinal structures. A central trachea from a right-sided paratracheal node is sometimes helpful. Of note, TB lymph nodes resolve very slowly, even with appropriate TB therapy, and often still are visible on the radiograph well after completion of successful therapy.

Parenchymal disease may be caused by a number of processes. The small alveolar parenchymal process associated with the primary process is a combination of infection and immune response. A larger consolidation may be associated with advancement of the infection—the so-called progressive primary process—or may be caused by atelectasis or collapse-consolidation secondary to lymph node obstruction. Lymph node obstruction also can cause air-trapping behind the node with resultant hyperinflation.³⁴

Infection sometimes is spread to other parenchymal locations after erosion of a lymph node with spilling of infectious material (bronchogenic spread). This can cause a segmental lesion when the material is contained to one bronchus, or may result in diffuse bronchopneumonia when the organism spreads throughout the lung.³⁴

Distribution of Mtb via the bloodstream to the lung usually is termed *miliary disease* because of the small round appearance of the diffuse lesions. The primary bacilleemia occurs during the initial process of sharing the original infection with the proximal lymph nodes and subsequently the thoracic duct. The infection also may be disseminated secondarily if a necrotizing lymph node or air-space focus erodes into a blood vessel. These disseminated processes do not always appear radiographically in the classic miliary pattern. Larger, patchy, reticulonodular lesions may be present and difficult to distinguish from other diffuse lung infections.

A CT scan with contrast can be a very helpful adjunct to chest radiography and is particularly sensitive for detection of adenopathy. Lymph nodes, calcification, and small unsuspected cavitations have been present on CTs of children with TB, but not evident on plain films.^{64,66} The use of

these studies generally should be reserved for clarification of abnormal but inconclusive radiographs because subclinical and subradiographic lymph node disease is likely part of the natural history of the primary complex.

Many TB clinicians obtain a chest radiograph at 2 months into therapy and when completion of therapy is considered. It should be noted that radiographic abnormalities in pediatric TB resolve slowly over time. More than 50% of children's films are not normal at the end of therapy, but gradually improve over time.⁵¹ Although it is frequently not normal, the completion of therapy radiographs should be improved significantly compared with the original and will serve as a baseline for monitoring future changes.

EXTRAPULMONARY TB IN CHILDREN

Extrapulmonary TB is more common in children than adults and usually is caused by hematogenous deposition. Shortly after infection, the organism appears in the bloodstream via the primary complex intrathoracic lymph node and the thoracic duct. After seeding distant sites, the organism usually is contained by cell-mediated immunity, but if not, very early disseminated disease may become evident. For example, the majority of pediatric TB meningitis occurs within 8 weeks of primary TB and may be diagnosed even before the chest radiograph is abnormal.⁶⁷ It is estimated that 20% to 25% of children will experience extrapulmonary TB (many children with intrathoracic lymphadenopathy are not classified by their providers as having extrapulmonary TB).⁶⁷

Lymphatic disease is the most common extrapulmonary TB site for children. Mycobacterial peripheral adenopathy is called *scrofula*. Scrofula is almost always in the neck, but may occur in other nodes. The nodes are generally quite indolent and enlarge and discolor slowly over time. Pain usually occurs only when the node grows quickly, resulting in capsular stretching. These nodes are to be distinguished from pyogenic nodes, which generally appear more quickly, are more erythematous, more tender, and more associated with systemic symptoms. The more pertinent differential diagnosis includes scrofula from nontuberculous mycobacteria and Cat Scratch disease. Large TST reactions, a chest radiograph consistent with TB (present in approximately 20% of TB scrofula cases), and exposure to TB are the most valuable clues that the lymph node disease is caused by Mtb.

Unfortunately, surgical excision is sometimes required to clarify the diagnosis. If there is significant doubt as to the diagnosis, it is best to excise the node rather than to aspirate or incise it for 2 reasons: (1) nontuberculous mycobacterial scrofula is difficult to cure medically and generally results in a poor cosmetic outcome when delayed or incomplete surgical procedures are used; (2) mycobacteria are not always easy to culture from lymph nodes and a significant amount of tissue should be sent for culture and pathology. Along the U.S.-Mexican border, *M. bovis* is a significant cause of scrofula after the child ingests infected unpasteurized milk products. *M. bovis* is inherently resistant to pyrazinamide and even when treated with the best antituberculous therapy (INH, rifampin, and ethambutol for 2 months, followed by at least 7 months of INH and rifampin), these nodes are sometimes slow to recover and require prolonged therapy (Alice Pong, personal communication).

