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Pediatric Tuberculosis

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Objectives   After completing this article, readers should be able to:

1. Discuss how the risk of disease, clinical presentation, and morbidity of tuberculosis (TB) vary by age and immune status.
2. Delineate the epidemiologic risk factors for the acquisition of TB infection, the subsequent development of TB disease in a minority of children, and the risk of multidrug-resistant TB.
3. Describe the presenting signs and symptoms of TB in children.
4. Recognize the extrapulmonary manifestations of TB and which children are at risk for these forms of disease.
5. Explain the utility of the tuberculin skin test, potential false-positive and false-negative results, and the effect of the bacillus Calmette-Guérin vaccine on the ability to interpret the test.
6. Discuss interferon-gamma release assays and their limitations.
7. List the primary findings seen on chest radiography in the child who has pulmonary TB.
8. Plan a therapeutic course for children who experience TB exposure, infection, and disease.
9. Describe the measures that can be taken to prevent the development of disease and to limit spread of TB within the community and the health-care setting.

Introduction

Tuberculosis (TB) is an ancient disease, with evidence of skeletal TB found in mummies in both the Old and New World. The causative agent is *Mycobacterium tuberculosis*, a fastidious, aerobic, acid-fast bacillus. In the wake of human immunodeficiency virus (HIV) infection, the number of children and adults afflicted with TB has escalated tremendously worldwide in the past 25 years. Control of TB in children often has been neglected because children are ineffective transmitters of the bacillus and frequently escape the attention of TB control programs. However, much of the morbidity and mortality of TB occurs in childhood, and acquisition of TB infection during childhood contributes to the future reservoir of cases. Risk factor-based screening of children for TB infection, appropriate implementation of chemoprophylaxis, and a high degree of suspicion for TB disease on the part of clinicians can decrease the disease burden in children.

Definitions

Individuals who have been in contact with a source case of TB generally are classified into one of three groups (Table 1). The first group includes persons exposed to someone who has TB but whose status is not yet clear, often because insufficient time has passed to rely on results of tuberculin

Abbreviations

AFB:	acid-fast bacilli
BCG:	bacillus Camille-Guérin
CNS:	central nervous system
CSF:	cerebrospinal fluid
CT:	computed tomography
DOT:	directly observed therapy
DR:	drug-resistant
HCW:	health-care worker
HIV:	human immunodeficiency virus
IGRA:	interferon-gamma release assay
INH:	isoniazid
LTBI:	latent tuberculosis infection
MDR:	multidrug-resistant
PZA:	pyrazinamide
TB:	tuberculosis
TST:	tuberculin skin testing

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Table 1. **Tuberculosis (TB) Disease Classification and Initial Treatment**

Classification	Initial Treatment*	Duration of Therapy	Other
TB exposure, ≥4 years old and immunocompetent	None	N/A	Repeat TST 2 to 3 months after contact with source case is broken; if second TST result is positive, see section on TB infection
TB exposure, <4 years old or immunocompromised	INH Second-line: Rifampin	2 to 3 months	Repeat TST 2 to 3 months after contact with source case is broken; if second TST result is positive, see section on TB infection
TB exposure, infant	INH Second-line: Rifampin	At least 2 to 3 months	Because TSTs are less reliable in infants compared with older children, the TST results of other children in the family should be considered when making decisions about terminating chemoprophylaxis; expert opinion should be sought
TB infection	INH Second-line: Rifampin	9 months 6 months	Biweekly therapy should be administered only via DOT
TB disease	Multiple drugs (Table 6)	6 months for pulmonary and most extrapulmonary forms 9 to 12 months for patients who have meningitis, disseminated disease, or persistent smear-positive sputum on adequate therapy	Medications should be administered only via DOT See section in text on indications for steroids

*Therapy should be modified based on source case susceptibility patterns or known resistance patterns within a given community. DOT=directly observed therapy, INH=isoniazid, N/A=not applicable, TST=tuberculin skin test

skin testing (TST), otherwise known as the Mantoux test. The treatment of children exposed to TB depends on age and immune status. The second class is termed latent TB infection (LTBI). Individuals who have LTBI have positive TST results but have no symptoms, physical findings, or radiographic anomalies consistent with TB. It is recommended that most children who have LTBI receive a course of therapy to prevent the development of TB disease in the future. The final group includes those persons who have clinical or radiographic manifestations of TB disease. These patients are treated with multiple drugs.

Epidemiology

On average, each adult who has pulmonary TB infects 8 to 15 individuals prior to having TB diagnosed. However, some patients are very contagious and some are not contagious at all. Of persons who have untreated LTBI, 5% to 10% ultimately develop TB disease; rates are higher in children and in immunocompromised hosts (Table 2). Approximately one third of the global population has LTBI, and at least 9 million new cases of TB disease and 2 million deaths from the disease occur annually. More than 90% of the burden of TB disease is in the developing world.

In the United States, about 13,000 new cases of TB disease were diagnosed in 2007, including approximately 820 in children younger than 15 years of age. Mandatory reporting exists for patients who have TB disease but not for persons who have been exposed to TB or have LTBI. Seven states (California, Florida, Georgia, Illinois, New Jersey, New York, and Texas) accounted for 60% of all cases in 2007. Foreign-born individuals in the United States have TB rates 9.5 times higher than those in

Table 2. **Risk of Progression from Tuberculosis (TB) Infection to Disease**

Age at Primary Infection (yr)	No Disease (%)	Pulmonary Disease (%)	Miliary or Central Nervous System TB (%)
<1	50	30 to 40	10 to 20
1 to 2	75 to 80	10 to 20	2.5
2 to 5	95	5	0.5
5 to 10	98	2	<0.5
>10	80 to 90	10 to 20	<0.5

Adapted from Marais, et al. Childhood pulmonary tuberculosis: old wisdom and new challenges. *Am J Resp Crit Care Med*. 2006;173:1078–1090.

