Tuberculosis in Children

Peter J. Holmberg, MD,* Zelalem Temesgen, MD,† Ritu Banerjee, MD, PhD‡

*Division of Pediatric Hospital Medicine, Department of General Pediatric and Adolescent Medicine, and †Division of Infectious Disease, Mayo Clinic, Rochester, MN

‡Division of Pediatric Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN

Practice Gaps

Although tuberculosis (TB) is an ancient disease, it continues to cause significant morbidity and mortality throughout the world, including among children. Knowledge of appropriate TB screening, diagnostic testing, and treatment recommendations is of vital importance for primary care providers when caring for children at high risk for TB.

Objectives

After completing this article, readers should be able to:

1. Understand the epidemiology of pediatric tuberculosis (TB).
2. Describe the mechanisms of TB acquisition and host response, including T-cell–mediated actions and granuloma formation.
3. Discuss the importance of comorbid conditions, specifically human immunodeficiency virus type 1, on the acquisition and progression of TB disease.
4. Identify risk factors for acquisition of TB infection.
5. Recognize the utility of tests for latent TB infection (LTBI), including the tuberculin skin test, interferon-γ release assays, and the effect of age and Bacille Calmette-Guérin vaccination status on interpretation of results.
6. Define the differences among TB, multidrug-resistant TB, and extensively drug-resistant TB.
7. Understand the principles of therapy and drug regimens for LTBI and TB disease (including drug-resistant TB).

AUTHOR DISCLOSURE Drs Holmberg and Temesgen have disclosed no financial relationships relevant to this article. Dr Banerjee has disclosed that she receives research funding from bioMérieux, BioFire, and Accelerate Diagnostics. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

BCG	Bacille Calmette-Guérin
CDC	Centers for Disease Control and Prevention
CXR	chest radiograph
DOT	directly observed therapy
EMB	ethambutol
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
IGRA	interferon-γ release assay
INH	isoniazid
LTBI	latent tuberculosis infection
Mtb	*Mycobacterium tuberculosis*
NTM	nontuberculous mycobacteria
RIF	rifampin
PZA	pyrazinamide
TB	tuberculosis
TST	tuberculin skin test

INTRODUCTION

One of the most common infectious diseases worldwide, tuberculosis (TB) is estimated to affect almost 1 in 3 individuals across the globe. Despite relatively cheap and accurate diagnostic assays as well as established effective treatment regimens, TB remains a leading cause of death annually. When diagnosed and appropriately treated, TB mortality in children approaches zero. However, with an estimated yearly burden of 1 million new pediatric cases worldwide and most

of these remaining undiagnosed, TB continues to pose a substantial threat to global child health. Furthermore, most pediatric infections in the United States occur in US-born individuals. All of these issues reveal the importance of pediatric providers being familiar with the epidemiology, natural history, clinical manifestations, diagnosis, and management of TB in children.

EPIDEMIOLOGY

Mycobacterium tuberculosis (Mtb), the pathogen that causes TB, infects up to one-third of the world's population. (1)(2) A chronic granulomatous infection, TB is a leading cause of death worldwide and results in greater mortality than any other single infectious organism, exceeding even human immunodeficiency virus (HIV). (2)(3) Despite drops in TB incidence and mortality over time, more than 2 billion people remain infected, and greater than 1 million individuals die yearly from TB, including approximately 200,000 children. (3) Primarily a disease of low- and middle-income countries, TB mortality is disproportionately concentrated in the youngest of children, with 80% of childhood TB deaths occurring in those younger than 5 years. (4) Historically, epidemiologic data on global mortality in children younger than 5 years have not included TB as a cause of death. (4)(5) However, recent modeling suggests that not only is TB the most common infectious cause of death in children younger than 5 years, but it is likely the sixth most common overall cause of death in young children. One of the most striking aspects of TB is that almost all (96%) of the deaths in children occur in those not receiving treatment for the infection. In fact, the mortality rate for children receiving appropriate therapy is less than 1%. (4) This is particularly worrisome given the fact that of the 1 million estimated new cases of TB yearly in children younger than 15 years, almost two-thirds are either undiagnosed or untreated. (6) In the United States, the overall number of TB cases increased in 2015 for the first time in 22 years, and this number included more than 1,000 newly documented infections in children. (7) These data highlight the importance of a pediatrician's familiarity with TB pathogenesis, symptoms, screening recommendations, and treatment.

