Chapter 12
Pediatric Tuberculosis and LTBI:
Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI) and Tuberculosis Disease in Children (under 15 years of age)

CONTENTS

Introduction

Purpose

Pediatric patients are **under 15 years** of age.

Use this section to understand and follow national and Nevada guidelines to

- detect and diagnose latent tuberculosis infection (LTBI) in children.
- detect and diagnose TB disease in children.
- know when to report suspected or confirmed cases of TB in children.
- follow basic treatment principles for latent tuberculosis infection and TB disease in children.
- select appropriate pediatric treatment regimens, dosages, and duration.
- monitor pediatric patients for side effects and adverse reactions.
- assess pediatric patients' response to treatment.
- determine completion of therapy for pediatric patients

Children, especially infants, because of immature immune function are at increased risk of progressing rapidly to active and sometimes severe TB disease after they become infected.

The diagnosis of TB in children, especially in children under 5 years of age, can be difficult because they often have nonspecific signs and symptoms and a small number of mycobacteria. Clinical symptoms, when present, may include fever, delayed growth of child, weight loss or poor weight gain, cough, night sweats, and chills.

Identification of a young child with TB usually indicates recent transmission from an infectious adult with TB. It is considered a sentinel event needing urgent and careful investigation.

All children suspected or diagnosed with active tuberculosis or LTBI should have a PHN Case Manager assigned.

Call your local TB Program for consultation regarding the evaluation and treatment of pediatric patients with TB and LTBI. For contact information, see Chapter 1, *Introduction*, in "Roles, Responsibilities, and Contact Information," pages 1.21 to 1.22.

For complicated pediatric TB cases, consult the Curry International Tuberculosis Center Warm line at: 415-502-4700 or 877-390-6682

Report suspected and confirmed cases of pediatric tuberculosis disease to the Nevada Division of Public and Behavioral Health TB Program at 775-684-5936, FAX 775-684-5999.

Background

Pediatric TB is defined by the World Health Organization and the U.S. Centers for Disease Control and Prevention as TB in children less than 15 years of age. Pediatric TB presents unique challenges. Infants and children are at increased risk of progression to active disease if infected. Unlike adults and older adolescents who most commonly have reactivation disease, TB disease in infants and children is usually related to primary TB, and this may occur quickly after they become infected. Infants and children have less specific signs and symptoms of disease, some are asymptomatic. The clinical manifestations and radiographic abnormalities seen in children are influenced more by the host inflammatory reaction than by the number of organisms. Administration of TB medications to infants and children is often difficult. It is also important to remember that pediatric TB is a sentinel event, reflecting recent infection from an infectious, often undiagnosed, source case in the community.

Pathogenesis of TB

Most children become infected with tuberculosis by inhaling droplet nuclei containing *Mycobacterium tuberculosis (M. tuberculosis)* bacteria that have been expelled by coughing persons with infectious pulmonary or laryngeal TB. Inhaled bacteria are taken up by alveolar macrophages and, if not immediately destroyed, may cause an initial "primary" pulmonary infection that consists of a small focus in the lung parenchyma that spreads via local lymphatics to regional lymph nodes. When all age groups are taken into account, most recent infection is asymptomatic and does not result in disease--the primary focus heals, and the bacteria continue to survive in a dormant state that is referred to as latent TB infection (LTBI). But in young children under five years of age and in children with immune deficiencies, there may be no latent period and the primary infection may progress. There may also be complications related to enlargement of the area of infection in the lung parenchyma or regional lymph nodes causing wheezing, pneumonia, or atelectasis by compressing or eroding through a bronchus.

Primary TB infection is usually accompanied by an occult, subclinical bacteremia that seeds distant sites, including the apices of the lungs, the lymph nodes and the central nervous system. In young children and children with immune disorders, severe TB disease, for example, disseminated (miliary) TB or TB meningitis, sometimes quickly follows the primary infection, even in the weeks before development of a positive Mantoux tuberculin skin test (TST). This is the reason why "window period prophylaxis" with isoniazid is recommended for exposed young children and immunocompromised children until infection can be excluded.

The risk of progression to TB disease following primary infection is mainly related to the age and immune status of the child. The risk is highest in young children under two to three years of age and immunocompromised children.[1] Table 1, below, "Average Age-specific Risk for Disease Development after Untreated Primary Infection," illustrates risk and age. Studies show that disease develops within 1 to 2 years in 40% to 50% of infants with untreated TB infection compared to 15% among older children. Other conditions associated with increased risk of progression include human immunodeficiency virus (HIV) infection; use of immunosuppressive drugs, such as prolonged or high-dose corticosteroid therapy or chemotherapy; intravenous drug use; and certain diseases or medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, and malnutrition. There have been reports of tuberculosis disease in adolescents being treated for arthritis with tumor necrosis factor (TNF) antagonists, such as infliximab and etanercept.

