**Tuberculosis**

**CLINICAL MANIFESTATIONS:** Tuberculosis (TB) disease is caused by organisms of the *Mycobacterium tuberculosis* complex. Most infections caused by *M. tuberculosis* complex in children and adolescents are asymptomatic. When pulmonary TB occurs, clinical manifestations most often appear 1 month to 2 years after infection and include fever, weight loss or poor weight gain, cough, night sweats, and chills. Chest radiographic findings rarely are specific for TB and include lymphadenopathy of the hilar, subcarinal, paratracheal, or mediastinal nodes; atelectasis or infiltrate of a segment or lobe; pleural effusion that can conceal small interstitial lesions; interstitial cavities; or miliary-pattern infiltrates. In selected instances, computed tomography or magnetic resonance imaging of the chest can clarify nonspecific or subtle radiographic findings. Although cavitation is a typical presentation of reactivated TB in adults (and sometimes in adolescents) who were infected as children, cavitation is uncommon in childhood TB. Necrosis and cavitation, however, can result from a progressive primary focus in very young or immunocompromised patients and in patients with lymphobronchial disease. Extrapulmonary manifestations include meningitis and granulomatous inflammation of the lymph nodes, bones, joints, skin, and middle ear and mastoid. Gastrointestinal tract TB can mimic inflammatory bowel disease. Renal TB is unusual in younger children but can occur in adolescents. In addition, chronic abdominal pain with peritonitis and intermittent partial intestinal obstruction can be present in disease caused by *Mycobacterium bovis*. Congenital TB can mimic neonatal sepsis, or the infant may come to medical attention in the first 90 days of life with bronchopneumonia and hepatosplenomegaly. Clinical findings in patients with drug-resistant TB disease are indistinguishable from manifestations in patients with drug-susceptible disease.
ETIOLOGY: The causative agent is *M tuberculosis* complex, a group of closely related acid-fast bacilli: *M tuberculosis, M bovis, Mycobacterium africanum*, and a few additional species infrequently associated with human infection. *M africanum* is rare in the United States, so clinical laboratories do not distinguish it routinely, and treatment recommendations are the same as for *M tuberculosis. M bovis* can be distinguished from *M tuberculosis* in reference laboratories, and although the spectrum of illness caused by *M bovis* is similar to that of *M tuberculosis*, the epidemiology, treatment, and prevention are different, as detailed later in the chapter.

Definitions:

- **Bacille Calmette-Guérin (BCG)** is a live attenuated vaccine strain of *M bovis*. BCG vaccine rarely is administered to children in the United States but is one of the most widely used vaccines in the world. An isolate of BCG can be distinguished from wild-type *M bovis* only in a reference laboratory.

- **Positive tuberculin skin test (TST).** A positive TST result (see Table 3.74) indicates possible infection with *M tuberculosis* complex. Tuberculin reactivity appears 2 to 10 weeks after initial infection; the median interval is 3 to 4 weeks (see “Tuberculin Skin Test,” p 791). BCG immunization can produce a positive TST result (see Diagnostic Tests, Testing for *M tuberculosis* Infection).

- **Positive interferon-gamma release assay (IGRA).** A positive IGRA result indicates probable infection with *M tuberculosis* complex. IGRA measure ex vivo interferon-gamma production from T lymphocytes in response to stimulation with antigens specific to *M tuberculosis* complex, including *M tuberculosis* and *M bovis*. The antigens used in IGRA are not found in BCG or most pathogenic nontuberculous mycobacteria (eg, are
not found in *Mycobacterium avium* complex, but are found in *Mycobacterium kansasii, Mycobacterium szulgai, and Mycobacterium marinum*).

- **TB infection (TBI)** is *M tuberculosis* complex infection in a person who has no symptoms or signs of disease and chest radiograph findings that are normal or reveal evidence of healed infection (e.g., calcification in the lung, lymph nodes, or both) and a positive TST or IGRA result. Note that hilar adenopathy is evidence of TB disease, not TBI. TBI is also known as latent tuberculosis infection, or LTBI, but TBI is a more accurate term, because infection is not actually “latent” prior to manifesting as TB disease.

- **TB disease** is illness in a person with infection in whom symptoms, signs, or radiographic manifestations caused by *M tuberculosis* complex are apparent; disease can be pulmonary, extrapulmonary, or both.

- **Multidrug-resistant TB** (MDR TB) is defined as infection or disease caused by a strain of *M tuberculosis* complex that is resistant to at least isoniazid and rifampin.

- **Extensively drug-resistant TB** (XDR TB) is defined as infection or disease caused by a strain of *M tuberculosis* complex that is resistant to isoniazid and rifampin, at least 1 fluorquinolone, and at least 1 of the following parenteral drugs: amikacin, kanamycin, or capreomycin.

- **Drug-resistant tuberculosis (DR TB)** is infection or disease caused by a strain of *M tuberculosis* that is resistant to any drug used to treat drug-susceptible tuberculosis and includes isoniazid-resistant TB, rifampin-resistant TB, MDR TB, and XDR TB.

- **Directly observed therapy (DOT)** is an intervention by which medications are taken by the patient while a health care professional or trained third party (not a relative or friend)
observes and documents that the patient ingests each dose of medication and assesses for possible adverse drug effects.

- **Exposed person** is anyone who has had recent (less than 3 months) contact with another person with suspected or confirmed contagious TB disease (ie, pulmonary, laryngeal, tracheal, or endobronchial disease) and has a negative TST or IGRA result, normal physical examination findings, and chest radiographic findings that are normal or not compatible with TB. Some exposed people are or become infected (and subsequently develop a positive TST or IGRA result), and others do not become infected after exposure; the 2 groups cannot be distinguished initially.

- **Source person** is the person who has transmitted *M tuberculosis* complex to another person who subsequently develops TB infection or disease.

**Epidemiology:** Case rates of TB in all ages in North America are higher in urban, low-income areas and in nonwhite racial and ethnic groups; more than 87% of reported cases in the United States occur in Hispanic and nonwhite people. In recent years, more than 70% of all US cases have been in people born outside the United States. Almost 80% of childhood TB disease in the United States is associated with some form of foreign contact of the child, parent, or a household member. Specific groups with greater rates of TB include immigrants, international adoptees, refugees from or travelers to high-prevalence regions (eg, Asia, Africa, Latin America, and countries of the former Soviet Union), people experiencing homelessness or those with unstable housing, people who inject or use drugs, people with alcohol use disorders, and residents of certain correctional facilities and other congregate settings. Secondhand smoke exposure increases the risk of TB disease developing in infected children.

Infants and postpubertal adolescents are at increased risk of progression from TBI to TB
disease. Other predictive factors for development of disease include recent infection (within the past 2 years); immunodeficiency, especially from human immunodeficiency virus (HIV) infection; use of immunosuppressive drugs, such as prolonged or high-dose corticosteroid therapy or chemotherapy and drugs for preventing transplant organ rejection (see Solid Organ Transplantation, p 84); and certain diseases or medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, and malnutrition. Patients with TBI who are being treated with tumor necrosis factor-alpha (TNF-alpha) antagonists or blocking agents (see Biologic Response-Modifying Drugs Used to Decrease Inflammation, p 82) are at higher risk of progressing to TB disease. A positive TST or IGRA result should be accepted as indicative of infection in individuals receiving or soon to receive these medications,\(^1,^2\) and the patient should be evaluated and treated accordingly.

A diagnosis of TBI or TB disease in a young child is a public health sentinel event often representing recent transmission. Transmission of \(M\) tuberculosis complex is airborne, with inhalation of droplet nuclei usually produced by an adult or adolescent with contagious pulmonary, endobronchial, or laryngeal TB disease. The probability of transmission increases if the index person has a positive acid-fast sputum smear, productive cough, or pulmonary cavities or is a household contact. Although contagiousness usually lasts only a few days to weeks after initiation of effective drug therapy, it can last longer if the source patient does not adhere to medical therapy or is infected with a drug-resistant strain. If the sputum smear becomes negative for acid-fast bacilli (AFB) on 3 separate specimens at least 8 hours apart after treatment is

initiated and the patient has improved clinically, the treated patient can be considered at low risk of transmitting *M tuberculosis*. Children younger than 10 years with only adenopathy in the chest or small pulmonary lesions (paucibacillary disease) and nonproductive cough are not contagious. Rare cases of pulmonary disease in young children, particularly with lung cavities or presence of AFB on sputum microscopy, and infants with congenital TB can be contagious.

*M bovis* is transmitted most often by unpasteurized dairy products, but airborne human-to-human transmission can occur.

The **incubation period** from infection to development of a positive TST or IGRA result is 2 to 10 weeks. The risk of developing TB disease is highest during the 12 months after infection and remains high for 2 years; however, many years can elapse between initial *M tuberculosis* infection and subsequent disease.

**DIAGNOSTIC TESTS:**

**Testing for *M tuberculosis* Infection**

*Tuberculin Skin Test.* The TST is one of two indirect methods for detecting *M tuberculosis* infection, the other method being IGRA (p 792). Both methods rely on specific lymphocyte sensitization after infection. Conditions that decrease lymphocyte numbers or function, including severe TB disease, can reduce the sensitivity of these tests. Tuberculin is a purified protein derivative (PPD) from heat-inactivated *M tuberculosis*. The routine (ie, Mantoux) technique of administering the skin test consists of 5 tuberculin units of solution (PPD; 0.1 mL) injected intradermally using a 27-gauge needle and a 1.0-mL syringe into the volar aspect of the forearm. Creation of a palpable wheal 6 to 10 mm in diameter is crucial to accurate testing.

Administration of TSTs and interpretation of results should be performed by trained and experienced health care personnel, because administration and interpretation by unskilled people
or family members are unreliable. The standardized time for assessing the TST result is 48 to 72 hours after administration. The diameter of induration is measured transversely to the long axis of the forearm, and the result should be recorded in millimeters. Positive TST results, as defined in Table 3.74 (p 788), can persist for several weeks.