United States-born persons, with most cases occurring in immigrants from Mexico, the Philippines, Vietnam, China, and India.

Other risk factors for development of TB disease in the United States include untreated HIV infection (10% annual risk of progressing from LTBI to disease) and other immunocompromising conditions, recent LTBI, intravenous drug use, and certain medical conditions such as diabetes and renal failure. Approximately 9% of adult TB patients in the United States are coinfected with HIV.

Drug-resistant (DR) TB should be suspected if certain epidemiologic risk factors are present, including known DR-TB in a potential source case, a history of treatment failure or relapse in the patient or the source case, travel to an area that has a high prevalence of endemic DR-TB, and positive sputum smears after 2 months of the usual combination chemotherapy. Drug resistance shows wide geographic variation. Multidrug-resistant (MDR) TB is defined as resistance to at least two of the first-line TB medications, isoniazid (INH) and rifampin. Fewer than 1% of TB cases in the United States are MDR-TB compared with rates of up to 15% in Kazakhstan. It is estimated that 500,000 new cases of MDR-TB occurred in the world in 2007. Extensively drug-resistant TB has been described more recently and is defined as resistance to INH, rifampin, any fluoroquinolone, and any second-line injectable agent (excluding streptomycin). Extensively drug-resistant TB remains exceedingly rare in the United States.

Pathogenesis

TB is transmitted most commonly via airborne spread. Lymph nodes frequently become infected with *M tuberculosis*. Such infection causes enlargement of the nodes with or without significant inflammation. Inhalation of the bacillus into a terminal airway can result in formation of a Ghon complex, which includes the initial focus of infection, the draining lymphatic vessels, and enlarged regional lymph nodes. Following this stage, the infection can be contained, spread rapidly, or reactivate at a later point in life. Different clinical manifestations of TB in children have varying incubation periods. Miliary or disseminated disease usually occurs 2 to 6 months after infection, renal TB manifests in 5 years, skeletal TB occurs 1 to 2 years after infection, and pulmonary and lymphatic TB occur within 4 to 12 months. Most clinical manifestations in children occur within 1 to 2 years of initial infection.

Clinical Manifestations

Only 5% to 10% of children older than 3 years of age who have untreated LTBI progress to disease, and most do so within 1 to 2 years of initial infection. The most common site of infection is the lung, which accounts for up to 80% of all cases of disease. The most common extrapulmonary manifestation is tuberculous lymphadenopathy (67%), followed by meningitis (13%, occurring most often in infants and toddlers), pleural TB (6%), miliary TB (5%), and skeletal TB (4%). Commonly involved areas in the teenager are the lymph nodes, pleural spaces, and bones. The risk of extrapulmonary disease is highest in immunocompromised children, infants, and adolescents. The best-studied group of immunocompromised patients is HIV-infected patients, but children who have other T-cell dysfunction and malnourished children also have a higher risk of progressing from LTBI to TB.

Pulmonary Disease

Pulmonary TB includes both intrathoracic lymphadenopathy and parenchymal disease. The three time frames for pulmonary involvement with TB are primary parenchymal, progressive primary, and reactivation disease. Primary parenchymal disease is one of the most common manifestations of disease. Infants and adolescents are more likely to be symptomatic than are 5- to 10-year-old children (Table 3). A variety of radiographic features may be seen, the most common being hilar or mediastinal

Table 3. **Signs and Symptoms of Pulmonary Tuberculosis**

Clinical Feature or Disease Type	Infants	Children	Adolescents
Symptom			
Fever	Common	Uncommon	Common
Night sweats	Rare	Rare	Uncommon
Cough	Common	Common	Common
Productive cough	Rare	Rare	Common
Hemoptysis	Never	Rare	Rare
Dyspnea	Common	Rare	Rare
Sign			
Rales	Common	Uncommon	Rare
Wheezing	Common	Uncommon	Uncommon
Decreased breath sounds	Common	Rare	Uncommon
Location of Disease			
Pulmonary	Common	Common	Common
Pulmonary + Extrapulmonary	Common	Uncommon	Uncommon

adenopathy (Fig. 1). Children become symptomatic when enlarging lymph nodes compress adjacent structures; collapse of a terminal bronchus from extrinsic compression leads to the collapse-consolidation pattern seen in the younger child. The most common symptoms are cough, low-grade fever, and rarely, weight loss.

Progressive primary disease results from poor containment of the initial infection and can be associated with lung tissue destruction and cavity formation (Fig. 2).

Pediatric tuberculous cavitary disease develops in three circumstances: a young infant or immunocompromised child as the host, lymph node erosion into airways leading to aspiration of bacilli (preschool-age child), and the development of adult-type cavitary disease (generally in children older than 10 years). Direct extension of disease into surrounding structures can result in invasion of the pericardium or pleural space or the creation of bronchopleural fistulas. Affected children usually appear more ill, having severe cough, fevers, occasional night sweats, and weight loss.