Miliary or acute disseminated TB occurs when large numbers of organisms are distributed into the bloodstream and the local immune response cannot control the infection. Symptoms may initially be nondescript and fever is present in only two thirds of children. Fever may precede radiographic changes by several weeks. Other symptoms include fatigue, anorexia, vomiting, diarrhea, and weight loss.⁶⁷ The nonspecific nature of the symptoms and the very young age of most of these children make the diagnosis difficult before the classic radiograph is obtained. Culture confirmation is difficult but the organism grows from 33% of gastric aspirates and also may grow from mycobacterial blood or bone marrow aspirate or biopsy cultures. Transbronchial biopsy examination is valuable in confirming the diagnosis in adults but is unstudied in children and more difficult to obtain. Most pediatric TB clinicians treat miliary disease for 12 months.

Tuberculous meningitis complicates approximately 20% of miliary TB cases and is the outcome of between 1% and 2% of untreated TB infections in children.⁶⁸ After lymphatic disease, TB meningitis is the most common form of extrapulmonary disease in children. Without treatment, TB meningitis is fatal and even with treatment, neurologic deficits are common when the child presents in an advanced stage. It is believed that hematogenous deposition seeds the brain or meninges and that subsequent discharge of bacilli into the subarachnoid space results in an intense

inflammatory response.⁶⁸ The symptoms of TB meningitis generally increase gradually over several weeks, but sometimes occur abruptly and dramatically. Three stages frequently are used to describe the clinical progression. The first stage consists of personality changes, irritability, listlessness, and anorexia with or without fever. The second stage of symptoms are associated with increased intracranial pressure and include drowsiness, stiff neck, cranial nerve palsies, and seizures. Headache and vomiting may be prominent in older children in stage 2. The third stage includes severe neurologic deficits of coma, papilledema, hemiplegia, more prominent fever, and autonomic instability. Many other neurologic abnormalities may be associated with CNS TB. Tuberculomas (intracranial granulomatous TB masses) also cause signs and symptoms of a space-occupying lesion including headache, seizures, and focal neurologic changes.

The diagnosis of TB meningitis is urgent, but difficult. The most helpful findings include (1) contact with a known TB case and (2) chest radiographic findings consistent with TB (which are apparent in about 40% to 90% of children).⁶⁷ Up to 50% of children with TB meningitis initially are nonreactive to TST.^{67,68} Classic cerebrospinal fluid (CSF) findings include moderate lymphocytic pleocytosis, modestly low glucose level, and an increased protein level. Early changes may not be impressive and serial examination may be helpful. Staining of the CSF for acid fast bacilli (AFB) should be performed after centrifuging 10 to 20 cc of fluid and preparing a thick smear of the pellet. These efforts may yield a positive smear in 90% of cases, compared with most series that report the CSF AFB smear positivity rate at only 20% of cases.⁶⁸ Culture is positive in 10% to 50% of cases. At least one study has shown promise for use of the Gen-Probe Amplified Direct Test (MTD) (Gen-Probe Incorporated, San Diego, CA) for CSF samples. Culture was 21% sensitive and MTD was 33% sensitive using the standard cut-off level used for respiratory specimens. The sensitivity was improved to 83% if the cut-off level was lowered. Using either cut-off level, the specificity of the test was 100%.⁶⁹ Another study evaluated the Roche AMPLICOR DAT (F. Hoffmann-La Roche Ltd, Basel, Switzerland) for diagnosis of tuberculous meningitis. The AMPLICOR was found to have 60% sensitivity and 100% specificity in patients treated for TB meningitis for less than 10 days.⁷⁰