Lack of reaction to a TST does not exclude TBI or TB disease. Approximately 10% to 40% of immunocompetent children with culture-documented TB disease do not react initially to a TST. Host factors, such as young age, poor nutrition, immunosuppression, viral infections (especially measles, varicella, and influenza), recent *M tuberculosis* infection, and disseminated TB disease, can decrease TST reactivity.

Classification of TST results is based on epidemiologic and clinical factors. Interpretation of the size of induration (mm) as a positive result varies with the person’s epidemiologic risk of TBI and likelihood of progression to TB disease. Current guidelines from the Centers for Disease Control and Prevention (CDC), the American Thoracic Society, and the American Academy of Pediatrics (AAP) recommend interpretation of TST findings on the basis of an individual’s risk stratification and are summarized in Table 3.74 (p 788). Prompt clinical and radiographic evaluation of all children and adolescents with a positive TST result is recommended (see Assessing for *M tuberculosis* Disease, p 795).

BCG immunization, because of cross-reacting antigens present in the PPD, can result in induration of a TST. Distinguishing between a positive TST result caused by *M tuberculosis* complex infection and that caused by BCG requires a qualitative assessment of several factors. Reactivity of the TST (ie, mm of induration) attributable to prior BCG immunization may be absent or variable and depends on many factors, including age at BCG immunization, quality and strain of BCG vaccine used, number of doses of BCG vaccine received, nutritional and
immunologic status of the vaccine recipient, frequency of TST administration, and time between immunization and TST. Evidence that increases the probability that a positive TST result is attributable to TBI includes known contact with a person with contagious TB, a family history of TB disease, more than 2 years since neonatal BCG immunization, and a TST reaction 15 mm or greater. Generally, interpretation of TST results in BCG recipients who are known contacts of a person with TB disease or who are at high risk of developing TB disease is the same as for people who have not received BCG vaccine.

**Blood-Based Testing With IGRAs.**[^3][^4][^5] IGRAs measure ex vivo interferon-gamma production from T lymphocytes in response to stimulation with proprietary polypeptide mixtures that simulate antigens specific to *M. tuberculosis* complex, which includes *M. tuberculosis* and *M. bovis*. The IGRA antigens used are not found in BCG or most pathogenic nontuberculous mycobacteria (eg, *M. avium* complex) but are found in the nontuberculous mycobacteria *M. kansasii*, *M. szulgai*, and *M. marinum*. Examples of IGRAs are the QuantiFERON-TB Gold Plus assay and the T-SPOT.TB assay. As with TSTs, IGRAs cannot distinguish between TBI and TB disease, and a negative result from these tests cannot exclude TBI or the possibility of TB disease in a patient with suggestive clinical findings. The sensitivity of IGRA tests is similar to that of TSTs for detecting infection in adults and children who have untreated culture-confirmed TB. In many clinical settings, the specificity of IGRAs is higher than that for the TST, because the antigens used are not found in BCG or most pathogenic nontuberculous mycobacteria. The published

experience testing children with IGRAs demonstrates that IGRAs consistently perform well in children 2 years and older, and some data support their use for even younger children. The negative predictive value of IGRAs is not clear, but in general, if the IGRA result is negative and the TST result is positive in an asymptomatic, unexposed child, the diagnosis of TBI is unlikely, especially if the child has received a BCG vaccine. A negative result for either a TST or an IGRA should be considered especially unreliable in infants younger than 3 months.

**TST Versus IGRA.** For children younger than 2 years, TST is the preferred method for detection of *M tuberculosis* infection. For children 2 years and older, either TST or IGRA can be used, but in people previously vaccinated with BCG, IGRA is preferred to avoid a false-positive TST result caused by a previous vaccination with BCG. Low-grade, false-positive IGRA results occur in some individuals. A negative IGRA result cannot be interpreted universally as evidence of absence of infection. Indeterminate or invalid IGRA results have several possible causes that could be related to the patient, the assay itself, or its performance; these results do not exclude *M tuberculosis* infection and may necessitate repeat testing, possibly with a different test. Indeterminate/invalid IGRA results should not be used to make clinical decisions.

Specific recommendations for TST and IGRA use are provided in Table 3.75 (p 789) and Fig 3.16 (p 793).

**Use of Tests for *M tuberculosis* Infection.** The most reliable strategies for identifying TBI and preventing TB disease in children are based on identification of known risk factors for TBI and thorough and expedient contact tracing associated with cases of TB disease rather than nonselective testing of large populations. Contact tracing is an intervention that should be coordinated through the local public health department. Universal testing with TST or IGRA, including programs based at schools, child care centers, and camps that include populations at
low risk, is discouraged because it results in either a low yield of positive results or a large proportion of false-positive results, leading to an inefficient use of health care resources. However, using a questionnaire to determine risk factors for TBI and identifying who should have a TST or IGRA performed can be useful (see Table 3.76). Risk assessment for TB should be performed at the first medical home encounter with a child and then annually if possible. Testing children for TBI and clinical evaluation for possible TB disease is indicated whenever a TST or IGRA result of a household member converts from a negative to positive result (indicating recent infection).

**HIV Infection.** Children living with HIV infection are considered at high risk for TB and should be tested annually beginning at 3 through 12 months of age if perinatally infected or at the time of diagnosis of HIV infection in older children or adolescents. Conversely, children who have TB disease should be tested for HIV infection. The clinical manifestations and radiographic appearance of TB disease in children living with HIV infection tend to be similar to those in immunocompetent children, but manifestations in these children can be more severe, unusual, and more often include extrapulmonary involvement of multiple organs. In HIV-infected patients, a TST induration of $\geq 5$ mm is considered a positive result (see Table 3.74, p 788); however, a false-negative TST or IGRA result attributable to HIV-related immunosuppression also can occur. Diagnosing TB disease in an HIV-infected child with microbiological specimens is challenging, given the paucibacillary nature of TB in this population. Antituberculosis therapy in HIV-infected children must be selected with careful consideration of antiretroviral drug interactions, which are very common.

**Organ Transplant Recipients.** The risk of TB in organ transplant recipients is several-fold greater than in the general population. A careful history of previous exposure to TB should be taken
from all transplant candidates, including details about previous TST or IGRA results and exposure to individuals with TB. All transplant candidates should undergo evaluation by TST or IGRA for TBI before the initiation of immunosuppressive therapy. A positive result of either test should be taken as evidence of \textit{M. tuberculosis} infection. In addition, donor-derived TB can be carried in an infected organ and should be considered as a possible cause of post-transplant fever and related symptoms.

\textit{Patients Receiving Immunosuppressive Therapies Including Biologic Response Modifiers.} In addition to a detailed history of risk factors for \textit{M. tuberculosis} complex infection, all patients should have a TST or IGRA performed before the initiation of therapy with high-dose systemic corticosteroids, antimetabolite agents, and tumor necrosis factor antagonists or blockers (eg, adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab; see Biologic Response-Modifying Drugs Used to Decrease Inflammation, p 82). Some experts recommend that if the child has at least 1 TB risk factor, both a TST and an IGRA should be performed to maximize sensitivity; a positive result of either test should be taken as evidence of \textit{M. tuberculosis} infection.

\textit{Other Considerations.} Testing for TB at any age is not required before administration of live-virus vaccines. Live attenuated measles, mumps, and rubella vaccines temporarily can suppress tuberculin reactivity for at least 4 to 6 weeks, and data suggest a similar suppression with varicella and yellow fever vaccines. The effect of live attenuated influenza vaccines on TST reactivity and IGRA results is not known. If indicated, a TST can be performed or blood drawn for an IGRA at the same visit during which these vaccines are administered (ie, before substantial replication of the vaccine virus). The effects of live-virus vaccination on IGRA characteristics have not been determined; the same precautions as for TST should be followed.

Sensitivity to PPD tuberculin antigen persists for years in most instances, even after
effective treatment. The durability of positive IGRA results has not been determined. Repeat
testing with either TST or IGRA has no known clinical utility for assessing the effectiveness of
treatment or for diagnosing newly acquired infection in patients who previously were infected
with *M tuberculosis*.

**Assessing for *M tuberculosis* Disease.** Although both IGRA and TST provide evidence for infection with
*M tuberculosis*, they cannot distinguish TBI from TB disease. Therefore, patients testing positive
for *M tuberculosis* infection by IGRA or TST should be assessed for TB disease before initiating
any therapeutic intervention. This assessment should include: (1) asking about symptoms of TB
disease and exposure to TB patients; (2) physical examination for signs of TB disease; and (3) a
chest radiograph. If radiographic signs of TB (eg, airspace opacities, pleural effusions, cavities,
or changes on serial radiographs) are seen, then sputum or gastric aspirate sampling should then
be performed, as described below. Most experts recommend that children younger than 12
months who are suspected of having pulmonary or extrapulmonary TB disease (eg, have a
positive TST result and symptoms, physical examination signs, or chest radiograph abnormalities
consistent with TB disease), with or without neurologic symptoms, should have a lumbar
puncture to evaluate for tuberculous meningitis. Children 12 months and older with TB disease
require a lumbar puncture only if they have neurologic signs or symptoms.

**Laboratory Confirmation of *M tuberculosis*.** Laboratory isolation of *M tuberculosis* complex by culture
from a specimen of sputum, gastric aspirate, bronchial washing, pleural fluid, cerebrospinal fluid
(CSF), urine, or other body fluid or a tissue biopsy specimen confirms the diagnosis of TB
disease. Positive results from a rapid molecular method (eg, nucleic acid amplification tests
[NAATs]) increasingly are also considered confirmatory, but culture isolation of the organism
still is required after diagnosis with molecular methods for phenotypical susceptibility testing,
genotyping, rapid molecular detection of drug-resistance genes, and species identification with
the *M tuberculosis* complex. Children older than 2 years and adolescents frequently produce
sputum spontaneously or by induction with aerosolized hypertonic saline. Studies have
demonstrated successful collection of induced sputum from infants with pulmonary TB, but this
requires special expertise. The best specimen for diagnosis of pulmonary TB in any child or
adolescent in whom cough is absent or nonproductive and sputum cannot be induced is an early-
morning gastric aspirate, which should be obtained with a nasogastric tube on awakening the
child and before ambulation or feeding. Aspirates collected on 3 separate mornings should be
submitted for AFB staining and culture.