Reactivation disease is more common in adolescents, particularly in geographic areas that have high rates of coinfection with HIV. Patients complain of constitu-

Figure 1. Right hilar tuberculous lymphadenopathy in a 2-year-old boy who has hepatoblastoma. This child's TB disease was diagnosed during his chemotherapeutic course. A medication catheter and port are present in the left chest wall.

Figure 2. Right upper lobe cavity seen in the father of a patient who has TB meningitis. This adult has no hilar or mediastinal adenopathy.

tional symptoms such as fever, weight loss, night sweats, and malaise, although physical findings may be unremarkable. Cough is common, and hemoptysis may occur. Reactivation disease in adults is somewhat more common in the apices of the lungs and primary disease in the basilar regions, but this pattern does not hold true for children, and the radiographic findings in reactivation disease overlap considerably with primary parenchymal and progressive pulmonary TB.

Lymphatic Disease
Superficial lymphadenopathy is the most common extrapulmonary form of TB. The most common route of transmission is hematogenous spread. Children who have TB lymphadenopathy tend to be older than those who have nontuberculous mycobacterial lymphadenopathy. The lymph nodes involved most commonly are anterior cervical, followed by posterior triangle, submandibular, and supraclavicular. Tuberculous lymph nodes usually measure 2 to 4 cm and lack the classic inflammatory findings of pyogenic nodes. There may be overlying violaceous skin discoloration. Systemic symptoms occur in 50% of children, abnormal chest radiographs are seen in approximately 33% of patients, and most have positive TST results. Untreated lymph nodes may caseate, spread to contiguous structures, and lead to formation of unsightly sinus tracts. Surgical node excision is not curative but may be necessary to establish the diagnosis. Most children respond well to a 6-month course of multidrug therapy, but occasionally therapy must be extended to 9 months, based on clinical response.

Central Nervous System (CNS) Disease
CNS involvement is rare, developing in fewer than 2% of all cases of TB. CNS TB usually occurs within months after infection with the organism; 50% of all patients are younger than 2 years of age. In many parts of the developing world, TB is the primary cause of subacute meningitis, and tuberculomas are common causes of mass-occupying CNS lesions.

Three clinical stages of CNS TB have been described. Nonspecific constitutional symptoms and headache are the initial symptoms in stage I, followed by cranial nerve palsies and evidence of meningeal inflammation in stage II. In the final stage, children have profoundly altered mentation due to increased intracranial pressure and vasculitis. The most common findings on CNS imaging are hydrocephalus and basilar enhancement. Vascular lesions involving the basal ganglia and midbrain also are common, and TB should be considered in cases of childhood stroke.

Tuberculomas, occurring in 5% of children who have CNS TB, appear as single rim-enhancing lesions ranging from 1 to 5 cm (Fig. 3). In TB meningitis, cerebrospinal fluid (CSF) analysis typically demonstrates lymphocytes, a low glucose concentration, and a high protein value. TST results are positive in only 33% of children. Chest radiographs are abnormal in almost 90% of patients, and a miliary pattern may be seen. Acid-fast bacilli (AFB) culture of the CSF is unlikely to be positive unless a large volume of CSF is cultured. Gastric aspirates are positive in a minority of children. Children who have CNS TB are treated for a minimum of 9 months. Placement of a ventriculoperitoneal shunt to relieve intracranial pressure and prevent herniation may be needed. This form of TB has the highest morbidity and mortality rates.

Pleural Disease
Pleural TB usually is a disease of the older child and adolescent and can occur in isolation from or concomitantly with pulmonary parenchymal disease (Fig. 4). Symptoms include chest pain, fever, cough, dyspnea, and anorexia. Auscultatory findings mimic those of bacterial pneumonia. Most children have positive TST results. Effusions are more common on the right and rarely are bilateral. The pleural fluid is exudative and lymphocytic, with high protein, low glucose, and elevated adenosine deaminase values. AFB cultures of pleural fluid are posi-
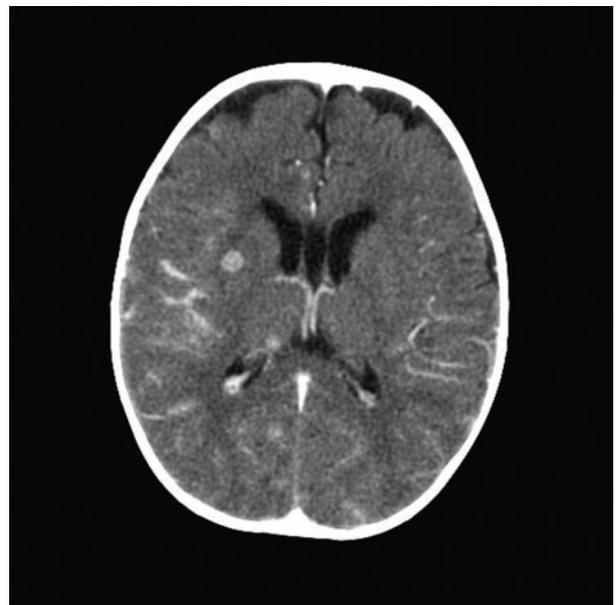

Figure 3. Central nervous system tuberculoma in the right thalamus and basal ganglia in a 7-month-old child who has TB meningitis and miliary TB. This child's chest radiograph is shown in Fig. 5.

Figure 4. Pleural TB in a 17–year–old male who has bilateral (right > left) pleural effusions and bibasilar and left lingular airspace disease. He also has TB peritonitis.