TRANSMISSION AND PATHOGENESIS OF INFECTION

TB can cause infection almost anywhere in the body but is primarily a disease of the lower respiratory tract. (2) Initial infection with Mtb is considered a primary infection and in children is almost exclusively the result of exposure to an adult with TB disease. (8) Bacilli are spread by the expectoration and subsequent inhalation of Mtb-containing droplet nuclei that are small enough to pass into the lower respiratory tract. Larger droplets are generally excluded by the upper airway structures and bronchial epithelial cells. (9)(10) Childhood acquisition of Mtb is almost always from adults because young children generally have paucibacillary and noncavitary disease, along with an inadequate cough physiology to expectorate infectious sputum.

In immunocompetent persons, inhaled Mtb is bound to the surface of alveolar macrophages and is phagocytosed into a tight vacuole. The intracellular phagosome fuses with a lysosome, forming a phagolysosome complex. Within this, bactericidal elements, including reactive nitrogen and oxygen species, suppress and kill the mycobacterial pathogens, limiting Mtb growth. (9)(11) This initial response involves the innate immune system and, in most patients, is sufficient to clear the initial bacillary burden, effectively eliminating infection. (11)

In other individuals, innate immunity is inadequate to control the infection, and bacilli continue to multiply inside macrophages. By several mechanisms, including the arrest of phagolysosome fusion, Mtb actively work to survive this first stage of the host immune response. (1)(2) When replication of Mtb continues, bacilli spread to the interstitium of the lungs. Here, monocytic and dendritic immune cells transfer Mtb to regional lymph nodes, both activating adaptive immunity and providing a means of extrapulmonary spread. (1)(2)

In most cases, a T-cell–mediated host response ensues over the following weeks and promotes T- and B-cell activation and migration to the focus of infection. (12)(13) As various immune cells accumulate at the site, a granuloma composed of macrophages, lymphocytes, and dendritic and epithelioid cells is formed. (9)(10) This granuloma consists of a central area of infected and apoptotic macrophages enclosed by a layer of T and B cells. (14) Most commonly, the granuloma that forms is sufficient to control but not eliminate the bacillary load, which can persist in that environment for decades. (14)(15) This is considered a latent TB infection (LTBI) and is defined as the evidence of immune sensitization to Mtb without clinical signs or symptoms of disease. (16)

In a small number of individuals, the adaptive immune activity is inadequate to control infection, and Mtb continue to replicate unabated. When this happens, bacilli spread inside and outside of the lungs, resulting in the active form of TB known as *primary disease*. (2) In more than 90% of patients, this occurs within the first 12 months after

exposure. (17) However, active disease at any point within 2 years of infection is considered primary TB. (1)(13) Not surprisingly, progression to primary disease occurs most frequently in infants. (1)(17) In fact, the risk of developing primary disease in infants is estimated to be 50%, including a 10% to 20% risk of disseminated disease or TB meningitis. For those aged 2 to 10 years, the risk of progression to active disease drops to less than 5%. A second peak in disease progression occurs in adolescence, when the risk of disease after primary infection increases to 10% to 20% (Table 1). (18)

Active TB includes a diverse spectrum of presentations and is perhaps better thought of as a continuum of disease instead of simply active TB. Individuals can be found anywhere along a spectrum from subclinical TB consisting of asymptomatic bacterial replication (1)(16) all the way to severe disease with septic shock, multiorgan failure, respiratory failure, and death. (19) Of the 3 initial outcomes of TB exposure (Fig), primary disease is by far the least common.

A second form of active TB is termed *reactivation disease*. After varying periods of latency, and generally in the setting of immune senescence or suppression, mycobacteria may begin to proliferate to the point that the granuloma can no longer control the microbial load. (2)(9)(10) Caseation necrosis occurs and granulomas eventually break down, allowing the release and spread of bacilli. Granulomatous decay into the distal bronchioles allows mycobacterial dissemination through expectoration. (15) The lifetime risk of reactivation has been estimated to be 5% to 10% in patients with LTBI. (9)(13)(20) Reactivation most often occurs in the first 2 to 5 years after primary infection and is generally not seen until late childhood and adolescence. (8)(20)(21) Of particular importance is the effect that HIV has on LTBI and the risk of reactivation.