Fluorescent staining methods for specimen smears are more sensitive than the traditional
Kinyoun acid fast smears and are preferred. The overall diagnostic yield of microscopy of gastric
aspirates and induced sputum is low in children with clinically suspected pulmonary TB, and
false-positive stain results caused by the presence of nontuberculous mycobacteria occur rarely.
Histologic examination for and demonstration of AFB and granulomas in biopsy specimens from
lymph node, pleura, mesentery, liver, bone marrow, or other tissues can be useful, but
*M tuberculosis* complex organisms cannot be distinguished reliably from other mycobacteria in
stained specimens; the CDC offers molecular species identification of mycobacteria including *
M tuberculosis* in fixed tissues. Regardless of results of the AFB smears, each specimen should be
cultured.

Because *M tuberculosis* complex organisms are slow growing, detection of these
organisms may take as long as 10 weeks using solid media; use of liquid media and continuous
monitoring systems allows detection within 1 to 6 weeks and usually within 3 weeks. Even with
optimal culture techniques, *M tuberculosis* complex organisms are isolated from fewer than 75%
of infants and 50% of children with pulmonary TB diagnosed by clinical criteria; the culture yields for most forms of extrapulmonary TB are even lower. Current methods for species identification of isolates from culture include molecular probes, NAATs, genetic sequencing, mass spectrometry, and biochemical tests. *M bovis* usually is suspected because of isolated pyrazinamide resistance, which is characteristic of almost all *M bovis* isolates, but further biochemical or molecular testing is required to distinguish *M bovis* from *M tuberculosis*.

For a child with clinically suspected TB disease, finding the culture-positive source person supports the child’s presumptive diagnosis and provides the likely drug susceptibility of the child’s organism. Culture material should be collected from children with evidence of TB disease, especially when (1) an isolate from a source person is not available; (2) the presumed source person has drug-resistant TB; (3) the child is immunocompromised or ill enough to require hospital admission; or (4) the child has extrapulmonary disease. Traditional methods of determining drug susceptibility require bacterial isolation. Several new molecular methods of rapidly determining drug resistance directly from clinical samples now are available.

NAATs cleared by the FDA are available for rapid detection of *M tuberculosis* complex organisms from smear-positive and smear-negative sputum specimens, and other laboratory-developed tests for rapid molecular detection are available locally. Some tests have been validated for specimens other than sputum: expert consultation is recommended for test availability and interpretation of results. Molecular methods that find *M tuberculosis* genetic markers associated with drug resistance are supplementing the culture-based (ie, phenotypic) methods for drug susceptibility testing as they decrease the time to detection of drug resistance from weeks to hours, and in some instances the results could be more reliable for patient care decisions. Some of the methods are verified for direct testing of patient specimens. However,
culture-based results are still required for confirming susceptibility to each drug when drug resistance genes are not detected, because the absence of resistance genes is not entirely predictive of susceptibility. The molecular methods are constantly evolving, and expert consultation should be sought for a testing strategy when drug resistance is suspected.

**TREATMENT (SEE TABLE 3.77)**

**Specific Drugs.** Regimen and dosage recommendations and the more commonly reported adverse reactions of first-line antituberculosis drugs are summarized in Tables 3.77, 3.78, and 3.79 (p 803). The less commonly used (eg, “second-line”) antituberculosis drugs, their doses, and adverse effects are listed in Table 3.80 (p 805). Some of these drugs have less effectiveness and greater toxicity; they should be used only in consultation with a specialist familiar with treatment of childhood TB. For treatment of TB disease, drugs always must be used in recommended combination and dosage to minimize emergence of drug-resistant strains. Use of nonstandard regimens for any reason (eg, drug allergy, drug resistance) should be undertaken only by an expert in treating TB.

Occasionally, a patient cannot tolerate oral medications. Isoniazid, rifampin, amikacin and related drugs, linezolid, and fluoroquinolones can be administered parenterally.

**Treatment Regimens for Tuberculosis Infection (TBI).** Several regimens are recommended, depending on the circumstances for individual patients. Dosages and intervals are provided in Table 3.78.

**Isoniazid-Rifapentine Therapy for TBI.** A 12-week course, comprising a once-weekly dose of isoniazid and rifapentine, is a regimen that is safe, well tolerated, and at least as efficacious as 9

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months of isoniazid taken daily. Extensive published and unpublished experience with this combination in children has demonstrated similar results. Most experts consider isoniazid-rifapentine to be the preferred regimen for treatment of TBI for children 25 years and older, and some experts prefer isoniazid-rifapentine therapy for TBI in children 2 years and older, although the pill burden in younger children is substantial and sometimes not well tolerated. Isoniazid-rifapentine should not be used in children younger than 2 years because of a lack of pharmacokinetic data in this age group.

*Rifampin Therapy for TBI.* A 4-month course of rifampin given daily also is an acceptable regimen for the treatment of TBI. It is the preferred regimen when isoniazid resistance is likely, as judged from the exposure history. The data supporting the efficacy and safety of this regimen are from randomized controlled trials and case control studies in adults and several studies that included children. The regimen has been as effective as 9 months of daily isoniazid, the rates of adverse effects have been low, and the completion rates of therapy have been much higher than for 9 months of isoniazid. There has been extensive published and unpublished experience with this regimen in children demonstrating safety, tolerability, and high rates of completion.

*Isoniazid-Rifampin Therapy for TBI.* An additional possible regimen for treatment of TBI is 3 months of daily isoniazid and rifampin, with no age restriction on its use. This regimen is quite similar in principle to the isoniazid-rifapentine option; however, the medications are given daily because of the relatively short half-life of rifampin compared with rifapentine. Efficacy and rates of completion of are comparable or better when compared with isoniazid monotherapy.

*Isoniazid Therapy for TBI.* Isoniazid monotherapy has been the most widely recommended and utilized treatment for pediatric TBI. The efficacy of isoniazid monotherapy reaches 98% against development of TB disease, but many studies have shown that the long duration of isoniazid
monotherapy results in poor adherence and low completion rates. The World Health Organization (WHO) recommends a treatment duration of 6 months to provide high coverage of the population in countries with a high disease burden. A 9-month regimen gives an additional 20% to 30% increase in efficacy. The CDC and National TB Controllers Association recommend 6-month or 9-month durations of isoniazid monotherapy, if shorter-course rifamycin-based regimens cannot be used. Although isoniazid is readily available, the long duration of isoniazid monotherapy results in poor adherence and low completion rates. This option may be very unattractive to patients and families. Many TB care providers and clinics use this regimen only when a rifamycin-containing regimen cannot be used because of drug interactions.

For infants, children, and adolescents, including those living with HIV infection or other immunocompromising conditions, the recommended duration of isoniazid therapy in the United States is 9 months. The WHO recommends a 6-month course of isoniazid, but modeling studies have shown that the efficacy of 6 months of treatment is approximately 30% less than that of a 9-month course. Although there have been no formal trials of interrupted 9-month courses, many experts in North America accept 6 months of uninterrupted treatment as adequate. When adherence with daily therapy with isoniazid cannot be ensured, twice-a-week DOT on the basis of expert opinion and published experience can be considered, but each dose should be observed. Determination of serum aminotransferase concentrations before or during therapy is not indicated except in patients with underlying liver or biliary disease, during pregnancy or the first 12 weeks postpartum, with concurrent use of other potentially hepatotoxic drugs (eg, anticonvulsant or HIV agents), or if there is clinical concern of possible hepatotoxicity.

Therapy for TBI and Contacts of Patients With Isoniazid-Resistant M tuberculosis and When Isoniazid Cannot Be Administered. The incidence of isoniazid resistance among M tuberculosis complex isolates from
US patients in 2017 was approximately 9%. Risk factors for drug resistance are listed in Table 3.81. If the source case is found to have isoniazid-resistant, rifampin-susceptible organisms, isoniazid should be discontinued and rifampin should be administered daily to contacts with TBI for a total course of 4 months. Optimal therapy for children with TBI caused by organisms with resistance to isoniazid and rifampin (ie, multidrug resistance) is not known. In these circumstances, a fluoroquinolone alone and multidrug regimens have been used in observational studies, but the safety and the efficacy of these empiric regimens have not been assessed in controlled clinical trials. Drugs to consider include levofloxacin or moxifloxacin, with or without the addition of pyrazinamide or ethambutol, depending on susceptibility of the isolate. Consultation with a TB specialist is indicated.

**Treatment of Tuberculosis Disease**

The goal of treatment is to achieve killing of replicating organisms in the tuberculous lesion in the shortest possible time. Achievement of this goal minimizes the possibility of development of resistant organisms. The major problem limiting successful treatment is poor adherence to prescribed treatment regimens. The use of DOT decreases the rates of relapse, treatment failures, and drug resistance; therefore, DOT is strongly recommended for treatment of all children and adolescents with TB disease in the United States. Intervals and dosages are provided in Tables 3.77, 3.79, and 3.80.

**Therapy for Presumed or Known Drug-Susceptible Pulmonary Tuberculosis**

trials have shown efficacy of shorter treatment regimens for children with pulmonary tuberculosis. For nonsevere pulmonary disease in children 3 months and older, defined as tuberculosis confined to 1 lobe with no cavities or isolated intrathoracic adenopathy, no signs of miliary tuberculosis, no complex pleural effusion, and no clinically significant airway obstruction or peripheral lymph node tuberculosis, a 4-month, 4-drug regimen consisting initially of rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) daily for the first 2 months and isoniazid and rifampin daily for the remaining 42 months daily is recommended for treatment of pulmonary disease, pulmonary disease with hilar adenopathy, and hilar adenopathy disease in infants, children, and adolescents when resistance to isoniazid, rifampin, or pyrazinamide is not suspected on the basis of exposure history or when favorable drug-susceptibility results are available from the patient or the likely source case. If the chest radiograph shows one or more pulmonary cavities and/or the sputum culture result remains positive after 2 months of therapy, the duration of therapy should be extended to at least 9 months. Some experts administer 3 drugs (isoniazid, rifampin, and pyrazinamide) as the initial regimen if a presumed source person has been identified with known pan-susceptible *M tuberculosis* or has no risk factors for drug-resistant *M tuberculosis*, and is HIV negative. For children with only hilar adenopathy in whom drug resistance is not a consideration, a 6-month regimen of only-isoniazid and rifampin is considered adequate by some experts.