Table 1: **AVERAGE AGE-SPECIFIC RISK FOR DISEASE DEVELOPMENT AFTER UNTREATED PRIMARY INFECTION**[2]

Age at primary infection	Manifestations of disease	Risk of disease (%)
<1 year	No disease	50
	Pulmonary disease	30-40
	TB meningitis or miliary disease	10-20
1-2 years	No disease	70-80
	Pulmonary disease	10-20
	TB meningitis or miliary disease	2-5
2-5 years	No disease	95
	Pulmonary disease	5
	TB meningitis or miliary disease	0.5
5-10 years	No disease	98
	Pulmonary disease	2
	TB meningitis or miliary disease	<0.5
> 10 years	No disease	80-90
	Pulmonary disease	10-20
	TB meningitis or miliary disease	<0.5

Latent Tuberculosis Infection (LTBI)

Diagnosis of latent TB infection

Latent TB infection (LTBI) is defined as M. tuberculosis infection in an asymptomatic person who has a positive Mantoux TST skin test or a positive interferon gamma release assay test (IGRA), no physical findings of disease, and chest radiograph findings that are normal or reveal evidence of healed infection, for example, granulomas or calcification in the lung, hilar lymph nodes, or both.

Mantoux Tuberculin Skin Testing (TST)

The Mantoux TST is the most commonly used method used in Nevada for identifying TB infection in children under 5 years. In children, the TST is an important part of the clinical case definition of TB, but it is important to remember that children with active TB may have a negative TST. This is especially true for infants under six months of age and for infants and children with immune disorders.

A negative TST does not guarantee that a child does not have latent TB infection or TB disease.

Candidates for Testing

Testing is recommended for children at high risk of LTBI or progression of LTBI to TB disease. Some examples are children who are contacts of a known case of TB, children with suspected active disease, children with known risk factors for progression of infection to disease, children traveling or residing for 3 months or longer in an area with a high incidence of TB, and children who arrived in United States from countries with a high TB incidence within the previous 2 years.

The American Academy of Pediatrics Committee on Infectious Diseases recommends testing of infants, children, and adolescents from several high-risk groups. These recommendations are summarized in Table 2 below.

TST Recommendations for Infants, Children, and Adolescents

See the following table, Table 2, Tuberculin skin test (TST) and IGRA recommendations for infants, children, and adolescents, page 12.5.

Table 2: **TUBERCULIN SKIN TEST (TST) AND IGRA RECOMMENDATIONS FOR INFANTS, CHILDREN, AND ADOLESCENTS** *

Children for whom immediate TST or IGRA is indicated**

- Contacts of people with confirmed or suspected infectious tuberculosis (contact investigation)
- Children with radiographic or clinical findings suggesting tuberculosis disease
- Children immigrating from countries with endemic infection (e.g., Asia, Middle East, Africa, Latin America, countries of the former Soviet Union) including international adoptees
- Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries***

Children who should have annual TST or IGRA:

- Children infected with HIV infection (TST only)

Children at increased risk of progression of LTBI to tuberculosis 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. Without recent exposure, these people are not at increased risk of acquiring *M. tuberculosis* infection. 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 of these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST or IGRA should be considered. **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.**

*Bacille Calmette-Guérin (BCG) immunization is not a contraindication to a TST.

**Beginning as early as 3 months of age for TST, 3 years of age for IGRAs for LTBI and disease.

***If the child is well and has no history of exposure, the TST or IGRA should be delayed for up to 10 weeks after return.

Definitions of abbreviations: IGRA indicates interferon-gamma release assay; HIV, human immunodeficiency virus; LTBI, latent *M. tuberculosis* infection.

Source: American Academy of Pediatrics. [Tuberculosis] In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases.* 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:[p.812].

Administration and Interpretation of the Tuberculin Skin Test

TSTs need to be administered and interpreted by experienced health care professionals who received appropriate training. Administration and interpretation by unskilled persons or family members are unreliable and may lead to errors in placement and interpretation.

The Mantoux method consists of 5 tuberculin units of purified protein derivative (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 visible wheal 6 to 10 mm in diameter is crucial to accurate testing.

The recommended time for assessing the TST result is 48 to 72 hours after administration. However, a reaction that develops at the site of administration more than 72 hours later should be measured and considered the result. The diameter of induration in millimeters is measured transversely to the long axis of the forearm.

Only the Mantoux TST should be used. Multiple puncture tests are not sufficiently accurate and should not be used.

History of BCG vaccination is not a contraindication to TST.

A TST can be administered before or at the same time as inactive and live-virus vaccines, including measles-containing vaccine and varicella vaccine. TST has no effect on the response to MMR vaccination. However, measles vaccine and mumps, rubella, and varicella vaccines may transiently suppress the TST in a person infected with *M. tuberculosis*. Simultaneously administering TST and live virus vaccine does not interfere with reading the TST at 48 to 72 hours. If the live virus vaccine has already been administered, the TST should be deferred for four to six weeks.[3]

Approximately 10% to 15% of immunocompetent children with culture-documented disease do not react initially to a TST. Host factors, such as young age, poor nutrition, immunosuppression, other viral infections (especially measles, varicella, and influenza), recent tuberculosis infection, and disseminated tuberculosis disease can decrease TST reactivity. Many children and adults co-infected with HIV and *M. tuberculosis* do not react to a TST. Control skin tests to assess cutaneous anergy are not recommended routinely.