CT or magnetic resonance imaging in TB meningitis frequently reveals thickened inflamed meninges (particularly in the basilar area), hydrocephalus, and ischemia (secondary to vasculitis and seen in 40% to 60% of cases).³⁴ Tuberculomas are parenchymal granulomatous mass lesions that are sometimes seen in central nervous system (CNS) TB disease.³⁴ They sometimes become apparent (clinically and radiographically) only after initiation of antituberculous therapy in an apparent paradoxical immune reaction. Neuroimaging also is vital for evaluating for other causes of CNS pathology.⁶⁸

Bone disease complicates TB in isolation or along with other sites in 1% to 2% of children. It is most frequently found in the spine, long bones, and hip. The TST is almost always reactive and the symptoms are typically slowly progressive with modest pain in comparison with bacterial bone disease.⁶⁷

Many other extrapulmonary sites have been described less commonly including eye, laryngeal, middle ear, mastoid, genitourinary and abdominal, pleural, skin, and others. Unlike miliary and CNS TB, many of the other extrapulmonary manifestations are seen some time after the primary infection and are caused by reactivation disease, direct extension from another focus, or an inflammatory response.

CONGENITAL AND NEONATAL TB

Congenital TB is a rare event with only a few hundred cases reported. It is hard to distinguish clearly from postnatal acquisition, which is a more common phenomenon. There are 3 modes of transmission of TB to the baby: (1) the baby's bloodstream can become seeded by maternal bacillemia or rupture of a placental tubercle into the fetal circulation causing disseminated disease; (2) the baby can ingest infected amniotic fluid (or cervical secretions) frequently causing primary gastrointestinal, ear, or parotid disease; (3) the baby can inspire amniotic fluid resulting in a primary lung process.⁷¹ These babies are diagnosed in the first weeks to months of life. Earlier presentation may be associated with bacillary seeding. Congenital TB appears to be associated with maternal disseminated disease and endometrial disease and in only 40% of cases in 2 series was the mother diagnosed with TB before the baby.^{72,73} New reports from South Africa suggest an increased association with maternal/child HIV.^{74,75}

Common clinical manifestations are nonspecific

and include respiratory symptoms (cough and increased work of breathing), fever, hepatic and/or splenic enlargement, poor feeding, irritability, lethargy, lymphadenopathy, skin lesions (papulopustular, necrotic, atrophic), and ear discharge.⁷¹⁻⁷³ Occasionally, these children can progress on to sepsis and disseminated intravascular coagulopathy.^{76,77} Mortality for congenital tuberculosis is around 40%.^{72,73} The diagnosis is difficult and many children have been diagnosed on autopsy. Common radiographic appearances include miliary and reticulonodular patterns, infiltrates, and pleural effusions. Evaluation of the placenta and biopsy specimen of the endometrium may reveal granulomata and may yield a positive *Mtb* culture. It must be noted that the placenta is an efficient organ and not all children born to mothers with granulomatous placentas will develop congenital TB. Smear and AFB culture of gastric aspirates and endotracheal aspirates in these children is very fruitful. Up to 88% of gastric aspirate cultures and 91% of smears are positive.^{71-73,76}

Infants with TB in the first year of life were reviewed by Vallejo et al.⁵⁰ The investigators reported that among 47 infants, 70% had intrathoracic TB, 23% had CNS TB, 4% had disseminated disease, and 2% had scrofula. Symptoms were noted at the time of diagnosis in 79%. Cultures of gastric aspirates were positive in 75% of babies with pulmonary disease and CSF cultures were positive in 40%.

TREATMENT OF ACTIVE TB

Current TB chemotherapy is based on several characteristics of the organism, host, and the drugs. The first goal of therapy is to kill the organism quickly (early bactericidal activity) to decrease morbidity and transmission. The next goal is to prevent emergence of drug resistance, and the third goal is to eliminate the persistent bacilli to prevent treatment failures and relapse.¹

Untreated, many children with active primary complex disease will resolve their disease process spontaneously. However, 25% of untreated children will die of TB or complications within 5 years.¹³ At this point in time, we have no way to discern which children are on their way to healing and need only to be treated for latent TB infection and which children are not controlling their infections and deserve full adult-type TB treatment. Complicating this conundrum is the fact that children with TB are very difficult to study. They have

small populations of organisms and do not readily share their secretions (at least not for culturing). Their radiographs frequently worsen before improving, even on appropriate and aggressive TB therapy. Relatively few children have a given form of TB in one geographic location and resources for meticulous studies in the areas of high TB rates are scarce. All these factors make the objective comparison of drug regimens in a study setting exceedingly difficult and logistically challenging.