If criteria are not met for the 4-month course of RIPE (ie, patient has severe pulmonary disease), at least 6 months of treatment should be administered. RIPE should be administered daily for the first 2 months, followed by isoniazid and rifampin for 4 months. If the initial chest radiograph shows one or more pulmonary cavities and/or the sputum culture result remains positive after 2 months of therapy, the duration of therapy should be extended to at least 9
An alternative regimen for patients ≥12 years of age (and weighing ≥40 kg) with nonsevere or severe, susceptible pulmonary disease is a 4-month regimen with isoniazid, rifapentine, moxifloxacin, and pyrazinamide daily for 8 weeks followed by daily isoniazid, rifapentine, and moxifloxacin daily for 9 weeks (4-month regimen; see www.cdc.gov/mmwr/volumes/71/wr/mm7108a1.htm).

All patients, and especially those who have received shorter courses of treatment, should have clinical follow-up to ensure there is not relapse. Tuberculosis in young infants should be managed together with an expert in tuberculosis.

In the 6-month regimen with 4-drug RIPE therapy, drugs are administered once a day for at least the first 2 weeks by DOT at least 5 days per week. An alternative to daily dosing between 2 weeks and 2 months of treatment is to administer these drugs 3 times a week by DOT (except in people living with HIV, in whom intermittent dosing is not recommended). After the initial 2-month period, a DOT regimen of isoniazid and rifampin usually is given daily or 3 times a week, although 2 times a week is acceptable (see Table 3.79, p 803, for doses). Several alternative regimens with differing durations of daily therapy and total therapy have been used successfully in adults and children. These alternative regimens should be prescribed and managed by a specialist in pediatric TB.

Drug resistance is more common in certain groups (Table 3.81). When resistance to drugs other than isoniazid is likely (see Table 3.81), initial therapy should be adjusted by adding at least 2 drugs to match the presumed drug susceptibility pattern until drug susceptibility results are available. If an isolate from the pediatric case under treatment is not available, drug susceptibilities can be inferred by the drug susceptibility pattern of isolates from the presumed source person. Data for guiding drug selection may not be available for foreign-born children or in circumstances of international travel or adoption. If this information is not available, a 4- or 5-drug initial regimen should be strongly considered with close monitoring for clinical response.

Most cases of pulmonary TB in children that are caused by an isoniazid-resistant but rifampin- and pyrazinamide-susceptible strain of *M tuberculosis* complex can be treated with a 6-month regimen of rifampin, pyrazinamide, and ethambutol. If disease is extensive, many experts add a fluoroquinolone to this regimen. For cases of MDR TB disease, the treatment regimen needed for cure should include at least 4 or 5 antituberculosis drugs to which the organism is susceptible. Bedaquiline is approved by the FDA as part of combination therapy in the treatment for adults with multidrug-resistant pulmonary TB for whom an effective regimen could not be instituted; there currently are few safety, tolerability, efficacy, or pharmacokinetic data on use of bedaquiline in children, but many experts recommend its use in children 12 years and older.12 The profile for delamanid is similar, but this drug is available under a compassionate use protocol only. Therapy for MDR TB is administered for 12 to 24 months from the time of culture conversion to negativity. An injectable drug initially administered 5 days per week, such as

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as amikacin, kanamycin, or capreomycin, often is used for the first 4 to 6 months of treatment, as tolerated; some experts, however, are no longer recommending injectable drugs. Regimens in which drugs are administered intermittently are not recommended for drug-resistant disease (with the exception of aminoglycosides and capreomycin, which are typically intermittent to limit toxicity); daily DOT is critical to prevent emergence of additional resistance. An expert in DR TB should be consulted for all drug-resistant cases.

**Extrapulmonary Tuberculosis Disease.** In general, extrapulmonary TB—with the exception of meningitis—can be treated with the same regimens as used for pulmonary TB. For suspected drug-susceptible tuberculous meningitis, daily treatment with isoniazid, rifampin, pyrazinamide, and ethionamide, if possible, or an aminoglycoside (parenteral streptomycin, kanamycin, amikacin) or capreomycin should be initiated. Many experts add a fluoroquinolone to this initial regimen. When used to treat CNS TB, rifampin should be given at a dose of 20 to 30 mg/kg/day to ensure adequate CNS penetration (see Table 3.79, footnote c). When susceptibility to first-line drugs is established, the ethionamide, aminoglycoside (or capreomycin), and/or fluoroquinolone can be discontinued. Pyrazinamide is given for a total of 2 months, and isoniazid and rifampin are given for a total of 6 to 12 months. Isoniazid and rifampin can be given daily or 3 times per week after the first 2 months of treatment if the child has responded well.

**Evaluation and Monitoring of Therapy in Children and Adolescents.** Careful monthly monitoring of clinical and bacteriologic responses to therapy is important. With DOT, clinical evaluation is an integral component of each visit for drug administration. For patients with pulmonary TB, chest radiographs often are obtained after 2 months of therapy to evaluate response. After initiation of treatment, alveolar or interstitial infiltrates often start to decrease within 1 to 2 weeks but take much longer to resolve completely. Pleural effusions are slower to resolve and may require
drainage for symptom relief; partial reaccumulation is common as an isolated finding but does not indicate treatment failure. Even with successful 6-month regimens, hilar adenopathy can persist for 2 to 3 years; normal radiographic findings are not necessary to discontinue therapy. Follow-up chest radiography beyond termination of successful therapy usually is not necessary unless clinical deterioration occurs.

If therapy has been interrupted, the date of completion should be extended. Although guidelines cannot be provided for every situation, factors to consider when establishing the date of completion include the following: (1) length of interruption of therapy; (2) time during therapy (early or late) when interruption occurred; and (3) the patient’s clinical, radiographic, and bacteriologic status before, during, and after interruption of therapy. The total doses administered by DOT should be calculated to guide the duration of therapy. Consultation with a specialist in TB is advised.

Untoward effects of TB therapy, including severe hepatitis in otherwise healthy infants, children, and adolescents, are rare. Routine determination of serum aminotransferase concentrations is not recommended (see “Isoniazid Therapy for TBI,” p 801) during treatment of TBI or in most cases of TB disease unless the child develops symptoms suggestive of hepatotoxicity. Monthly clinical evaluations to observe for signs or symptoms of hepatitis and other adverse effects of drug therapy without routine monitoring of aminotransferase concentrations is appropriate follow-up. Regular physician-patient contact to assess drug adherence, efficacy, and adverse effects is an important aspect of management. DOT visits also are opportunities for checking on well-being and treatment tolerance. Patients should be provided with written instructions and advised to call a physician immediately if symptoms of adverse events, in particular hepatotoxicity (ie, nausea, vomiting, abdominal pain, jaundice),
develop.

**Other Treatment Considerations**

*Corticosteroids.* The evidence supporting adjuvant treatment with corticosteroids for children with TB disease is incomplete. Corticosteroids are definitely indicated for children with tuberculous meningitis, because corticosteroids decrease rates of mortality and long-term neurologic impairment. Corticosteroids can be considered for children with pleural and pericardial effusions (to hasten reabsorption of fluid), severe miliary disease (to mitigate alveolocapillary block), endobronchial disease (to relieve obstruction and atelectasis), and abdominal TB (to decrease the risk of strictures). Corticosteroids should be given only when accompanied by appropriate antituberculosis drug therapy. Most experts give 2 mg/kg per day of prednisone (maximum, 60 mg/day) or its equivalent for 4 to 6 weeks followed by tapering.

*Tuberculosis Disease and HIV Infection.* Most adults living with HIV with drug-susceptible TB respond well to standard treatment regimens. However, optimal therapy for TB in children living with HIV infection has not been established. Treating TB in a child living with HIV infection is complicated by antiretroviral drug interactions with the rifamycins and overlapping toxicities. Therapy always should include at least 4 drugs initially, should be administered daily via DOT, and should be continued for at least 6 months unless it is nonsevere pulmonary disease (defined as tuberculosis confined to 1 lobe with no cavities, no signs of miliary tuberculosis, no complex pleural effusion, and no clinically significant airway obstruction or peripheral lymph node tuberculosis), in which case a 4-month treatment course is acceptable. Rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) should be administered for at least the first 2 months.

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Ethambutol can be discontinued once DR TB disease is excluded. Rifampin may be contraindicated in people who are receiving antiretroviral therapy. Rifabutin is substituted for rifampin in some circumstances. Consultation with a specialist who has experience in managing patients living with HIV infection with TB is strongly advised. If TB is diagnosed in an HIV-infected individual who is not yet receiving antiretroviral therapy, even in the presence of severe immune suppression, antiretroviral therapy can be safely initiated within 2 weeks of antituberculosis therapy, despite the risk of inciting immune reconstitution syndrome.

**Immunizations.** Patients who are receiving treatment for TB can receive measles and other age-appropriate attenuated live-virus vaccines unless they are receiving high-dose systemic corticosteroids, are severely ill, or have other specific contraindications to immunization.

**Tuberculosis During Pregnancy and Breastfeeding.** Pregnant women who have a positive TST or IGRA result, are asymptomatic, have a normal chest radiograph, and had recent contact with a contagious person should be considered for therapy, which usually should begin after the first trimester. If there has been no recent contact with a contagious case, therapy can be delayed until after delivery. Pyridoxine supplementation is indicated for all pregnant and breastfeeding women receiving isoniazid.