Figure 5. Miliary TB in a 7–month–old male who also has TB meningitis with left upper lobe infiltrate and air bron–chograms. Hilar or mediastinal adenopathy is difficult to discern in this infant, whose thymus is not yet atrophied.

tive in approximately 33% of patients; biopsy of pleural tissue has a higher culture yield, and histologic examination often shows caseating granulomatous inflammation of the pleura. A 6-month course of therapy is recommended.

Miliary Disease
Miliary tuberculosis due to lymphohematogenous spread is a disease of the younger or immunocompromised child (Fig. 5). Miliary disease can present shortly after primary infection, and multiorgan involvement is common. Most affected children have fever and other constitutional symptoms, and pyrexia, hepatomegaly, and splenomegaly commonly are seen on physical examination. CNS involvement occurs in up to 20% of children, and a young child who has miliary TB always should be evaluated for meningitis. The TST is insensitive in these patients because disseminated disease can produce TST anergy. AFB culture from gastric aspirates can have a yield as high as 50%. A prolonged course of therapy (9 to 12 months) should be administered to patients who have disseminated disease.

Skeletal Disease
Skeletal TB is a disease of the older child, and most patients are in the second decade of life, with the exception of spinal involvement (Pott disease), which can affect even young children (Fig. 6). Skeletal lesions can develop more than 10 years after initial infection. Solitary lesions in the axial skeleton typically are seen in the otherwise healthy host, whereas multiple lesions with systemic symptoms are more common in the immunocompromised child. Local signs of inflammation predominate, and systemic symptoms occur in only 33% of children.

The most common manifestations of skeletal disease are spondylitis, arthritis, and osteomyelitis. Spondylitis is seen most frequently, affecting the thoracic and lumbar spines preferentially (Pott disease). Dactylitis is most common in the infant and young child. Magnetic resonance imaging is the preferred imaging choice because it can demonstrate lesions months before plain radiographs. Chest radiographs are positive in 50% of children who have skeletal TB, and TST results are positive in most. AFB cultures of bone are positive in up to 75% of cases, and histopathology often is diagnostic.

Congenital Disease
Congenital TB is encountered infrequently in the United States. It occurs in infants born to mothers who have endometrial or disseminated TB and presents with con-

Figure 6. Pott disease involving near–complete destruction of the L4 vertebral body, with posterior displacement of the L3 vertebral body and resultant kyphosis.

stitutional symptoms, difficulty breathing, and failure to thrive in the first 3 months after birth. Physical findings can include hepatomegaly, evidence of respiratory distress, and peripheral lymphadenopathy. CNS involvement occurs in up to 20% of children. TST results rarely are positive in this age group. Chest radiography yields abnormal results in almost all children. Gastric or tracheal aspirates and hepatic biopsy cultures are positive in most infants.

Other Forms
Less commonly encountered forms of TB include abdominal, renal, and cutaneous disease. These forms often are difficult to diagnose because they frequently are late manifestations, epidemiologic links are more difficult to establish, the yield of AFB cultures can be lower than for children who have extensive pulmonary disease, and clinical findings can overlap with those of numerous other disease processes. Diagnosis may be facilitated by obtaining a chest radiograph and placing a TST.

Children coinfected with HIV and TB present with symptoms similar to those of HIV-uninfected children who have TB. However, in the former group, the differential diagnosis is much broader, and clinical presentation can overlap with many opportunistic infections. HIV-infected children are more likely to have abnormal chest radiography results compared with HIV-uninfected children and to have either parenchymal infiltrates or cavitary lesions. Extrapulmonary disease appears to be more common in HIV-infected children and is difficult to diagnose without performing tissue examination and culture.

Diagnosis
TB disease often is diagnosed by a positive TST result, epidemiologic information (exposure to a known source case), and a compatible clinical and radiographic presentation. In children, symptoms frequently are due to a vigorous immune response to a relatively small number of organisms, which greatly limits the feasibility of using culture alone as the diagnostic test for TB disease. Only 30% to 40% of children who have clinically suspected pulmonary TB have positive cultures. Cultures can be obtained by sequential sputum sampling or by gastric aspiration of early morning secretions in the younger child. Culture yield is highest in neonates (up to 70%), adolescents who have cavitary disease, and children who have tuberculous lymphadenopathy and undergo biopsy or fine-needle aspiration. The bacillus grows slowly, often taking up to 6 to 8 weeks to grow on Lowenstein-Jensen media and 2 to 3 weeks to grow in liquid media. AFB stains include Kinyoun, auramine-rhodamine (Truant), and Ziehl-Neelsen; Truant stains are the most sensitive. Microscopic observation drug susceptibility assays were developed recently to identify resistant isolates rapidly and to permit direct drug susceptibility testing concomitant with detecting bacterial growth in liquid media, but these assays are not yet widely available.

The TST comprises antigens (purified protein derivative) that are not all specific to *M tuberculosis*. The antigens trigger a delayed hypersensitivity reaction in persons who have come in contact with TB bacilli. The size of the TST is measured in millimeters of induration (not erythema) approximately 48 to 72 hours after placement, but if a child returns for TST interpretation after 72 hours and has induration meeting the criteria for positivity (Table 4), the skin test still should be interpreted. The TST usually becomes positive 3 weeks to 3 months after infection occurs and should remain positive for life or until immune system dysfunction or senescence occurs. Sensitivity and specificity of the test are estimated to be 95%. Once a TST yields a positive result, a patient should be counseled to avoid any additional TSTs because the test no longer is a useful tool and subsequent skin tests can cause scarring. The determination of a TST as positive depends on several variables (Table 4), including patient age and immune status, clinical probability of having TB disease, and risk factors for exposure. The use of control skin tests (*Candida*, tetanus toxoid) is not recommended when TSTs are placed.