HIV CO-INFECTION

HIV plays a major role in much of the disease burden seen in children in low- and middle-income countries, and those with HIV co-infection have a substantially higher case fatality rate than those without. (6)(22) No other factor has as large an effect on the progression of LTBI to active disease as HIV infection. (8) Indeed, individuals with HIV have a 20- to 40-fold greater risk of developing primary, active disease and a 50- to 110-fold greater risk of progressing from LTBI to active disease. (10) Initially, the reason behind the increased risk was thought to be due to the reduction in $CD4^+$ T-lymphocyte count. Although this does play a role, (2) it has more recently been shown that the risk of active TB increases in HIV-infected persons soon after acquiring HIV, when CD4 counts are normal, suggesting a role beyond simply total CD4 levels. (22) Other factors, including the recruitment and function of CD4 cells at sites of infection, are, therefore, important in TB and HIV co-infection, although more work is needed to clearly define these. (9)

RISK FACTORS FOR TB INFECTION IN CHILDREN

LTBI occurs when an individual has an immunologic test positive for infection with Mtb but is asymptomatic and has no abnormalities on physical examination or chest radiography (CXR). It is difficult to ascertain the number of children living with LTBI, although 1 study estimates that more than 7 million children acquire TB infection each year

TABLE 1. **Age-Related Risk of Evolution from Primary Infection to Primary Disease**

AGE AT PRIMARY INFECTION, Y	RISK OF PROGRESSION TO PULMONARY DISEASE, %	RISK OF PROGRESSION TO CENTRAL NERVOUS SYSTEM/MILIARY DISEASE, %
<1	30–40	10–20
1–2	10–20	2–5
>2–5	5	0.5
>5–10	2	<0.5
>10	10–20	<0.5

Adapted from Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. *2004;8(4):397. Reprinted with modifications with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union.*

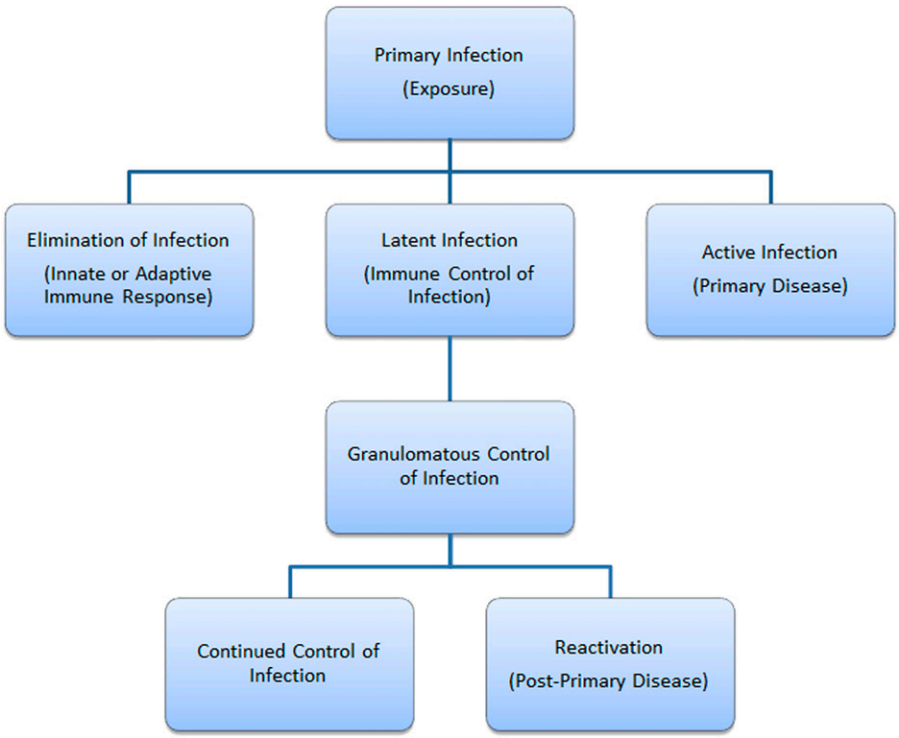


Figure. Outcomes of tuberculosis exposure.

throughout the world. (4) Newly diagnosed TB infection in a child is considered a sentinel event that indicates recent transmission of Mtb and should prompt investigation for the source TB case.

As the number of TB cases has declined in the United States, TB control efforts have shifted from identification and treatment of individuals with TB disease to identification and treatment of individuals with LTBI because latent organisms can reactivate and cause TB disease later in life. The US Centers for Disease Control and Prevention (CDC) approach for elimination of TB emphasizes the need to assess patients for risk of TB infection, test them appropriately, and treat those with LTBI to prevent the development of disease. (23)