If TB disease is diagnosed during pregnancy, a standard 6-month regimen for drug-susceptible TB is usually initiated; however, 9 months of therapy is indicated if pyrazinamide is not used initially. Prompt initiation of therapy is mandatory to protect mother and fetus.

There are no adequate and well-controlled studies evaluating the adverse effects of isoniazid, rifampin, ethambutol, and pyrazinamide on the fetus. Isoniazid, ethambutol, and rifampin are believed to be relatively safe for the fetus. The benefit of ethambutol and rifampin for therapy of TB disease in the mother outweighs the risk to the infant. Because
aminoglycosides (streptomycin, kanamycin, amikacin) or capreomycin may cause ototoxic effects in the fetus, they should not be used unless administration is essential for effective treatment. Ethionamide has been demonstrated to be teratogenic, so its use during pregnancy is contraindicated. The effects of other second-line drugs on the fetus are unknown.

Women with tuberculosis who have been treated appropriately for 2 or more weeks and who are not considered contagious (smear-negative sputum) may breastfeed. Women with tuberculosis disease suspected of being contagious should refrain from breastfeeding and from other close contact with the infant because of potential spread of *M tuberculosis* through respiratory tract droplets or airborne transmission (see Breastfeeding and Human Milk, p 107). However, expressed human milk can be fed to the infant, as long as there is no evidence of tuberculosis mastitis, which is rare. Although isoniazid is secreted in human milk, no adverse effects of isoniazid on nursing infants have been demonstrated. Breastfed infants do not require pyridoxine supplementation unless they are receiving isoniazid, but breastfeeding mothers who are taking isoniazid should take pyridoxine. The isoniazid dosage of a breastfed infant whose mother is taking isoniazid does not require adjustment for the small amount of drug in the milk.

*Congenital Tuberculosis.* Congenital TB is rare, but in utero infections can occur after maternal bacillemia and have been reported following in vitro fertilization of women from countries with endemic disease in whom infertility likely was related to subclinical maternal genitourinary tract TB.

None of the possible signs of congenital TB, such as fever, tachypnea, lethargy, organomegaly, or pulmonary infiltrates, distinguish it from other systemic infections of the newborn infant. The prognosis is poor without prompt treatment. If a newborn infant is suspected of having congenital TB, a TST and IGRA test, chest radiography, lumbar puncture, and
appropriate cultures and radiography should be performed promptly. The TST result usually is negative in newborn infants with congenital or perinatally acquired infection; IGRA sensitivity in this context is not known but is likely to be low. Regardless of the TST or IGRA results, treatment of the infant should be initiated promptly with rifampin, isoniazid, pyrazinamide, and either ethambutol (RIPE) or an aminoglycoside (streptomycin, kanamycin, amikacin) or capreomycin. If meningitis is confirmed, corticosteroids should be added (see Corticosteroids, p 809). The placenta should be examined histologically for granulomata and AFB, and a specimen should be cultured for *M tuberculosis* complex. The mother should be evaluated for presence of pulmonary or extrapulmonary disease, including genitourinary tuberculosis. HIV testing of the mother is essential.

*Management of the Newborn Infant Whose Mother Has TBI or Tuberculosis Disease.* Management of the newborn infant is based on categorization of the maternal infection. Although protection of the infant from exposure and infection is of paramount importance, contact between infant and mother should be allowed when possible. Differing circumstances and resulting recommendations are as follows:

- **Mother has a positive TST or IGRA result and normal chest radiographic findings.** If the mother is asymptomatic, no separation is required. The mother usually is a candidate for treatment of TBI after the initial postpartum period. The newborn infant needs no special evaluation or therapy. Because of the young infant’s exquisite susceptibility and because the mother’s positive TST or IGRA result could be a marker of an unrecognized case of contagious TB within the household, other household members should be questioned about having symptoms of TB and have a TST or IGRA and further evaluation; this should not delay the infant’s discharge from the hospital. These mothers
can breastfeed their infants.

- **Mother has clinical signs and symptoms or abnormal findings on chest radiograph consistent with TB disease.** Cases of suspected or proven TB disease in mothers should be reported immediately to the local health department, and evaluation of all household members should be initiated as soon as possible. If the mother has TB disease, the infant should be evaluated for congenital TB (see Congenital Tuberculosis, p 810), and the mother should be tested for HIV infection. The mother and the infant should be separated until the mother has been evaluated and, if TB disease is suspected, until the mother and infant are receiving appropriate antituberculosis therapy, the mother wears a mask, and the mother understands and is willing to adhere to infection control measures. Women with tuberculosis who have been treated appropriately for 2 or more weeks and who are not considered contagious (smear-negative sputum) may breastfeed; women with tuberculosis disease suspected of being contagious should refrain from breastfeeding and from other close contact with the infant because of potential spread of *M tuberculosis* through respiratory tract droplets or airborne transmission (see Tuberculosis During Pregnancy and Breastfeeding, p 809). During separation, expressed human milk can be fed to the infant unless mother has signs of tuberculous mastitis, which is rare. Once the infant is receiving isoniazid (see next paragraph), separation is not necessary unless the mother has possible isoniazid-resistant TB disease or has poor adherence to treatment and DOT is not possible. If the mother is suspected of having isoniazid-resistant TB disease, an expert in TB disease management should be consulted.

If congenital TB is excluded, isoniazid is administered until the infant is 3 or 4 months of age, when a TST should be performed. If the TST result is negative at 3 to 4
29

months of age and the mother has good adherence and response to treatment and no longer is contagious, isoniazid should be discontinued. If the TST result is positive, the infant should be reassessed for TB disease. If TB disease is excluded, isoniazid alone should be continued for a total of 9 months, or a 4-month course of rifampin can be given. The infant should be evaluated monthly during treatment for signs of illness or poor growth.

- **Mother has a positive TST or IGRA result and abnormal findings on chest radiography but no evidence of TB disease.** If the chest radiograph of the mother appears abnormal but is not suggestive of TB disease and the history, physical examination, and sputum smear indicate no evidence of TB disease, the infant can be assumed to be at low risk of *M. tuberculosis* infection and need not be separated from the mother. The mother and her infant should receive follow-up care and the mother should be treated for TBI. Other household members should have a TST or IGRA and further evaluation.

**Tuberculosis caused by *M. bovis***. Infections with *M. bovis* account for approximately 1% to 2% of TB cases in the United States, with higher rates along the border with Mexico. Children who come from countries where *M. bovis* is prevalent in cattle or whose parents come from those countries are more likely to be infected. Most infections in humans are transmitted from cattle by unpasteurized milk and its products, such as fresh cheese, although human-to-human transmission by the airborne route has been documented. In children, *M. bovis* more commonly causes cervical lymphadenitis, intestinal TB disease and peritonitis, and meningitis. In adults, *M*

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"bovis" infection can progress to advanced pulmonary disease with a risk of transmission to others. The TST result typically is positive in a person infected with *M bovis*; IGRAs have not been studied systematically for diagnosing *M bovis* infection in particular, but theoretically they should have acceptable test characteristics (see Blood-Based Testing With Interferon-Gamma Release Assays [IGRAs], p 792). The definitive diagnosis of *M bovis* infection requires an isolate. The commonly used methods for identifying a microbial isolate as *M tuberculosis* complex do not distinguish *M bovis* from *M tuberculosis*, *M africanum*, and BCG, which is a live attenuated vaccine strain of *M bovis*; *M bovis* is suspected in clinical laboratories by its typical resistance to pyrazinamide. This approach can be unreliable, and species confirmation at a reference laboratory should be requested when *M bovis* is suspected. Molecular genotyping through the state health department may assist in identifying *M bovis*. BCG rarely is isolated from pediatric clinical specimens in the United States; however, it should be suspected from localized BCG suppuration or draining lymphadenitis in children who recently (within several months) received BCG vaccine, or in infants with selected congenital immunodeficiency syndromes who received a BCG vaccine. Only a reference laboratory can distinguish an isolate of BCG from an isolate of *M bovis*.

**Therapy for *M bovis* Disease.** Controlled clinical trials for treatment of *M bovis* disease have not been conducted, and treatment recommendations for *M bovis* disease in adults and children are based on results from treatment trials for *M tuberculosis* disease. Although most strains of *M bovis* are pyrazinamide-resistant and resistance to other first-line drugs has been reported, MDR strains are rare. Initial therapy for disease caused by *M bovis* should include 3 or 4 drugs, excluding pyrazinamide, that would be used to treat disease attributable to *M tuberculosis*. For isoniazid- and rifampin-susceptible strains, a total treatment course of at least 9 months is recommended.
Parents should be counseled about the many infectious diseases transmitted by unpasteurized milk and its products,\textsuperscript{15} and parents who might import traditional, unpasteurized dairy products from countries where \textit{M bovis} infection is prevalent in cattle should be advised against giving those products to their children. When people are exposed to an adult who has pulmonary disease caused by \textit{M bovis} infection, they should be evaluated by the same methods as for \textit{M tuberculosis}.

**ISOLATION OF THE HOSPITALIZED PATIENT:** Most children with TB disease, especially children younger than 10 years, are not contagious. Exceptions are the following: (1) children with pulmonary cavities; (2) children with positive sputum AFB smears; (3) children with laryngeal involvement; (4) children with extensive pulmonary infection; or (5) neonates or infants with congenital TB undergoing procedures that involve the oropharyngeal airway (eg, endotracheal intubation). In these instances, airborne infection isolation precautions for TB are indicated until effective therapy has been initiated, sputum smears are negative, and coughing has abated. Additional criteria apply to suspected or known MDR TB.

Children with no cough and smear-negative sputum AFB smears can be hospitalized in an open ward. Infection prevention measures for hospital personnel and visitors exposed to contagious patients should include the use of personally “fit tested” and “sealed” N95 particulate respirators for all patient contacts (see Infection Prevention and Control for Hospitalized Children, p 133). If they have or are suspected to have DR TB, consultation regarding infection prevention and control should be made with public health authorities.