Table 4. **Reaction Size of Tuberculin Skin Test Considered Positive**

Reaction Size	Risk Factors
≥5 mm	Human immunodeficiency virus infection or other immunocompromising conditions Abnormal chest radiograph consistent with tuberculosis Contact with an infectious case
≥10 mm	Age <4 years Birth or residence in high-prevalence country Residence in a correctional or long-term care facility Certain medical conditions (eg, diabetes, renal failure, silicosis) Health-care workers exposed to patients who have tuberculosis Any child who is a close contact of an adult who has any of the previously noted high-risk factors
≥15 mm	No risk factors

Both false-negative and false-positive results plague the TST. A negative result never eliminates the possibility of TB disease because many disseminated forms of TB, including miliary and meningitis, can induce anergy to the skin test. Up to 15% of children who have clinical TB have negative TST results. A false-negative TST result also can be seen in association with recent measles infection, high-dose corticosteroid treatment, irradiation, other immunosuppressive therapy, or immunocompromising medical conditions. False-positive results occur primarily in children exposed to nontuberculous (environmental) mycobacteria or in those who have recently received a bacillus Calmette-Guérin (BCG) vaccine. A boosting phenomenon has been noted in some sensitized persons who receive multiple sequential TSTs and only then develop a positive result, which usually represents a false-positive result in children. However, there is no way to distinguish these positives from true positives. Therefore, it is recommended that children be screened for risks of exposure to TB by history initially, with a TST used only for those who have epidemiologic risk factors (Tables 4 and 5).

There are common misconceptions about the utility of the TST in children who have received the BCG vaccine. Several well-designed studies have implied that a TST can be interpreted normally in a child who received a single dose of the BCG vaccine as a young child. Having received a BCG as an infant may not explain a positive skin test result later in life. The assumption that BCG receipt is the cause of a positive TST result overlooks that BCG is, for the most part, used in parts of the world that have high rates of TB. Consequently, this assumption could lead to a lack of treatment for high-risk children who potentially could benefit from LTBI therapy.

For decades, the TST was the only test available to diagnose LTBI. More recently, new tests for LTBI have been introduced: whole blood interferon-gamma release assays (IGRAs). These tests measure the patient's ability to produce interferon-gamma after their lymphocytes are stimulated by two or three antigens found on *M tuberculosis*. One of the available tests measures whole blood interferon-gamma and the other measures the number of lymphocytes that produce interferon-gamma.

These assays have several potential advantages. Only one office visit is required (versus two to have the TST placed and read); there is no risk of the boosting phenomenon; and they have more specificity for LTBI because the antigens in the IGRAs are shared less commonly with nontuberculous mycobacteria and are not found on BCG, which is derived from *M bovis*. Like the TST, they cannot distinguish LTBI from TB disease. The primary drawback is that the tests have been studied primarily in adults, and fewer data are available on the

Table 5. **Risk Factor-based Questionnaire for Exposure to Tuberculosis**

- Has the child received a bacillus Camille-Guérin vaccination?
- Was the child born outside of the United States?
- Has the child lived outside of the United States?
- Is there a household member who has a history of tuberculosis?
- Is the child Hispanic or Asian?

Answering yes to one question had a sensitivity for latent tuberculosis infection of 83%, with a specificity of 48%. With increasing responses of "yes" to the questions, specificity increased, but sensitivity decreased. From Froehlich et al. Targeted testing of children for tuberculosis: validation of a risk assessment questionnaire. *Pediatrics.* 2001;107:e54.

performance characteristics in young children. The greatest usefulness of IGRAs may be in determining if a positive TST result in a child who received a BCG vaccine is from the BCG (negative IGRA) or from LTBI (positive IGRA).

Chest radiography should be obtained routinely in children being evaluated for TB disease or in any child who has a positive TST or IGRA result. Children who have LTBI usually have normal-appearing chest radiographs. An isolated calcified lesion in a child who has a positive TST result can be treated as LTBI. The most common abnormal radiographic finding is hilar or mediastinal adenopathy; other findings can include infiltrates, atelectasis, pleural effusions, cavities, or miliary disease. Chest radiographs often indicate more severe disease than would be suspected based on physical examination. Most studies of the radiographic diagnosis of TB have used chest radiography as the reference standard. Computed tomography (CT) scan is much more sensitive in detecting atelectatic regions and adenopathy, but the clinical significance of CT scan findings that are not also seen on chest radiography is unclear. CT scan is not recommended routinely for the evaluation of the child who has a positive TST result or suspected disease.

Treatment

Deciding which medications to prescribe for a child suspected of having TB disease or infection depends on several factors: disease classification (exposure versus LTBI versus disease), anatomic location of disease, route of administration, medication adverse effect profiles and potential medication interactions, and data on isolate susceptibility, when available.

TB Exposure

TB exposure is a category used to describe asymptomatic children who have had contact with a person suspected of having TB disease and in whom the TST result and chest radiograph are normal. Children younger than 4 years of age and immunocompromised children should be started on medication, usually INH, pending results of repeated skin testing, because they are at higher risk of rapid progression to clinical disease. If the second skin test result is negative, medication can be discontinued. Children experiencing TB exposure who are older than age 3 years and immunocompetent can be observed off of medications pending the second skin test result.