For all these reasons, we have relied on data from adult trials to choose pediatric TB regimens—particularly the 6-month short-course regimens that have become standard for most cases of nondisseminated TB. The following are brief summaries of some of the pediatric short-course TB trials.

Two pediatric trials studied the use of 2 months of INH, rifampin, and pyrazinamide daily followed by 4 months of INH and rifampin twice weekly compared with the same regimens with daily therapy used throughout. In the U.S. trial, no failures or relapses were noted over a short follow-up time. In the trial from India, 3 of 250 children died, apparently of TB disease. Two of these deaths were in the first 2 weeks of therapy, and one child died 3 months into therapy.⁷⁸

In another trial from India, 76 children were enrolled. Children with primary complex disease, CNS disease, underlying kidney, liver or heart disease, and those less than 1 year of age were excluded. Fully intermittent therapy (2 months of twice-weekly INH, rifampin, and pyrazinamide, followed by 4 months of twice-weekly INH and rifampin) was compared with daily therapy for the first 2 months (INH, rifampin, and pyrazinamide) followed by 2 months of twice-weekly INH and rifampin. Two children died: one died of complications of extensive bronchiectasis and the other died of complications of bronchospasm. At autopsy the second child had AFB visualized, but cultures were not performed so we do not know if he had active TB at the time of death. There were no relapses in either group and 70% of children had marked clinical response to therapy in the first 3 months.⁷⁹

Starke et al⁵¹ treated 175 children with pulmonary, pleural, or lymph node TB whom they deemed to be at low risk for drug resistance with 2 weeks of daily INH, rifampin, and pyrazinamide (PZA), followed by 3 drugs twice weekly, followed by INH and rifampin twice weekly in the

continuation phase. Fifteen percent of children received ethambutol until information about susceptibilities was available.

They found the regimen to be well tolerated and had only one treatment failure (a girl admitted to keeping the medication in her cheek during the first course of treatment and relapsed 4 years later). Of the 175 evaluable patients, 33 (19%) required treatment longer than 6 months. Approximately half of these were extended because of inadequate initial response to therapy and half because of poor adherence with DOT. Only 2 children required course extension owing to significant adverse events. Cultures were collected from 48% of children and, of these, 43% had positive cultures for *Mtb*. None of the TB isolates from the children or their source cases were found to have drug resistance.⁵¹

Four-drug empiric therapy is becoming the standard of care for adults with suspected active TB because of concern for possible drug resistance. Clinicians have been reluctant to use ethambutol routinely for children because of the difficulty in monitoring children's vision and color discrimination. There are no confirmed reports of optic toxicity in children caused by ethambutol in the literature. In adults, optic toxicity is dose related and doses over 30 mg/kg/d were associated with optic toxicity rates of 18%. The use of ethambutol at doses of 15 mg/kg/d are recommended when toxicity cannot be monitored carefully. Graham et al⁸⁰ provide a nice review and reassurance regarding the use of ethambutol in children.

The AAP recommends the use of an empiric 4-drug TB regimen for children who live in areas of more than 4% INH resistance or who are exposed to adults who come from an area of more than 4% resistance.¹⁶ The American Thoracic Society recommends the use of a 4-drug empiric regimen for children with: (1) adult-type pulmonary disease, (2) disseminated or CNS disease, (3) travel to an area of high prevalence of drug resistance, or (4) exposure to an individual with risk for resistance (known drug-resistant TB, history of previous TB treatment, residence in an area of high prevalence of drug resistance, or poor response to therapy). Other children can be treated with an initial 3-drug TB regimen.⁸¹

There is a paucity of data regarding the outcome of TB in children with INH-resistant disease treated with a 3-drug regimen. Some experts argue that children with TB have so few organisms that

3-drug therapy may be sufficient even for drug-resistant cases. I have been involved in the care of 3 children with INH-resistant disease who were treated empirically with INH, rifampin, and pyrazinamide. On this regimen, all 3 had progression of disease. One child underwent a surgical biopsy examination of a pleural-based mass to diagnose INH-resistant disease after several months of therapy and required extended therapy. The other 2 children (siblings) have required prolonged therapy including the use of a fluoroquinolone drug. A treatment failure associated with resistance to INH and streptomycin is reported in a child treated with 2 months of daily INH, rifampin, pyrazinamide, and streptomycin followed by twice-weekly INH, pyrazinamide, and streptomycin.⁸²

In contrast, I have treated many children with INH, rifampin, pyrazinamide, and ethambutol until the susceptibilities returned as INH resistant, then rifampin, pyrazinamide, and ethambutol twice weekly for 6 months with good response and no toxicity.