The major concern in infection control relates to adult household members and contacts

who can be the source of infection. Visitation should be limited to people who have been
evaluated by symptom screening and chest radiograph and do not have TB.

**CONTROL MEASURES**\(^{16,17}\): Reporting of suspected and confirmed cases of TB disease is mandated by
law in all states. TBI is reportable in some states. Control of TB disease in the United States
requires collaboration between health care providers and health department personnel, obtaining
a thorough history of exposure(s) to people with contagious TB, timely and effective contact
tracing, proper interpretation of TST or IGRA results, and appropriate antituberculosis therapy,
including DOT services. A plan to control and prevent XDR TB has been published.\(^ {18}\)
Eliminating ingestion of unpasteurized dairy products will prevent most *M. bovis* infection.\(^ {19}\)

**Management of Contacts, Including Epidemiologic Investigation.**\(^ {20,21}\) Children with a positive TST or IGRA
result or TB disease ideally should be the starting point for epidemiologic investigation by the
local health department. Close contacts of a TST- or IGRA-positive child, if the test was
performed because the child has 1 or more risk factors, should have a TST or IGRA, and people
with a positive TST or IGRA result or with symptoms consistent with TB disease should be
investigated further. Because children with TB usually are not contagious unless they have an

\(^{16}\) American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of
America. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society,
\(^{17}\) Starke JR; American Academy of Pediatrics, Committee on Infectious Diseases. Technical report: interferon-γ
(Reaffirmed July 2018)
\(^{18}\) Centers for Disease Control and Prevention. Plan to combat extensively drug-resistant tuberculosis:
\(^{19}\) American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Nutrition. Consumption
(Reaffirmed November 2019)
\(^{20}\) National Tuberculosis Controllers Association and Centers for Disease Control and Prevention. Guidelines for the
investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis
\(^{21}\) Starke JR; American Academy of Pediatrics, Committee on Infectious Diseases. Technical report: interferon-γ
(Reaffirmed July 2018)
adult-type multibacillary form of pulmonary or laryngeal disease, their contacts are not likely to
be infected unless they also have been in contact with an adult source person. After the
presumptive adult source of the child’s TB is identified, other contacts of that adult should be
evaluated.

**Therapy for Contacts.** Children and adolescents recently exposed to a contagious case of TB
disease should have a TST or IGRA test performed and should have an evaluation for TB disease
(history and physical examination, as well as chest radiography if symptomatic or positive TST
or IGRA results) performed. For exposed contacts with impaired immunity (eg, HIV infection)
and all contacts younger than 5 years, treatment for presumptive TBI should be initiated, even if
the initial TST or IGRA result is negative, once TB disease is excluded (see Treatment Regimens
for TBI, p 796). Infected children can have a negative TST or IGRA result because a cellular
immune response has not yet developed or because of anergy. Children with a negative TST or
IGRA result should be retested 8 to 10 weeks after the last exposure to a source of infection. If
the TST or IGRA result still is negative in an immunocompetent person, treatment can be
discontinued. If the contact is immunocompromised and TBI cannot be excluded, after an
evaluation for TB disease, treatment should be continued to the completion of the regimen. If a
TST or IGRA result of a contact becomes positive, the regimen for TBI should be completed
after an evaluation for TB disease.

**Child Care and Schools.** Children with TB disease can attend school or child care if they are
receiving therapy (see Children in Group Child Care and Schools, p 116). They can return to
regular activities as soon as effective therapy has been instituted, adherence to therapy has been
documented, and clinical symptoms have diminished. Children with TBI can participate in all
activities whether they are receiving treatment or not.
BCG Vaccines. BCG vaccine is a live vaccine originally prepared from attenuated strains of *M. bovis*. Use of BCG vaccine\(^\text{22}\) is recommended by the Expanded Programme on Immunization of the World Health Organization for administration at birth (see Table 1.7, p 15). BCG is used in more than 100 countries to reduce the incidence of disseminated and other life-threatening manifestations of TB in infants and young children. Although BCG immunization appears to decrease the risk of serious complications of TB disease in children, the various BCG vaccines used throughout the world differ in composition and efficacy.

Two meta-analyses of published clinical trials and case-control studies concerning the efficacy of BCG vaccines concluded that BCG vaccine has relatively high protective efficacy (approximately 80%) against meningeal and miliary TB in children. The protective efficacy against pulmonary TB differed significantly among the studies, precluding a specific conclusion. Protection afforded by BCG vaccine in one meta-analysis was estimated to be 50%. Comparative evaluations of the BCG vaccine that is licensed in the United States for the prevention of TB disease versus other BCG vaccines globally have not been performed.

**Indications.** In the United States, administration of BCG vaccine should be considered only in limited and select circumstances, such as unavoidable risk of exposure to TB and failure or unfeasibility of other control methods. Recommendations for use of BCG vaccine for control of TB among children and health care personnel have been published by the Advisory Committee on Immunization Practices of the CDC and the Advisory Council for the Elimination of Tuberculosis.\(^\text{23}\) For infants and children, BCG immunization should be considered only for those

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\(^{22}\) www.bcgatlas.org

who have a negative TST result and who do not have contraindications in the following circumstances:

- The child is exposed continually to a person or people with contagious pulmonary TB resistant to isoniazid and rifampin and the child cannot be removed from this exposure, OR
- The child is exposed continually to a person or people with untreated or ineffectively treated contagious pulmonary TB and the child cannot be removed from such exposure or given antituberculosis therapy.

Careful assessment of the potential risks and benefits of BCG vaccine and consultation with personnel in local TB control programs are strongly recommended before use of BCG vaccine.

**Adverse Reactions.** Uncommonly (1%–2% of immunizations), BCG vaccine can result in local adverse reactions, such as subcutaneous abscess and regional lymphadenopathy, which generally are not serious. One rare complication, osteitis affecting the epiphysis of long bones, can occur as long as several years after BCG immunization. Disseminated fatal infection occurs rarely (approximately 2 per 1 million people), primarily in people who are severely immunocompromised, such as children with poorly controlled HIV infection or severe combined immunodeficiency. Antituberculosis therapy is recommended to treat osteitis and disseminated disease caused by BCG vaccine. Pyrazinamide is not believed to be effective against BCG and should not be included in treatment regimens.

Children with complications caused by BCG vaccine should be referred for management, if possible, to a TB expert and also should have consideration of evaluation for an immune deficiency.

**Contraindications.** People with burns, skin infections, and primary or secondary
immunodeficiencies should not receive BCG vaccine. The World Health Organization no longer recommends BCG in healthy children living with HIV infection, because an increasing number of cases of localized and disseminated BCG have been described in infants and children living with HIV infection. Use of BCG vaccine is contraindicated for people receiving immunosuppressive medications including high-dose corticosteroids (see Corticosteroids, p 809). Although no untoward effects of BCG vaccine on the fetus have been observed, immunization of women during pregnancy is not recommended.
Table 3.74. Definitions of Positive Tuberculin Skin Test (TST) Results in Infants, Children, and Adolescentsa,b

<table>
<thead>
<tr>
<th>Induration 5 mm or greater</th>
<th>Children in close contact with known or suspected contagious people with tuberculosis (TB) disease</th>
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<tbody>
<tr>
<td></td>
<td>Children suspected to have TB disease:</td>
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<tr>
<td></td>
<td>• Findings on chest radiograph consistent with active or previous TB disease</td>
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<tr>
<td></td>
<td>• Clinical evidence of TB diseasec</td>
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<tr>
<td></td>
<td>Children receiving immunosuppressive therapyd or with immunosuppressive conditions,</td>
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<tr>
<td></td>
<td>including human immunodeficiency (HIV) infection</td>
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<th>Induration 10 mm or greater</th>
<th>Children at increased risk of disseminated TB disease:</th>
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<tbody>
<tr>
<td></td>
<td>• Children younger than 4 y</td>
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<td></td>
<td>• Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus,</td>
</tr>
<tr>
<td></td>
<td>chronic renal failure, or malnutrition (see Table 3.75)</td>
</tr>
<tr>
<td></td>
<td>• Children born in high-prevalence regions of the world</td>
</tr>
<tr>
<td></td>
<td>• Children with significant travel to high-prevalence regions of the worlde</td>
</tr>
<tr>
<td></td>
<td>• Children frequently exposed to adults who are living with HIV, experiencing homelessness, or</td>
</tr>
<tr>
<td></td>
<td>incarcerated, or to people who inject or use drugs or have alcohol use disorder</td>
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</table>

| Induration 15 mm or greater | Children without any risk factors |

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b These definitions apply regardless of previous bacille Calmette-Guérin (BCG) immunization (see Testing for *M tuberculosis* Infection, p 791); erythema alone at TST site does not indicate a positive test result. Tests should be read at 48 to 72 hours after placement.

c Evidence by physical examination or laboratory assessment that would include tuberculosis in the working differential diagnosis (eg, meningitis).

d Including immunosuppressive doses of corticosteroids (see Corticosteroids, p 809) or tumor necrosis factor-alpha antagonists or blockers (see Biologic Response-Modifying Drugs Used to Decrease Inflammation, p 82) or immunosuppressive drugs used in transplant recipients (see Solid Organ Transplantation p 84).

e Some experts define significant travel as travel or residence in a country with an elevated TB rate for at least 1 month.
Table 3.75. Tuberculin Skin Test (TST) and IGRA Recommendations for Infants, Children, and Adolescents\textsuperscript{a}

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
</table>
| Children for whom immediate TST or IGRA is indicated\textsuperscript{b}:
| • Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation) |
| • Children with radiographic or clinical findings suggesting tuberculosis disease |
| • Children immigrating from countries with endemic infection (eg, Asia, Middle East, Africa, Latin America, countries of the former Soviet Union), including international adoptees |
| • Children with history of significant\textsuperscript{c} travel to countries with endemic infection who have substantial contact with the resident population\textsuperscript{d} |
| Children who should have annual TST or IGRA:                                    |
| • Children living with HIV infection                                            |

\textit{Children at increased risk of progression of TBI to TB disease:} Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, congenital or acquired immunodeficiencies, and children receiving tumor necrosis factor (TNF) antagonists, deserve special consideration. Underlying immune deficiencies associated with these conditions theoretically would enhance the possibility for progression to severe disease. Initial histories of potential exposure to tuberculosis should be included for all these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST or IGRA should be considered. \textbf{A TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged systemic corticosteroid administration, organ transplantation, use of TNF-alpha antagonists or blockers, or other immunosuppressive therapy in any child requiring these treatments.}

\textsuperscript{a} Bacille Calmette-Guérin (BCG) immunization is not a contraindication to a TST; IGRA is generally preferred for BCG-vaccinated children.
\textsuperscript{b} Beginning as early as 3 months of age for TST and 2 years of age for IGRAs, for TBI and disease.
\textsuperscript{c} Some experts define significant travel as birth, travel, or residence in a country with an elevated tuberculosis rate for at least 1 month.
\textsuperscript{d} If the child is well and has no history of exposure, the TST or IGRA should be delayed for 8 to 10 weeks after return.
### Table 3.76. Validated Questions for Determining Risk of TBI in Children in the United States

- Has a family member or contact had tuberculosis disease?
- Has a family member had a positive tuberculin skin test result?
- Was your child born in a high-risk country (countries other than the United States, Canada, Australia, New Zealand, or Western and North European countries)?
- Has your child traveled to a high-risk country? How much contact did your child have with the resident population?