TB Infection (LTBI)

The child demonstrating a positive skin test result should be treated for LTBI to decrease the risk of disease progression later in life. The mainstay of therapy for LTBI is INH administered for a 9-month course. An alternative for patients intolerant of INH is rifampin, which is administered for 6 months. Therapy for LTBI can be daily and self-administered or intermittent (biweekly or thrice-weekly) and supervised through directly observed therapy (DOT). Patients never should receive self-administered intermittent therapy because missed doses in this regimen increase the likelihood of failure. Children whose source cases have isolates resistant to INH but susceptible to rifampin can be treated with rifampin alone. Children exposed to or infected by contacts infected with DR-TB should be managed in coordination with a TB expert, usually by attempting to find one or more oral agents to which the organism has documented susceptibility.

TB Disease

Children who have TB disease have a higher organism burden, and the mathematical likelihood of their having resistant organisms is higher. Consequently, any child suspected of having TB disease should be started on combination therapy. All cases of TB disease should have medication administered via DOT, whereby a public health worker supervises medication administration. DOT has been shown to increase medication compliance and decreases the emergence of resistant isolates.

The standard initial regimen should be the four most commonly used agents in the treatment of TB disease: INH, rifampin, pyrazinamide (PZA), and ethambutol. INH, rifampin, and ethambutol are administered for 6 months and PZA is stopped after the first 2 months. If the source case's isolate is known to be susceptible to the other three drugs, ethambutol need not be given. These medications are efficacious, available in oral formulation, and well-tolerated by children. The doses, drug interactions, adverse effect profiles, and monitoring parameters for these medications, as well as for second-line medications, are listed in Table 6. Other drugs are considered second-line medications for reasons that may include route of administration (parenteral), toxicities, cost, availability, or limited experience in children.

Medications usually are administered daily for the first 2 to 4 weeks and then can be changed to biweekly. For infants and toddlers, the increased medication volume required when changing from daily to biweekly or thrice-weekly therapy can result in medication intolerance and vomiting. Therefore, it may be reasonable to continue young children on daily therapy for a longer time. Another concern for the young child is that INH suspension is sorbitol-based and can cause gastrointestinal distress.

Table 6. **Drugs Used for the Treatment of Tuberculosis in Children and Adults**

| Agent | Daily Dose | | Biweekly dose | | Drug Interactions[1] | Toxicities | CNS Penetrance[2] | Monitoring Parameters | Hepatic or Renal Dosing Necessary |
	Children (mg/kg per day)	Maximum Dose	Children (mg/kg per day)	Maximum Dose					
First-line Agents									
Isoniazid[3]	10 to 15	300 mg	20 to 30	900 mg	+	Hepatitis, peripheral neuropathy	100%	†	*
Rifampin	10 to 20	600 mg	10 to 20	600 mg	++	Hepatitis	10% to 20%	†	*
Pyrazinamide	30 to 40	2 g	50	2 g	−	Gout, rash	100%	†	*Renal
Ethambutol	20	2.5 g	50	2.5 g	−	Optic neuritis	Minimal†	†	*Renal
Agents for Drug-resistant TB									
Amikacin	15 to 30	1 g	Few data available on the efficacy of biweekly dosing of second-line agents in children	−		Nephrotoxicity, ototoxicity	Low	Baseline and monthly creatinine, drug concentrations, and hearing screen	Renal
Capreomycin	15 to 30	1 g		−		Nephrotoxicity, ototoxicity	Minimal†	Baseline and monthly creatinine and hearing screen	Renal
Kanamycin	15 to 30	1 g		−		Nephrotoxicity, ototoxicity	Low	Baseline and monthly creatinine and hearing screen	Renal
Streptomycin	20 to 40	1 g		−		Ototoxicity, nephrotoxicity	Minimal	Baseline and monthly creatinine and hearing screen	Renal
Ethionamide	15 to 20	1 g		−		Hepatotoxicity, GI distress, hypersensitivity reactions, hypothyroidism, peripheral neuropathy, optic neuritis	100%	Consider baseline ALT and TSH	*Renal
Levofloxacin	7.5 to 10†	1 g†		++		Arthropathy, CNS stimulation	16% to 20%		Renal
Ciprofloxacin	20 to 30†	1.5 g†		++		Arthropathy, CNS stimulation	10%		Renal
Cycloserine	10 to 20	1 g		−		Rash, seizures, psychosis	100%	Monthly neuro-psychiatric evaluation; serum concentrations available	Renal
Para-aminosalicylic acid	200 to 300	10 g		+		Hepatotoxicity, GI distress, hypersensitivity reactions, hypothyroidism	10% to 50%†	Baseline ALT, TSH; check monthly if used >3 months	Renal

[1]For drug interactions: −=minimal interactions, +=few interactions, ++=multiple interactions
[2]Percentage of serum concentrations reached in cerebrospinal fluid.
[3]Isoniazid metabolism can vary by how rapidly a child acetylates the medication, but specific testing or dosage modifications are not indicated based on whether a child is a slow or fast acetylator.
†Routine baseline laboratory evaluation not necessary except in children who have known underlying hepatic disease.
*Can be used, but with more frequent monitoring, in patients who have underlying hepatic disease.
‡Only marginally efficacious for tuberculous meningitis.
ALT=alanine aminotransferase, CNS=central nervous system, GI=gastrointestinal, TSH=thyroid-stimulating hormone

Once a child is taking soft foods, consideration should be given to changing to INH tablets, which can be crushed and mixed with semisolid foods.