The CDC currently recommends screening for TB infection only in children with risk factors for TB, including birth, travel, or previous residence outside of the United States, and close contact with an individual with infectious TB. (23) The American Academy of Pediatrics recommends assessing a child for TB risk factors at the first health-care visit, every 6 months during the first year, and then annually thereafter by asking questions about location of birth, travel history, and exposure to individuals with a history of TB disease, incarceration, homelessness, and foreign travel. (24) A tool has been developed by the Pediatric Tuberculosis Collaborative Group to aid TB risk assessment. (25) Foreign-born children who should be screened for TB include international adoptees, refugees, and immigrants. Screening requirements for immigrants before arrival in the United States vary by age. Immigrant children 2 to 14 years of age from countries with high TB prevalence should have a tuberculin skin test (TST) or interferon-γ release assay (IGRA), and any child with a positive TST or IGRA result should have a CXR obtained before arrival in the United States. Children younger than 2 years are not routinely tested for TB before immigration. Children aged 15 years and older generally have a CXR, and if the findings are abnormal they should have sputum smears and cultures obtained, all before immigration. (24) (26)

DIAGNOSTIC TESTS FOR TB INFECTION IN CHILDREN

There are 2 kinds of tests to diagnose TB infection, both based on host response and not on detection of the organism. Neither test can distinguish between LTBI and active TB disease. The oldest and most commonly used test is the TST, in which a purified protein derivative is injected intradermally. Induration at the injection site within 48 to 72 hours indicates a delayed-type hypersensitivity reaction and infection with Mtb. The size of induration combined with risk factors for TB is used to

determine positive or negative TST test results (Table 2). Receipt of the Bacille Calmette-Guérin (BCG) vaccine should not affect what size TST induration is considered positive. Although the TST has many advantages, including vast clinical experience, provider familiarity with the test, and low cost, it has technical and logistical disadvantages. False-positive TSTs can occur due to infection with nontuberculous mycobacteria (NTM) or previous BCG vaccination. There is significant interobserver variation in TST result interpretation and TST placement, and TST assessment review requires 2 health-care visits. Many children do not return for the second visit to have the TST read. False-negative TST results can also occur in patients with recent infection before a robust immune response has developed, in very young children, in those who are malnourished or immunosuppressed, and in children with recent measles infection or vaccination.

Since 2005, IGRAs have been Food and Drug Administration (FDA) approved to diagnose LTBI in the United States. IGRAs are based on measurement of IFN-γ production in response to in vitro T-cell stimulation after exposure to Mtb antigens. Because IGRAs do not involve antigens from *M bovis* or common NTM species, false-positive IGRAs are less likely to occur from previous BCG vaccination or NTM infection. IGRAs also have operational advantages, including requiring a single health-care visit, a faster turnaround time than a TST, and standardized cutoff values that eliminate interobserver variation in test interpretation. IGRAs are also run with positive and negative controls to confirm adequate immunologic function. However, IGRAs are more expensive than the TST and require venipuncture. Two commercially available IGRAs exist: QuantiFERON-TB gold in-tube (Qiagen, Germantown, MD) and the T-SPOT.*TB* (Oxford Immunotec USA Inc, Marlborough, MA). Characteristics and test performance of the TST and IGRAs are compared in Table 3. Overall, IGRAs are at least as sensitive as, and more specific for, Mtb infection than the TST. (29)(30)(31)(32) Despite the advantages of IGRAs over the TST, the uptake of IGRAs by pediatric providers has been variable, likely because of lack of familiarity with the test. (33)

A recent joint guideline from the American Thoracic Society, the Infectious Diseases Society of America, and the CDC recommends use of an IGRA rather than a TST in children 5 years and older who require testing for TB. In children younger than 5 years, these guidelines recommend use of a TST. (23) However, based on more recent data, the American Academy of Pediatrics has expanded use of IGRAs to children as young as 2 years, (28) particularly in those who are BCG-vaccinated or unlikely to return for a TST reading visit. There are few data on IGRA performance in infants and very young children, so TST remains the preferred strategy to evaluate children younger than 2 years. Some experts prefer using IGRAs in BCG-vaccinated older children to eliminate the chance of false-positive TST results from vaccination. Some also suggest using both TST and IGRAs in situations where maximal sensitivity is needed and then

TABLE 2. **Definition of Positive Tuberculin Skin Test Results in Children (24)(27)**

INDURATION ≥5 MM	INDURATION ≥10 MM	INDURATION ≥15 MM
Clinical evidence of TB disease	Recent immigration from a high-prevalence[a] country	Age ≥4 y without any risk factors
Close contact with a person with known or suspected TB disease	Children exposed to individuals who are infected with HIV, injectable drug users, incarcerated individuals, or residents of nursing homes	
Radiographic changes consistent with active or previous TB	Medical conditions such as lymphoma, diabetes, renal failure, and malnutrition	
Immunosuppression due to medications, immunosuppressive conditions, or HIV infection	Age <4 y	