TBI indicates *M. tuberculosis* infection.
Fig 3.16. Guidance on strategy for use of TST and IGRA for diagnosis of TBI in children with at least 1 risk factor, by age and BCG immunization status

*Criteria A
1. High clinical suspicion for TB disease and/or
2. High risk for infection, progression or poor outcome

*Criteria B
1. Additional evidence needed to ensure adherence and/or
2. Child healthy and at low risk and/or
3. NTM suspected
Table 3.77. Recommended Usual Treatment Regimens for Drug-Susceptible TB Infection and TB Disease in Infants, Children, and Adolescents

<table>
<thead>
<tr>
<th>Infection or Disease Category</th>
<th>Regimen</th>
<th>Remarks</th>
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<tbody>
<tr>
<td><strong>M. tuberculosis</strong> infection (positive TST or IGRA result, no disease)<strong>a</strong></td>
<td>12 weeks of isoniazid plus rifapentine, once a week</td>
<td>Most experts consider isoniazid-rifapentine to be the preferred regimen for treatment of TBI for children 25 years and older, and some experts prefer isoniazid-rifapentine therapy for TBI in children 2 years and older.</td>
</tr>
<tr>
<td>• Isoniazid susceptible</td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 mo of rifampin, once a day</td>
<td>Continuous daily therapy is required. Intermittent therapy even by DOT is not recommended.</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mo of isoniazid plus rifampin, once a day</td>
<td>To be considered if above 2 regimens are not feasible.</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 or 9 mo of isoniazid, once a day</td>
<td>If daily therapy is not possible, DOT twice a week can be used; medication doses differ with daily and twice-weekly regimens.</td>
</tr>
<tr>
<td>• Isoniazid resistant</td>
<td>4 mo of rifampin, once a day</td>
<td>Continuous daily therapy is required. Intermittent therapy even by DOT is not recommended.</td>
</tr>
<tr>
<td>• Isoniazid-rifampin resistant</td>
<td>Consult a tuberculosis specialist</td>
<td>Moxifloxacin or levofloxacin with or without ethambutol or pyrazinamide are most commonly given.</td>
</tr>
<tr>
<td>**Pulmonary and extrapulmonary disease (except meningitis)**b</td>
<td>If nonsevere pulmonary disease, c, 2 mo of rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) daily, followed by 2 mo of isoniazid and rifampin by DOT for hilar adenopathy only and the risk of drug resistance is low, a 6-</td>
<td>Some experts recommend a 3-drug initial regimen (isoniazid, rifampin, and pyrazinamide) if the risk of drug resistance is low. DOT is highly desirable.</td>
</tr>
</tbody>
</table>

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**Notes:**
- **a**: Most experts consider isoniazid-rifapentine to be the preferred regimen for treatment of TBI for children 25 years and older, and some experts prefer isoniazid-rifapentine therapy for TBI in children 2 years and older.
- **b**: Continuous daily therapy is required. Intermittent therapy even by DOT is not recommended.
- **c**: Consult a tuberculosis specialist.
- **d**: Moxifloxacin or levofloxacin with or without ethambutol or pyrazinamide are most commonly given.
### tubercle bacillus

**drug-susceptible *M tuberculosis***

If severe pulmonary disease, 2 mo of rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) daily or 3 times per week, followed by 4 mo of isoniazid and rifampin by DOT for drug-susceptible *M tuberculosis*

If severe or nonsevere pulmonary disease in a patient ≥12 years of age, an alternative regimen is 4 mo of isoniazid, rifapentine, pyrazinamide, and moxifloxacin daily

At least 9 mo of isoniazid and rifampin for *Mycobacterium bovis* susceptible to these drugs

**Meningitis**

2 mo of isoniazid, rifampin, pyrazinamide, and ethionamide, if possible, or an aminoglycoside or capreomycin, once a day; followed by 4–10 mo of isoniazid and rifampin, once a day or 3 times per week (9–12 mo total) for drug-susceptible *M tuberculosis*

At least 12 mo of therapy without pyrazinamide for *M bovis* susceptible to isoniazid and rifampin

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TST indicates tuberculin skin test; IGRA, interferon-gamma release assay; DOT, directly observed therapy.

*a* See text for comments and additional acceptable/alternative regimens.

*b* Duration of therapy may be longer for people living with HIV infection, and additional drugs and dosing intervals may be indicated (see Tuberculosis Disease and HIV Infection, p 809).
Nonsevere pulmonary disease is defined as tuberculosis confined to one lobe with no cavities or isolated intrathoracic adenopathy, no signs of miliary tuberculosis, no complex pleural effusion, and no clinically significant airway obstruction or peripheral lymph node tuberculosis.

Medications should be administered daily for the first 2 weeks to 2 months of treatment and then can be administered daily or 3 times per week by DOT; twice weekly is acceptable if resources for DOT are limited. Intermittent therapy is not recommended for people living with HIV infection.

If initial chest radiograph shows pulmonary cavities and/or sputum culture after 2 months of therapy remains positive, the continuation phase is extended to 7 months, for a total treatment duration of 9 months.

Parenteral streptomycin, kanamycin, or amikacin.

Many experts add a fluoroquinolone to this initial regimen.

When susceptibility to first-line drugs is established, the ethionamide, aminoglycoside (or capreomycin), and/or fluoroquinolone can be discontinued.

In children and adolescents with TB meningitis presumed to be drug susceptible, the WHO states that 6 months of isoniazid, rifampin, pyrazinamide, and ethionamide daily may be used, but the longer treatment regimen in this table is preferred.
### Table 3.78. Regimens and Dosages Used in Pediatric Patients With TB Infection (TBI)

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Dose and Age Group</th>
<th>Administration</th>
<th>Duration (months)</th>
<th>Age Restriction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INH + Rifapentine (3HP)</strong></td>
<td><strong>Age ≥12 y</strong>&lt;br&gt;INH: 15 mg/kg, rounded up to nearest 50 or 100 mg (max 900 mg)&lt;br&gt;Rifapentine (by weight):&lt;br&gt;10–14 kg: 300 mg&lt;br&gt;14.1–25 kg: 450 mg&lt;br&gt;25.1–32 kg: 600 mg&lt;br&gt;32.1–49.9 kg: 750 mg&lt;br&gt;≥50.0 kg: 900 mg</td>
<td>Weekly (SAT or DOT)</td>
<td>3</td>
<td>Not for children &lt;2 y</td>
<td>Take with food, containing fat if possible; pyridoxine for selected patients*</td>
</tr>
<tr>
<td><strong>Age 2–11 y</strong>&lt;br&gt;INH: 25 mg/kg, rounded up to nearest 50 or 100 mg (max 900 mg)&lt;br&gt;Rifapentine: see above</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rifampin (4R)</strong></td>
<td><strong>Adult</strong>: 10 mg/kg (max 600 mg)&lt;br&gt;<strong>Child</strong>: 15–20 mg/kg (max 600 mg)</td>
<td>Daily (SAT)</td>
<td>4</td>
<td>None</td>
<td>Drug-drug interactions</td>
</tr>
<tr>
<td><strong>INH + Rifampin</strong></td>
<td>Same doses as when drugs are used individually</td>
<td>Daily (SAT)</td>
<td>3</td>
<td>None</td>
<td>Not considered unless 3HP or 4R are not feasible</td>
</tr>
<tr>
<td><strong>INH</strong></td>
<td><strong>Adult</strong>: 5 mg/kg (max dose 300 mg)&lt;br&gt;<strong>Child</strong>: 10–15 mg/kg (max 300 mg)</td>
<td>Daily (SAT)</td>
<td>6 or 9</td>
<td>None</td>
<td>Seizures with overdose; pyridoxine for selected patients*</td>
</tr>
<tr>
<td><strong>Adult</strong>: 15 mg/kg (max dose 900 mg)&lt;br&gt;<strong>Child</strong>: 20–30 mg/kg (max 900 mg)</td>
<td>Twice weekly (DOT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


INH, isoniazid; DOT, directly observed therapy; SAT, self-administrated therapy.