Pyrazinamide resistance is an important clinical consideration in children infected with *M. bovis*. The organism inherently is resistant to pyrazinamide and recommended treatment is 9 months of INH and rifampin, with 2 months of ethambutol during the initial phase. *M. bovis* scrofula frequently is difficult to manage and requires prolonged medical therapy.

Corticosteroids have been shown to be beneficial in CNS disease, particularly stages 2 and 3. Some clinicians would use steroids for any child with symptomatic TB meningitis. Steroids also are used frequently for TB pericarditis and some types of pleural disease. Two reports support the use of steroids in children with symptomatic airway compression caused by lymphatic disease.¹ Prednisone at 1 to 2 mg/kg/d for 4 to 8 weeks and tapered over several weeks frequently is used.

The most important element of treatment of TB therapy is the actual ingestion of the drugs. Children are difficult to dose with TB drugs because the formulations are not particularly child friendly. Only INH comes as a commercially available liquid product. This product causes diarrhea and abdominal pain in more than half of children owing to the osmotic load of sorbitol in which it is suspended. INH crushed into sugary liquids is unstable and should be avoided. Rifampin frequently is compounded into a suspension by pharmacists, but the stability and homogeneity are unproven. I favor

Table 3. Treatment Regimens for TB in Children*

TB Manifestation	Minimum Duration of Therapy	Initial Regimen	Follow-Up Regimen	Comments
Pulmonary TB	6 mo	INH, rifampin, pyrazinamide, and either ethambutol or streptomycin daily for 2 months (3-drug therapy only if no risk for resistance)	Drop the fourth drug as soon as the patient or reliable source case isolate is found to be drug susceptible Many pediatricians document a follow-up chest radiograph around 2-3 months into therapy If the isolate is sensitive, the patient is clinically well and radiographically stable, change to INH and rifampin at 2 months to complete a 6-month course; if directly observed therapy is used, twice-weekly therapy can be given Document chest radiograph at end of treatment—frequently not quite normal	Four-drug initial therapy is recommended if there are any risks for drug resistance including previous TB treatment, foreign born, or residence in an area with >4% INH resistance (for child or source)
Extrapulmonary (meningitis, bone or joint, miliary)	9-12 mo	Same as pulmonary	7-10 mo of INH and rifampin, either daily or if directly observed, twice weekly	Some clinicians use an injectable drug (usually streptomycin) for initial treatment of disseminated or meningeal disease; consider steroids for some types of extrapulmonary disease
Other extrapulmonary (cervical adenopathy)	Same as pulmonary disease	Same as pulmonary disease	Same as pulmonary disease except no need to follow-up chest radiographs if initially normal	Same as pulmonary disease

*DOT is strongly recommended for all children with active TB.

Adapted with permission from Pediatric Tuberculosis: A Video Guide to Diagnosis and Treatment.³⁵

crushing the tablets into a semisoft vehicle (such as pudding, baby food, yogurt, Nutella (Ferrero, New York, NY), and chocolate sauce) and warning the parents that there will be a several-week period of trial and error.³⁵

Adherence to therapy is as much an issue in children as it is in adults. Many factors contribute to poor adherence, not the least of which are the great difficulty in getting the drugs into the child and the long duration of treatment. To maximize the benefits of therapy, all children should be treated by DOT.⁸¹ The reversal of the TB resurgence experienced in the United States from the mid-1980s to 1992 and the decline in drug-resistance in New York City are largely attributable to the widespread application of DOT.⁸³ The experience of Starke et al⁵¹ in treating 175 children with as few as 58 doses by DOT with only one relapse, is a testament to the benefits of this approach.⁵¹