HIV=human immunodeficiency virus, TB=tuberculosis.
[a]*Countries with a high absolute burden of incident TB cases according to the World Health Organization.*

TABLE 3. **Comparison of the TST and IGRAs**

CHARACTERISTIC	TST	IGRAS
Recommended age, y	All	>2 (28); >5 (23)
Cross-reactivity with BCG	Yes	No
Cross-reactivity with NTM species (23)	Yes	Little[a]
Sensitivity, % (29)(30)	67–81	57–76
Specificity, % (29)(30)	79–92	85–98
Testing variability	Yes, interobserver variation	No, fixed cutoff value
Distinguish LTBI versus disease	No	No
Health-care encounters, No.	2	1
Venipuncture	No	Yes
Cost	Low	Higher
Laboratory capacity	No	Yes
Turnaround time, h	48–72	24
Can be falsely negative in immunosuppressed patients	Yes	Yes

BCG=Bacille Calmette-Guérin, IGRA=interferon-γ release assay, LBTI=latent tuberculosis infection, NTM=nontuberculous mycobacteria, TST=tuberculin skin test.

[a]*IGRAs can be positive after exposure to* Mycobacterium flavescens, Mycobacterium kansasii, Mycobacterium marinum, Mycobacterium szulgai, *and other species in the* Mycobacterium tuberculosis *complex (*Mycobacterium africanum, Mycobacterium bovis, Mycobacterium canetti, *and* Mycobacterium microti).

treating for LTBI if either test is positive. Examples of this are an immunocompromised child who is at high risk for LTBI reactivation, or a child in close contact with a contagious TB case. In children at low risk for LTBI, use of both TST and IGRA is generally not indicated and may lead to discordant test results that need to be interpreted on a case-by-case basis, focusing on epidemiologic risk factors and clinical context, often with the assistance of providers experienced in treating people infected with TB.

EVALUATION OF A CHILD FOR TB INFECTION OR DISEASE

All children being evaluated for TB infection or disease should have a careful history obtained to assess for epidemiologic risk factors for TB exposure along with a thorough physical examination. Children with pulmonary TB can have diverse clinical manifestations that vary by age. School-aged children may be relatively asymptomatic; infants may demonstrate failure to thrive, respiratory distress, organomegaly, or skin lesions; and older children may have respiratory symptoms similar to those seen in adults, including cough, dyspnea, hemoptysis, crackles (rales), wheeze, and fever. Generally, more symptoms are present in very young infants and adolescents compared with school-aged children. Extrapulmonary manifestations of TB vary by the site of disease. TB lymphadenitis may present as painless, nontender lymph node swelling without fever or other systemic symptoms. TB osteomyelitis may present as localized pain, fever, and refusal to ambulate or bear full weight on the affected extremity.

All children with suspicion of TB infection or disease should undergo a TST or an IGRA, depending on the child's age. Children who are symptomatic or at high risk for TB disease (eg, close contact with an individual with infectious TB) should have CXR performed, regardless of the TST or IGRA result. Asymptomatic children who do not have risk factors for TB acquisition should have a CXR performed only if the TST or IGRA result is positive. Generally, asymptomatic children with positive TST and IGRA results and normal CXRs are considered to have LTBI and are treated accordingly. Children with symptoms or abnormal CXR findings consistent with TB should have gastric aspirate or sputum samples sent for acid-fast bacillus (AFB) staining of smear and culture and in high-risk situations should be started on empirical multidrug TB treatment while awaiting culture results.

Evaluation and management of children with positive TST or IGRA results should be performed in conjunction with state or local public health departments.

TREATMENT OF TB EXPOSURE IN YOUNG OR IMMUNOCOMPROMISED CHILDREN

Children younger than 4 years and those who are immunocompromised are at high risk for progression from TB infection to TB disease. If such children are exposed to an individual with infectious TB they should receive "window prophylaxis" or anti-TB therapy, usually with isoniazid (INH), even if initial TST or IGRA results are negative because delayed-type hypersensitivity reactions may not be detectable until several weeks to months after TB exposure. As part of routine contact investigation, repeated TST or IGRA is performed 8 to 10 weeks after contact with the source case ends. If repeated test results are negative, window prophylaxis can be discontinued. If repeated TST or IGRA results are positive, the child will need a thorough medical evaluation and CXR to assess for TB infection or disease.