* Exclusively breastfed infants and for children and adolescents on meat- and milk-deficient diets; children with nutritional deficiencies, including all symptomatic children living with HIV infection; and pregnant adolescents and women.
Table 3.79. Drugs for Treatment of Drug-Susceptible TB Disease in Infants, Children, and Adolescents

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dosage Forms</th>
<th>Daily Dosage (Range), mg/kg</th>
<th>Three Times per Week Dosage, mg/kg per Dose</th>
<th>Maximum Dose</th>
<th>Most Common Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin (^{a,b})</td>
<td>Vials, 500 mg and 1 g</td>
<td>15–30 mg/kg (intravenous or intramuscular administration)</td>
<td>1 g</td>
<td>Auditory and vestibular toxic effects, nephrotoxic effects</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Tablets 100 mg, 400 mg</td>
<td>20 (15–25)</td>
<td>50</td>
<td>Daily, 1 g Twice a week, 2.5 g</td>
<td>Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Tablets, 250 mg</td>
<td>15–20 mg/kg, given in 2–3 divided doses</td>
<td>1 g</td>
<td>Gastrointestinal tract disturbances, hepatotoxic effects, hypersensitivity reactions, hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Isoniazid (^{a,c})</td>
<td>Scored tablets 100 mg</td>
<td>10 (10–15) (^{b,d})</td>
<td>20–30</td>
<td>Daily, 300 mg</td>
<td>Mild hepatic enzyme elevation, hepatitis, (^{b,d}) peripheral neuritis, hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
<td></td>
<td></td>
<td>Twice a week, 900 mg</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin (^{a,e})</td>
<td>Tablets 250 mg, 500 mg</td>
<td>Adults: 750–1000 mg (once daily)</td>
<td>1 g</td>
<td>Hypersensitivity reactions; theoretical effect on growing cartilage, tendonitis, gastrointestinal tract disturbances, cardiac disturbances, peripheral</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Amikacin is usually administered intravenously or intramuscularly.

\(^{b}\) Amikacin is contraindicated in children under the age of 12 years.

\(^{c}\) Isoniazid is contraindicated in patients with a history of hepatitis or those with a positive hepatitis B surface antigen test.

\(^{d}\) Isoniazid is usually administered daily.

\(^{e}\) Levofloxacin is contraindicated in pregnant women and in children under the age of 18 years.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Form</th>
<th>Strength</th>
<th>Children</th>
<th>Adults</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moxifloxacin</strong>&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Tablet</td>
<td>400 mg</td>
<td>10 mg/kg (once daily)</td>
<td>400 mg</td>
<td>Hypersensitivity reactions; theoretical effect on growing cartilage; tendonitis, gastrointestinal tract disturbances, cardiac disturbances, peripheral neuropathy, rash, headache, restlessness, confusion; can prolong QTc interval</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>400 mg/250 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pyrazinamide</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Scored tablets</td>
<td>500 mg</td>
<td>35 (30–40)</td>
<td>50</td>
<td>2 g</td>
<td>Hepatotoxic effects, hyperuricemia, arthralgia, gastrointestinal tract upset, pruritus, rash</td>
</tr>
<tr>
<td><strong>Rifampin</strong>&lt;sup&gt;ac&lt;/sup&gt;</td>
<td>Capsules</td>
<td>150 mg</td>
<td>15–20&lt;sup&gt;d&lt;/sup&gt;</td>
<td>15–20&lt;sup&gt;d&lt;/sup&gt;</td>
<td>600 mg</td>
<td>Orange discoloration of secretions or urine, staining of contact lenses, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus; oral contraceptives may be ineffective</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syrup formulated capsules</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> These drugs do not have an indication from the US Food and Drug Administration (FDA) for treatment of TB.

<sup>b</sup> Dose adjustment in renal insufficiency.

<sup>ac</sup> Rifamate is a capsule containing 150 mg of isoniazid and 300 mg of rifampin. Two capsules provide the usual adult (greater than 50 kg) daily doses of each drug. Rifater, in the United States, is a capsule containing 50 mg of isoniazid, 120 mg of rifampin, and 300 mg of pyrazinamide. Isoniazid and rifampin also are available for parenteral administration.

<sup>bd</sup> When isoniazid in a dosage exceeding 10 mg/kg/day is used in combination with rifampin, the incidence of hepatotoxic effects may be
Levofloxacin and moxifloxacin are not approved for use in children younger than 18 years; its use in younger children necessitates assessment of the potential risks and benefits (see Antimicrobial Agents and Related Therapy, p 863).

Many experts recommend using a daily rifampin dose of 20–30 mg/kg/day for infants and toddlers and for serious forms of tuberculosis, such as meningitis and disseminated disease.
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dosage, Forms</th>
<th>Daily Dosage</th>
<th>Maximum Dose</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Vials, 500 mg and 1 g</td>
<td>15–30 mg/kg (intravenous or intramuscular administration)</td>
<td>1 g</td>
<td>Auditory and vestibular toxic effects, nephrotoxic effects</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>Tablets, 100 mg</td>
<td>Children ≥5 y: ≥15 kg through &lt;30 kg: 200 mg daily for first 2 wk, then 100 mg 3 times/wk with 48 h between doses for wk 3-24 ≥30 kg: 400 mg daily for first 2 wk, then 200 mg 3 times/wk with 48 h between doses for wk 3-24</td>
<td>400 mg</td>
<td>Arthralgia, nausea, abdominal pain, headache; can prolong QTc interval, can elevate hepatic enzymes</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Vials, 1 g</td>
<td>15–30 mg/kg (intramuscular administration)</td>
<td>1 g</td>
<td>Auditory and vestibular toxicity and nephrotoxic effects</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Capsules, 250 mg</td>
<td>10–20 mg/kg, given in 2 divided doses</td>
<td>1 g</td>
<td>Psychosis, personality changes, seizures, rash</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Tablets, 250 mg</td>
<td>15–20 mg/kg, given in 2–3 divided doses</td>
<td>1 g</td>
<td>Gastrointestinal tract disturbances, hepatotoxic effects, hypersensitivity reactions, hypothyroidism</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Vials 75 mg/2 mL</td>
<td>15–30 mg/kg (intramuscular or intravenous)</td>
<td>1 g</td>
<td>Auditory and vestibular toxic effects, nephrotoxic effects</td>
</tr>
<tr>
<td>Drugs</td>
<td>Dosage, Forms</td>
<td>Daily Dosage</td>
<td>Maximum Dose</td>
<td>Adverse Reactions</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------------------------</td>
<td>---------------------------</td>
<td>--------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>500 mg/2 mL 1 g/3 mL</td>
<td>administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin&lt;sup&gt;b,e&lt;/sup&gt;</td>
<td>Tablets 250 mg 500 mg 750 mg</td>
<td>Adults: 750–1000 mg (once</td>
<td>1 g</td>
<td>Hypersensitivity reactions; theoretical effect on growing cartilage, tendonitis, gastrointestinal tract disturbances, cardiac disturbances, peripheral neuropathy, rash, headache, restlessness, confusion; can prolong QTc interval</td>
</tr>
<tr>
<td></td>
<td>Oral solution 25 mg/mL Vials</td>
<td>Children: 15–20 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg/mL 25 mg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid&lt;sup&gt;b,f&lt;/sup&gt;</td>
<td>Adults: 600 mg (once daily)</td>
<td>600 mg</td>
<td></td>
<td>Used for treatment of multidrug-resistant TB; adverse events include bone marrow suppression</td>
</tr>
<tr>
<td></td>
<td>Children &lt;10 y: 10 mg/kg/dose,</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>every 12 h Children ≥10 y: 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mg/kg/dose daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin&lt;sup&gt;b,e&lt;/sup&gt;</td>
<td>Tablet 400 mg Intravenous 400</td>
<td>Adults: 400 mg (once daily)</td>
<td>400 mg</td>
<td>Hypersensitivity reactions; theoretical effect on growing cartilage; tendonitis, gastrointestinal tract disturbances, cardiac disturbances, peripheral neuropathy, rash, headache, restlessness, confusion; can prolong QTc interval</td>
</tr>
<tr>
<td></td>
<td>mg/250 mL</td>
<td>Children: 10 mg/kg (once</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>daily)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>200–300 mg/kg (2–4 times a day)</td>
<td></td>
<td>10 g</td>
<td>Gastrointestinal tract disturbances, hypersensitivity, hepatotoxic effects, hypothyroidism</td>
</tr>
<tr>
<td>Paraaminosalicylic acid (PAS)</td>
<td>Packets, 3 g</td>
<td>20–40 mg/kg (intramuscular</td>
<td>1 g</td>
<td>Auditory and vestibular toxic effects, nephrotoxic effects and rash</td>
</tr>
<tr>
<td></td>
<td>Vials 1 g</td>
<td>administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Dosage, Forms</td>
<td>Daily Dosage</td>
<td>Maximum Dose</td>
<td>Adverse Reactions</td>
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</tr>
<tr>
<td></td>
<td>4 g</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* These drugs should be used in consultation with a specialist in TB.

*b* These drugs do not have an indication from the US Food and Drug Administration (FDA) for treatment of TB.

*c* Dose adjustment in renal insufficiency; capreomycin and kanamycin are not recommended for longer individualized regimens of multidrug-resistant TB.

*d* Bedaquiline is not FDA-approved for use in children <18 years. It has been used for children ≥12 years and ≥30 kg together with 4 other drugs for which the patient’s MDR TB isolate is likely to be susceptible; safety and efficacy have not established in children <12 years. Use with caution in end-stage renal impairment.

*e* Levofloxacin and moxifloxacin are not approved for use in children younger than 18 years; its use in younger children necessitates assessment of the potential risks and benefits (see Antimicrobial Agents and Related Therapy, p 863).

*f* Linezolid pharmacokinetics have not been well established in children. The doses listed will yield a drug exposure approximately equal to that in adults taking 600 mg daily.
Table 3.81. People at Increased Risk of Drug-Resistant Tuberculosis Infection or Disease

| People with a history of treatment for tuberculosis disease (or whose source case for the contact received such treatment) |
| Contacts of a patient with drug-resistant contagious tuberculosis disease |
| People from countries with high prevalence of drug-resistant tuberculosis, such as Russia and certain nations of the former Soviet Union, Asia, Africa, and Latin America |
| Infected people whose source case has positive smears for acid-fast bacilli or cultures after 2 months of appropriate antituberculosis therapy and patients who do not respond to a standard treatment regimen |
| Residence in geographic area with a high percentage of drug-resistant isolates |