Table 3 shows recommended treatment regimens for active TB in children. For children who live in areas with more than a 4% risk for INH resistance or who have other risk factors for resistance, 4-drug empiric therapy is recommended. After the initial 2-month period, a repeat radiograph should be performed. If the patient has been adherent to therapy there is no reason to suspect drug resistance, and if the radiograph is not worse the regimen can be changed to 2 drugs (INH and rifampin) to complete a 6-month course. DOT is recommended for treatment of TB in children. Doses of drugs observed should be counted when considering whether a patient has completed therapy. Patients receiving daily doses for the first 2 months typically will receive 45 observed doses (Monday through Friday for approximately 9 weeks) followed by 34 twice-weekly doses in the following 4 months.

Patients should be followed-up monthly during therapy. Routine laboratory evaluation need not be performed unless the patient has symptoms of toxicity, underlying liver disease, or is taking other medications that might interfere with TB medications or cause similar toxicities.

An end-of-therapy radiograph should be obtained. Most children do not have a normal radiograph at the end of therapy, but significant improvement is expected. The patient should be followed-up for at least for 1 year clinically and radiographically to ensure continued resolution.

Tables 4 and 5 show recommend doses for TB drugs in children when used daily or twice weekly.

Drug Resistance

Children diagnosed with active TB caused by a monoresistant isoniazid strain can receive rifampin, pyrazinamide, and ethambutol for 6 months. Patients with monoresistant pyrazinamide TB should receive INH, rifampin, and ethambutol for 2 months, followed by INH and rifampin for an additional 7 months (minimum based on clinical response).

Children with rifampin monoresistance or multidrug-resistant TB (resistant to INH and rifampin) should be managed by an expert in pediatric TB because of the difficulty in using second-line drugs in children.

Most second-line TB drugs can be used with caution in children. Fortunately, many of them are better tolerated in children than in adults. An important class of second-line drugs, the fluoroquinolones, should be used with caution in children. Dog model studies have resulted in arthropathy when puppies were treated with flouroquinolone drugs. Many thousands of children have received quinolones, many for treatment of infectious complications of cystic fibrosis. Although some children have reported reversible arthralgias (which is often a clinical aspect of cystic fibrosis), none have suffered arthropathy.⁸⁴ Most of these therapies were used for short or intermittent periods of times. Few reports of the safety of prolonged therapy used in treatment of multidrug-resistant TB are found in the literature. If the fluoroquinolones are used, the parents should be alerted as to the risk and advised to report any musculoskeletal symptoms immediately.

Schaaf et al¹¹ report on 125 children exposed to adults with pulmonary multidrug-resistant TB in South Africa. Of the 119 followed-up, 29 (24%)

Table 4. Pediatric TB Drug Dosing Tables by Weight—Daily Dosing

Child's Weight		Daily INH Dose (10-15 mg/kg)		
kg	lbs	mg	100-mg tablets	300-mg tablets
Isoniazid daily dosing				
3-5	6.6-11	50	0.5	0
5-7.5	11-16.4	75	0.75	0
7.5-10	16.5-22	100	1	0
10-15	22-33	150	0	0.5
15-20	33-44	200	2	0
Over 20	Over 44	300	0	1
Maximum daily dose is 300 mg				
Child's Weight		Daily Rifampin Dose (10-20 mg/kg/dose)		
kg	lbs	mg	150-mg caplets	300-mg caplets
Rifampin daily dosing				
4-7.5	9-16	75	0.5	0
7.5-12.5	17-27	150	1	0
12.5-17.5	28-38	225	1.5	0
17.5-25	39-55	300	0	1
25-35	55-77	450	1	1
Over 35	Over 77	600	0	2
Maximum daily rifampin dose is 600 mg				
Child's Weight		Daily Pyrazinamide Dose (20-40 mg/kg/dose) ¹⁶		
kg	lbs	mg	500-mg tablets	
Pyrazinamide daily dosing				
3-6.25	6.6-13	125	0.25	
6.25-12.5	14-27	250	0.5	
12.5-20	27-44	500	1	
20-27	44-59	750	1.5	
27-35	59-77	1,000	2	
35-46	77-101	1,250	2.5	
46-54	102-119	1,500	3	
54-62	119-136	1,750	4	
Over 62	Over 136	2,000	5	
Maximum daily pyrazinamide dose is 2,000 mg (2 g)				
Child's Weight		Ethambutol Daily Dose (15-25 mg/kg/dose)		
kg	lbs	mg	100-mg tablets	400-mg tablets
Daily Ethambutol dosing				
4-6	9-13	100	1	0
6-8	14-17	150	1.5	0
8-12.5	18-27	200	2	0
12.5-17.5	28-38	300	3	0
17.5-22.5	39-49	400	0	1
22.5-27.5	50-60	500	1	1
27.5-32.5	61-71	600	2	1
32.5-37.5	72-82	700	3	1
37.5-42.5	83-93	800	0	2
42.5-47.5	94-104	900	1	2
47.5-52.5	105-115	1,000	2	2
52.5-57.5	116-126	1,100	3	2
57.5-62.5	127-137	1,200	0	3
62.5-67.5	138-148	1,300	1	3
67.5-72.5	149-159	1,400	2	3
Maximum daily ethambutol dose is 1,600 mg. ⁹¹				
Dose obese children on lean body weight				