TREATMENT OF LTBI IN CHILDREN

A variety of drugs and regimens are available for the treatment of LTBI in children. (34)(35) (Table 4) A single daily dose of INH for 9 months is the preferred regimen for treatment of LTBI in children known to or deemed to have INH-susceptible infection. (34)(36) Alternative regimens include 4 months of daily rifampin (RIF), 3 months of daily INH and RIF, and a 3-month, once-weekly dose of INH and rifapentine. (34)(35)(37) These shorter regimens have been shown to be as effective and as well tolerated as 9 months of INH therapy, with significantly higher completion rates. (38)(39)(40)(41)(42) However, the once-weekly INH and rifapentine regimen should not be used in children younger than 2 years because the safety and pharmacokinetics of this regimen have not been established for this age group. Furthermore, because the once-weekly INH and rifapentine regimen is administered intermittently at weekly intervals, and because missed doses could jeopardize efficacy or safety, directly administered therapy (DOT) is recommended.

The optimal treatment for LTBI in children exposed to drug-resistant, particularly multidrug-resistant, TB is unknown. (43)(44)(45)(46) When monoresistance to INH or RIF is likely, INH or RIF, whichever drug is effective, can be used, similar to what was detailed previously herein. In patients with exposure to multidrug-resistant TB, options include close observation without therapy using a fluoroquinolone if presumed fluoroquinolone susceptible, or combination drug regimens such as pyrazinamide (PZA) and ethambutol (EMB). (47)(48)(49)(50) The optimal duration for any of these regimens is undefined. Infants who are exclusively breastfeeding and receiving INH, or whose mother is receiving INH, should receive a multivitamin to minimize the risk of neurologic toxicity associated with INH.

TREATMENT OF ACTIVE TB IN CHILDREN

In general, the principles of treatment and the drugs used for the treatment of TB in children are the same as in adults. (51)(52) Treatment of extrapulmonary TB, except for TB meningitis, in children is generally similar to the treatment of pulmonary disease. Drugs for the treatment of TB in children are shown in Table 5.

Laboratory confirmation of TB in children (in particular, children <5 years of age) is challenging because of the paucibacillary nature of their disease and because of the

TABLE 4. **Treatment Regimens for Latent Tuberculosis Infection in Children**

DRUG	DOSE	DURATION, MO	INTERVAL
Isoniazid	10–15 mg/kg 20–30 mg/kg	9	Daily Twice weekly
Isoniazid and rifapentine	Isoniazid: 10–15 mg/kg Rifapentine: 10–14 kg: 300 mg >14–25 kg: 450 mg >25–32 kg: 600 mg >32–49 kg: 750 mg >50 kg: 900 mg	3	Once weekly
Rifampin	10–20 mg/kg	4	Daily

TABLE 5. **Antituberculous Drugs**

GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5
Isoniazid	Amikacin	Levofloxacin	Ethionamide	Linezolid
Rifampin	Capreomycin	Moxifloxacin	Cycloserine	Clofazimine
Pyrazinamide	Kanamycin		Para-aminosalicylic acid	High-dose isoniazid
Ethambutol	Streptomycin			Amoxicillin/clavulanate
				Imipenem
				Clarithromycin
				Thiacetazone
				Bedaquiline
				Delamanid
First line	Second line	Second line	Second line	Third line

difficulties in obtaining specimens for culture. In addition, TB can rapidly advance and pose serious risk to life in young children. For these reasons, a presumptive diagnosis should be made on epidemiologic, clinical, and radiographic grounds, and empirical treatment should be promptly initiated. A 4-drug combination of INH, RIF, PZA, and EMB is the recommended first-line regimen. The duration of such treatment that has been empirically initiated depends on the clinical course, radiographic changes, and identification of alternative diagnoses.

For drug-susceptible TB, a 4-drug regimen of INH, RIF, PZA, and EMB for 2 months followed by a 2-drug regimen of INH and RIF for an additional 4 months is recommended. Programmatically, treatment should be administered under the DOT approach; parents should not supervise DOT for their children. Contrary to the practice in the treatment of TB in adults, where pyridoxine supplementation is recommended during INH therapy to prevent the development of peripheral neuropathy, this is necessary only in children with nutritional deficiencies, with symptomatic HIV infection, or who are breastfeeding.

DRUG-RESISTANT TB

Drug-resistant TB defines infection caused by strains of Mtb resistant to at least 1 of the first-line anti-TB drugs: INH, RIF, PZA, or EMB. Multidrug-resistant TB denotes Mtb that is resistant to at least INH and RIF. Extensively drug-resistant TB refers to Mtb resistant to at least INH and RIF plus any resistance to the fluoroquinolones or injectable anti-TB agents.