MDR-TB, defined as resistance to at least INH and rifampin, presents many challenges to the clinician. No large-scale studies have investigated the efficacy of spe-

cific treatments in adults or children, and in most circumstances, therapy needs to be individualized based on the exact drug resistance pattern. Consultation with a TB expert always should be sought.

The usual treatment duration for pulmonary and most extrapulmonary forms of TB is 6 months for isolates that

are susceptible to all first-line TB drugs. Exceptions are treating children who have disseminated or CNS TB, where treatment courses of 9 to 12 months often are used; children infected with MDR-TB, who often are treated for 12 to 18 months; and patients who have cavitary disease and persistently positive sputum cultures on appropriate therapy, when it is recommended that therapy be extended to 9 months. If therapy is interrupted for more than 14 days, the treatment course should be restarted in its entirety. Chest radiographs obtained at the end of therapy continue to appear abnormal, but improved, in most children who have adenopathy. This finding is not an indication to continue therapy until resolution of radiographic disease.

Children coinfected with TB and HIV pose a number of treatment challenges. These include higher mortality rates; increased likelihood of malabsorption of TB medications; drug-drug interactions between rifampin and many antiretrovirals (protease inhibitors and non-nucleoside reverse transcriptase inhibitors); and paradoxic worsening of TB symptoms after initiation of antimycobacterial therapy, the immune reconstitution inflammatory syndrome. These challenges have led the Centers for Disease Control and Prevention to recommend 9 months of treatment for HIV-infected United States children who have TB. Initial therapy should include four drugs, if possible. Treatment of an HIV-infected child who also has TB should be directed by subspecialists well versed in the care of both diseases.

Corticosteroids have been used as adjunctive therapy in certain forms of TB to try to decrease the damage caused by a profound inflammatory response. Indications for corticosteroid use include CNS involvement, pericarditis, pleural or severe miliary disease, endobronchial TB, and abdominal TB. The usual dose is 2 mg/kg per day (maximum, 60 mg/day) of prednisone or prednisolone for 4 to 6 weeks, followed by a slow taper.

Clinical scenarios that can challenge the pediatrician include the family in which an adult has TB and the infant whose mother has active TB. The scenario encountered most commonly is one in which an adult in the household has infectious TB. All children in the household should have chest radiographs and TSTs performed. Children younger than 4 years of age should be started empirically on INH until the TST is repeated in 2 to 3 months. If the second TST result is

negative and the child is immunocompetent, INH can be discontinued. If the TST result is positive or the child is immunocompromised, INH should be continued for 9 months.

Management of the infant whose mother has TB is more difficult because infants are more likely to progress rapidly to pulmonary or extrapulmonary disease and the TST is helpful only if the result is positive, which is very rare. If the mother has a positive TST result and negative chest radiograph (LTBI), the child needs no evaluation. If the mother has a positive skin test result and an abnormal radiograph but one that is not consistent with TB, sputum smears should be obtained from the mother. If the mother is AFB sputum smear-negative, the infant does not need to be isolated from the

> "**Management** of the infant whose mother has TB is more difficult because infants are more likely to progress rapidly to pulmonary or extrapulmonary disease. . . ."

mother or started on INH; the mother should be treated for LTBI. In contrast, if the mother has radiographic features consistent with TB, the neonate requires evaluation for congenital TB. If the infant does not have congenital TB (normal chest radiograph and physical examination findings), he or she should be separated from the mother until the infant is receiving INH (and pyridoxine if the mother is breastfeeding) and the mother is receiving appropriate multidrug therapy. Once the infant is receiving INH, separation is unnecessary and breastfeeding should be encouraged unless INH resistance is suspected.

Health-care workers (HCWs) who have positive TST results should receive chest radiographs. If the chest radiograph is negative, the HCW may be offered therapy for LTBI after weighing the risks and benefits of INH in adults. If the chest radiograph is positive, the HCW needs to be evaluated further. Contact investigations are performed by the health department in a concentric circle pattern; that is, the first group (circle) evaluated is the HCW's closest contacts, such as family and friends. The concentric circles are used to evaluate individuals of different levels of exposure to the source case, and screening is stopped once a given group has no evidence of TST conversion.

Follow-up

Children who have TB disease should be seen monthly while receiving therapy to document medication tolerance and adherence, weight gain, and achievement of appropriate milestones (especially with TB meningitis) and to assure that the disease is not spreading. Children who have pulmonary TB should have repeat chest radiographs after 1 to 2 months of therapy; subsequent radiographs usually are unnecessary except for the child who has extensive pulmonary involvement. Children who have TB meningitis often require sequential CNS imaging by CT scan or magnetic resonance imaging.

Prevention

Prevention of TB disease can be conceptualized in at least three ways. First, prevention can occur via chemoprophylaxis of children who have been exposed or who have LTBI to prevent future disease cases, as has been discussed. Second, infection control and contact investigations can serve to limit the spread of TB in a variety of settings. Finally, the BCG vaccine can be used to prevent disease in babies and, in select circumstances, in the older child.