Adapted with permission from Pediatric Tuberculosis: A Video Guide to Diagnosis and Treatment.³⁵

Table 5. Pediatric TB Drug Dosing Tables by Weight—Twice weekly dosing

Child's Weight		Twice Weekly INH Dose (20-30 mg/kg)		
kg	lbs	mg	100-mg tablets	300-mg tablets
Isoniazid twice-weekly dosing				
3-5	6.6-11	100	1	0
5-7.5	11-16.4	150	0	0.5
7.5-10	16.5-22	200	2	0
10-15	22-33	300	0	1
15-20	33-44	450	0	1.5
20-25	44-55	600	0	2
25-30	55-66	700	1	2
30-35	66-77	800	2	2
Over 35	Over 77	900	0	3
Maximum twice-weekly dose is 900 mg				
Child's Weight		Twice-Weekly Rifampin Dose (generally 15-20 mg/kg/dose)		
kg	lbs	mg	150-mg caplets	300-mg caplets
Twice-weekly rifampin dosing				
4-7.5	9-16	75	0.5	0
7.5-11.25	16-24	150	1	0
11.25-15	25-33	225	1.5	0
15-22.5	33-49	300	0	1
22.5-30	50-66	450	1	1
Over 30	Over 66	600	0	2
Maximum twice-weekly rifampin dose is 600 mg				
Child's Weight		Twice-Weekly PZA Dose 50 mg/kg/dose		
kg	lbs	mg	500-mg tablets	
Pyrazinamide twice-weekly dosing				
4.5-7.5	10-16	250	0.5	
7.5-12.5	17-27	500	1	
12.5-17.5	28-38	750	1.5	
17.5-22.5	39-49	1,000	2	
22.5-27.5	50-60	1,250	2.5	
27.5-32.5	61-71	1,500	3	
32.5-37.5	72-82	1,750	3.5	
37.5-48	83-105	2,000	4	
48-58	106-127	2,500	5	
58-68	128-149	3,000	6	
68-78	150-171	3,500	7	
Over 78	Over 172	4,000	8	
Maximum twice-weekly pyrazinamide dose is 4 g. ⁹¹				
Child's Weight		Ethambutol Twice-Weekly Dose 50 mg/kg/dose		
kg	lbs	mg	100-mg tablets	400-mg tablets
Twice-weekly ethambutol dosing				
4-5	9-11	200	2	0
5-7	11-15	300	3	0
7-9	15-19	400	0	1
9-11	20-24	500	1	1
11-13	25-28	600	2	1
13-15	29-33	700	3	1
15-17	34-37	800	0	2
17-19	38-41	900	1	2
19-21	42-46	1,000	2	2
21-23	47-50	1,100	3	2
23-27	51-59	1,200	0	3
27-31	59-68	1,400	2	3
31-35	68-77	1,600	0	4
35-39	78-85	1,800	2	4
39-47	86-103	2,000	0	5
47-52	104-114	2,400	0	6
52-60	115-132	2,800	0	7
60-68	132-149	3,200	0	8
68-76	150-167	3,600	0	9
Maximum twice-weekly ethambutol dose is 4,000 mg. ⁹¹ Dose obese children on lean body weight				