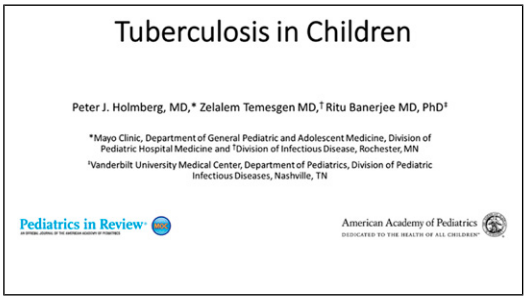
In young children, drug-resistant TB is primarily a consequence of transmission of drug-resistant TB to the child rather than a reflection of previous exposure to TB treatment. Drug-resistant TB is essentially a microbiological diagnosis; there are no clinical or radiologic clues to distinguish it from drug-susceptible TB. Therefore, when drug-resistant TB is suspected, every effort should be made to obtain specimens for culture and drug susceptibility testing. In situations in which microbiologic confirmation of resistant TB is lacking, resistance can be inferred from the drug susceptibility profile of a known adult contact, if available. If no drug susceptibility is available for the child or an adult contact, drug resistance may be inferred if the child is failing therapy (clinical or radiographic worsening). In such cases, treatment decisions may have to be based on the prevailing regional resistance pattern in Mtb isolates.

In general, the principles of the treatment of drug-resistant TB in children are similar to those of adults. (53)(54)(55) When possible, drug susceptibility test results should drive the regimen selection. A single drug should never be added to a failing regimen. Depending on the degree of resistance, the regimen used should consist of at least 4 drugs to which the child or the adult contact is naive or their isolates are susceptible. All treatment should be given daily through DOT, ideally with the oversight of the local public health department. Management includes monthly monitoring for adherence, response to treatment, and adverse events. Direct evidence informing optimal duration of treatment for drug-resistant TB in children is lacking. Therefore, treatment duration is adopted from guidelines for the treatment of TB in adults. Often, second- and third-line TB medications have more adverse effects than first-line medications.

Summary

- Based on research evidence and consensus, newly diagnosed tuberculosis (TB) infections in children are sentinel events that indicate recent transmission of *Mycobacterium tuberculosis* (Mtb) and require prompt investigation for the source TB case. (24)
- Based on research evidence and consensus, screening for TB infection should be performed only in children with risk factors for TB (including birth, travel, or previous residence outside of the United States, and close contact with an individual with infectious TB) using a questionnaire. (24)
- Based on strong research evidence, interferon-γ release assays (IGRAs) have several advantages over the tuberculin skin test (TST), including higher specificity and lower likelihood of false-positive results due to previous Bacille Calmette-Guérin vaccination or nontuberculous mycobacteria infection. (23)
- Due to insufficient evidence, the youngest age at which IGRAs are reliable is not clear. The American Thoracic Society/Centers for Disease Control and Prevention (CDC)/Infectious Diseases Society of America consensus guidelines favor use of the TST rather than IGRAs in children younger than 5 years. (23) However, the American Academy of Pediatrics recommends the use of IGRAs in children as young as 2 years old in some circumstances. (28) The TST remains the preferred strategy to evaluate children younger than 2 years for TB infection due to limited data regarding the use of IGRAs in this age group.
- Based on research evidence and consensus, children younger than 4 years and those who are immunocompromised are at high risk for progression from TB infection to TB disease, and if exposed to an individual with infectious TB require "window prophylaxis," usually with isoniazid (INH), even if initial TST or IGRA test results are negative.
- Based on strong research evidence, a shorter (3-month) treatment regimen for latent TB infection in children older than 2 years and using once weekly INH and rifapentine administered via directly observed therapy has high rates of efficacy and adherence. (56)
- Based on research evidence and consensus, treatment of TB disease in children requires multidrug therapy for a minimum of 6 months, depending on the site of infection and drug susceptibility of the Mtb isolate. Treatment for TB should be provided via directly observed therapy through local or state public health departments. (52)

To view teaching slides that accompany this article, visit **http://pedsinreview.aappublications.org/content/40/3/168.supplemental.**



References for this article are at http://pedsinreview.aappublications.org/content/40/4/168.

PIR Quiz

There are two ways to access the journal CME quizzes:
1. Individual CME quizzes are available via the blue CME link under the article title in the Table of Contents of any issue.
2. To access all CME articles, click "Journal CME" from Gateway's orange main menu or go directly to: http://www.aappublications.org/content/journal-cme.
3. To learn how to claim MOC points, go to: http://www.aappublications.org/content/moc-credit.