Isolation in the hospital is unnecessary for many children who have TB disease because the younger child rarely has a sufficiently forceful cough or a high enough organism burden in the airways to be infectious. However, the same individuals who brought the children to medical attention often have disease and have infected the children. Consequently, obtaining chest radiographs on caregivers is one method of identifying potential source cases (in whom culture yield is higher) rapidly and limiting health-care-associated transmission. Negative-pressure isolation rooms and HCW use of N95 respirators should be implemented in the care of children hospitalized because of cavitary or extensive pulmonary involvement, AFB smear-positive TB, or laryngeal TB or during procedures in which the risk of aerosolization of the bacteria is high (eg, bronchoscopy). Such children should remain isolated until effective therapy has been initiated, cough has diminished, and sputum AFB smears convert to negative.

The BCG vaccine is administered routinely in most countries, with the exceptions of the United States and the Netherlands. Vaccination has been shown to decrease the risk of life-threatening forms of TB, primarily meningitis and miliary disease, in infants. The BCG vaccine has no proven efficacy outside this age group. The two groups who should receive BCG vaccine in the United States are HIV-negative and TST-negative infants and children continually exposed to MDR-TB and children continually exposed to adults who have infectious TB and who cannot be removed from that setting or who receive long-term chemoprophylaxis.

Prognosis

LTBI therapy is close to 100% effective in children for preventing future disease if adherence is excellent. Treatment of drug-susceptible TB disease in children results in cure rates of approximately 95% to 100%. In contrast, clinical cure is achieved in only 50% to 70% of adult patients infected with MDR-TB. The overall mortality rate from TB in childhood is low. The highest rates of worldwide mortality and long-term sequelae in children occur in those who have TB meningitis; of these children, as many as 33% die and almost 50% of survivors have residual neurologic deficits. However, effective treatment of LTBI and prompt recognition of TB disease can decrease both the morbidity and mortality of childhood TB.

Summary

- Childhood TB is, in large part, a preventable and treatable disease.
- The risk of acquiring TB infection is not evenly distributed across the population, with higher risk seen in immigrants and members of minority groups. The risk of a child progressing from TB infection to disease and the clinical manifestations of disease depend on the child's age and immune status.
- The most common forms of TB disease in childhood are pulmonary disease infection, lymphadenopathy, and meningitis.
- Because culture yield in children is low, TB often is diagnosed by the combination of a positive TST or IGRA, consistent radiographic information, appropriate epidemiologic links, and exclusion of other possible diagnoses. However, the TST produces a number of false-positive and false-negative results for a variety of reasons, and knowledge of how to use the TST is important for clinicians.
- Prompt diagnosis and appropriate implementation of therapy are facilitated by maintaining suspicion for TB, using public health resources, and knowing the epidemiologic face of TB in a community.

Suggested Reading

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PIR Quiz

Quiz also available online at pedsinreview.aappublications.org.

6. An 8-month-old boy who had acquired human immunodeficiency virus infection perinatally presents with fever and cough. A chest radiograph reveals lesions consistent with tuberculosis (TB), and a gastric aspirate is positive for *Mycobacterium tuberculosis.* The *most* likely site of extrapulmonary disease in this infant is the:

   A. Lymph nodes.
   B. Meninges.
   C. Miliary.
   D. Pleura.
   E. Skeleton.

7. An 8-year-old boy is brought to you for a health supervision visit. The family returned from a visit to their family in India 2 months ago. The mother was just told that the child's paternal grandfather, whom they all visited in India, has cavitary TB. The child has been well and has normal physical examination findings. The tuberculin skin test (TST) result is positive. Of the following, the *most* appropriate next investigation is:

   A. Bone scan.
   B. Chest computed tomography scan.
   C. Chest radiography.
   D. Sputum acid-fast bacilli (AFB) stain.
   E. Sputum culture for AFB.

8. Which of the following best describes the use of the TST in the treatment of children?

   A. It becomes positive within 2 weeks of exposure to TB.
   B. It should be used routinely to screen all children.
   C. Prior bacillus Camille-Guérin vaccination routinely causes a false-positive result.
   D. The TST is the only appropriate screening test for TB.
   E. Up to 15% of children who have clinical TB have a negative TST result.

9. During a health supervision visit, you learn that a 10-year-old girl returned from a 3-week trip to Kenya to visit her family 3 months ago. You perform a TST and identify 14 mm of induration 72 hours later. The child otherwise is well and has normal findings on physical examination. Chest radiograph reveals hilar adenopathy. The *most* appropriate agent(s) to be prescribed with direct observation is (are):

A. Isoniazid monotherapy for 9 months.
B. Isoniazid, pyrazinamide, and ethambutol for 9 months.
C. Isoniazid, rifampin, and ethambutol for 6 months and pyrazinamide for 2 months.
D. Isoniazid, rifampin, and ethambutol for 9 months.
E. Rifampin monotherapy for 6 months.

10. You are called to the nursery to evaluate a 1-day-old girl whose mother had no prenatal care. On admission to the hospital, the mother reported that she had several weeks of low-grade fever and cough. A maternal TST placed yesterday has a 7-mm induration, chest radiography reveals a cavitary lesion, and sputum for AFB is negative. The baby has normal findings on physical examination and chest radiograph. The *most* appropriate treatment for this infant is to:

A. Begin isoniazid and rifampin therapy.
B. Begin isoniazid, but isolation is not necessary.
C. Begin isoniazid, pyrazinamide, and ethambutol therapy.
D. Isolate the infant from the mother until isoniazid is started for the infant and the mother is receiving appropriate therapy.
E. Wait to see if the maternal TST induration becomes ≥10 mm.

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