Adapted with permission from Pediatric Tuberculosis: A Video Guide to Diagnosis and Treatment.³⁶

developed active disease and 64 (54%) had LTBI. Interestingly, 2 of 41 (5%) children who received appropriate treatment of multidrug-resistant LTBI developed active TB compared with 13 of 64 (20%) who did not. Regimens for treatment of LTBI included high-dose INH (15-20 mg/kg/d) for all but 4 children and usually 2 other drugs based on susceptibility of the source case (pyrazinamide, ethambutol, or ethionamide). Of the 29 diseased children, 26 were diagnosed within 12 months of exposure, consistent with historic data. Treatment for active disease was given with 4 to 5 oral drugs only (no injectable drugs were used). Most treatment regimens lasted 9 to 12 months, but children with hilar adenopathy only received 6 months of treatment. Drugs included in the regimens included high-dose isoniazid, pyrazinamide, ethambutol, ethionamide, and ofloxacin. Fifteen children received ofloxacin for 6 to 12 months. One child discontinued ofloxacin because of arthralgia. The children who received ofloxacin were 7 to 63 months of age (median, 37 mo).

Most U.S. literature of multidrug-resistant TB describes treatment and outcomes in adults. Commonly described treatment regimens include 3 or more drugs to which the isolate is susceptible. Treatment duration is usually 18 to 24 months after sputum culture conversion. An injectable drug (an aminoglycoside or capreomycin) is included in the regimen and is used until the cultures are sterile for 4 to 6 months. Unfortunately, culture conversion is difficult to document in children and the toxicities of second-line drugs also may be more difficult to monitor (ototoxicity and psychiatric/neurologic toxicities in particular). Without more compelling clinical trials to suggest that less-aggressive treatment regimens are effective, children should be treated with regimens similar to adults. At least 3 drugs to which the isolate is susceptible and a regimen of at least 18 months should be the goal.⁸⁵

HIV

Children with HIV infection are at increased risk for TB for 2 reasons. They are exposed to their parents, who also usually are HIV infected and therefore at risk for active and contagious TB. Second, if infected, they are more likely to develop active TB because of their deficient immune system. HIV testing is recommended for all individuals diagnosed with active TB.^{16,81} Few U.S. studies have reported a major impact from HIV on pediatric TB disease. One series from Miami de-

scribed 9 children with acquired immune deficiency syndrome and TB. Only one child had a positive TST, 4 had extrapulmonary disease, and 3 diagnosed after January 1989 had *Mtb* strains resistant to multiple antituberculous drugs. Median survival after the TB diagnosis was 20 months.⁸⁶ Through 1998, 27 cases of TB were diagnosed in 3,331 HIV-infected children enrolled in 13 pediatric acquired immune deficiency syndrome trials (0.4 cases per 100 person-years). The median age was 7.6 years and the median CD4 count was 189.⁸⁷

SUMMARY

Pediatric TB is a huge global problem and a somewhat focal problem within the United States. Elimination of TB in adults will stop the spread to children, but we must address the large pool of latently infected children if we have any hope of substantial declines in TB disease. To use resources wisely, we should screen children for TB risk factors before placing a TST. A child at risk should have complete evaluation and treatment. These should include proper placement and reading of the skin test, evaluation by history, physical examination, 2-view radiograph if the skin test is

positive, and the full duration of best therapy. Creative efforts are required to maximize these efforts without wasting time, energy, and money of all involved.

The diagnosis of TB in a child is somewhat challenging because of the lack of a single diagnostic test or feature. The TST is not universally positive, the child may or may not have symptoms of TB, the radiograph may look similar to many other lung processes, and cultures are difficult to collect and frequently negative. The history of exposure to an adult case with active TB is one of the most helpful features.

Treatment of active TB in children requires at least 6 months of multidrug therapy. Serious consideration should be given to the child's risk for drug resistance when choosing an empiric drug regimen. Four-drug therapy (INH, rifampin, pyrazinamide, and ethambutol) should be used when the child has extensive disease or any individual or exposure risks of drug resistance.

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