1. An 8-year-old girl with Crohn disease has a positive interferon-γ release assay (IGRA) result before being started on a tumor necrosis factor antagonist. She has been afebrile and is not coughing. Her chest radiograph is normal, and she is diagnosed as having latent tuberculosis infection (LTBI). Exposure to which of the following contacts is the most likely source from which she acquired *Mycobacterium tuberculosis* (Mtb)?
    A. An 8-year-old classmate with cough and congestion who immigrated to the United States from South Korea 9 months earlier.
    B. An 8-year-old classmate who was born in Romania and was treated for LTBI at 3 years of age.
    C. Her 42-year old uncle who was recently diagnosed as having active TB.
    D. Her 7-year-old cousin who traveled to Mexico 2 years ago.
    E. Her 2-year-old brother who has had intermittent cough and wheezing.
2. A 16-year-old boy is applying to be a hospital volunteer and the hospital requires a TB screening test. He is well and immigrated to the United States from India when he was 3 years old. He received Bacille Calmette-Guérin vaccine as an infant. He returned to India 3 years ago to visit family. Which of the following is the most appropriate next step in management?
    A. Chest radiography.
    B. Gastric aspirate for Mtb polymerase chain reaction.
    C. IGRA.
    D. Induced sputum for acid-fast bacillus (AFB) smear and culture.
    E. Tuberculin skin test (TST).
3. A healthy 15-month-old girl is brought to the office by her mother who states that the girl's paternal grandmother was diagnosed as having active TB the past week and has been started on multidrug treatment. The paternal grandmother has had close contact with the girl during the past 2 months when she moved close to the family. The paternal grandmother has no history of being treated for TB. A TST is placed on the girl. Which of the following is the most appropriate next step in management?
    A. Begin isoniazid therapy.
    B. Begin isoniazid therapy if her TST shows at least a 15-mm induration.
    C. Begin isoniazid, rifampin, and ethambutol therapy.
    D. Obtain gastric aspirate the next 3 mornings for AFB smear and culture.
    E. Obtain gastric aspirate the next 3 mornings for AFB smear and culture and begin isoniazid, rifampin, pyrazinamide, and ethambutol therapy.
4. A healthy 14-year-old boy is brought to the office due to concern for TB exposure. His aunt who lives in Bangladesh visited the family 2 months ago for a week and had a cough at that time. When she returned to Bangladesh she was diagnosed as having active TB that was isoniazid-resistant but susceptible to rifampin, ethambutol, pyrazinamide, linezolid, and amikacin. The boy feels well and has not had fever or cough. The IGRA results are positive. Findings on a chest radiograph are normal. Which of the following is the most appropriate next step in management?
    A. Daily ethambutol therapy for 9 months.
    B. Daily isoniazid therapy for 9 months.
    C. Daily rifampin therapy for 4 months.
    D. Weekly ethambutol and linezolid therapy for 6 months.
    E. Weekly isoniazid and pyrazinamide therapy for 6 months.

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2019 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2021, however, credit will be recorded in the year in which the learner completes the quiz.

2019 *Pediatrics in Review* now is approved for a total of 30 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics through the AAP MOC Portfolio Program. Complete the first 10 issues or a total of 30 quizzes of journal CME credits, achieve a 60% passing score on each, and start claiming MOC credits as early as October 2019. To learn how to claim MOC points, go to: http://www.aappublications.org/content/moc-credit.

5. A 2-year-old boy is admitted to the hospital with a 1-day history of left-sided hemiparesis and a 2-week history of fever and intermittent cough. He attends child care and his child care provider has had a persistent cough. A chest radiograph shows a right lower lobe infiltrate and hilar adenopathy. IGRA results are positive. Cerebrospinal fluid Mtb polymerase chain reaction is positive, and AFB culture is pending. Gastric aspirate AFB cultures are also pending. Which of the following is the most appropriate initial treatment?

   A. Amikacin, pyrazinamide, and ethambutol.
   B. Amikacin, pyrazinamide, ethambutol, rifapentine, and rifampin.
   C. Ethambutol and linezolid.
   D. Isoniazid, rifampin, pyrazinamide, and ethambutol.
   E. Rifampin and isoniazid.

Tuberculosis in Children

Peter J. Holmberg, Zelalem Temesgen and Ritu Banerjee

Pediatrics in Review 2019;40;168
DOI: 10.1542/pir.2018-0093

Tuberculosis in Children

Peter J. Holmberg, Zelalem Temesgen and Ritu Banerjee

Pediatrics in Review 2019;40;168
DOI: 10.1542/pir.2018-0093