Classification of TST results are based on epidemiologic and clinical factors. The size of induration (mm) required for a positive result varies with the person's risk of LTBI and progression to tuberculosis disease. Table 3, below, summarizes the size of reaction and interpretation of results for children.

The interpretation of TST results in children who have received BCG vaccination is the same as for persons who have **not** received BCG vaccine. For more information, see the BCG Section that follows.

The Nevada TB Program recommends prompt clinical and radiographic evaluation of all children and adolescents with positive TST reactions. For children under 5 years of age with positive TST or IGRAs a two-view chest radiograph is required; PA (posterior/anterior) and lateral.

LTBI in children under 5 years of age is a Reportable condition under Nevada law, NAC 441A.350.

Table 3: **DEFINITIONS OF POSITIVE TUBERCULIN SKIN TEST (TST) RESULTS IN INFANTS, CHILDREN, AND ADOLESCENTS ***

Induration 5 mm or greater

Children in close contact with known or suspected contagious people with tuberculosis disease

Children suspected to have tuberculosis disease:

- Findings on chest radiograph consistent with active or previous tuberculosis disease
- Clinical evidence of tuberculosis disease**

Children receiving immunosuppressive therapy*** or with immunosuppressive conditions, including human immunodeficiency (HIV) infection

Induration 10 mm or greater

Children at increased risk of disseminated tuberculosis disease:

- Children younger than 4 years
- Children with other medical conditions, including Hodgkin's disease lymphoma, diabetes mellitus, chronic renal failure or malnutrition (see table 2)

Children with likelihood of increased exposure to tuberculosis disease:

- Children born in high-prevalence regions of the world
- Children who travel to high-prevalence regions of the world
- Children frequently exposed to adults who are HIV infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated, or institutionalized

Induration 15 mm or greater

Children age 4 years or older without any risk factors

*****These definitions apply regardless of bacilli Calmette-Guerin(BCG) immunization (see table 2, page 12.6). Erythema alone at TST site does not indicate a positive test result. Tests should be read at 48 to 72 hours after placement.

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

*** Including immunosuppressive doses of corticosteroids or tumor necrosis factor-alpha antagonists or blockers.

Adapted from American Academy of Pediatrics. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 25th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:642–660.

Interferon-Gamma Release Assays

New tests referred to as interferon-gamma release assays (IGRAs) are an alternative to the tuberculin skin test. One advantage of these tests over the TST is that they are unaffected by BCG vaccination and infections with common non-tuberculous mycobacteria. Two examples are the QuantiFERON-TB Gold In Tube (QFT-GIT) test and the T-SPOT TB test. [4,5]

These tests involve incubation of peripheral blood T-lymphocytes with antigens that are specific to *M. tuberculosis*. If an individual has been infected with *M. tuberculosis,* his or her T-lymphocytes will respond to the antigens by releasing interferon gamma. The sensitivity of IGRAs is similar to that of TST for detecting infection in adults with untreated culture-confirmed tuberculosis. The specificity of IGRAs is higher than that for TSTs, because the antigens used are not found in BCG or most nontuberculous mycobacteria.[6]

Although these tests are approved by the FDA and recommended by the CDC for use in adults in all circumstances in which the TST is used, the TST remains the test of choice for children under the age of 2, per the American Academy of Pediatrics Committee on Infectious Diseases publication, *2018 Red Book*.[7]

As with TSTs, IGRAs cannot distinguish between latent infection and disease, and a negative result from these tests cannot exclude the possibility of tuberculosis infection or disease in a patient with findings that raise suspicion for these conditions.

IGRAs are recommended by the Centers for Disease Control and Prevention, and some experts prefer IGRAs for use in adults in all circumstances in which a TST is used. The published experience with testing children with IGRAs is less extensive than for adults, but a number of studies have demonstrated that IGRAs perform well in most children 4 years of age and older.[8]

According to the American Academy of Pediatrics Committee on Infectious Diseases, neither an IGRA nor the TST can be considered a 'gold standard' for diagnosis of LTBI. Current recommendations for use of IGRAs in children can be summarized as follows:

- For immunocompetent children 2 years of age and older (updated 2018), IGRAs can be used in place of a TST to confirm cases of tuberculosis or cases of LTBI and likely will yield fewer false- positive test results.
- Children with a positive result from an IGRA should be considered infected with *M tuberculosis* complex. A negative IGRA result cannot universally be interpreted as absence of infection.
- Because of their higher specificity and lack of cross-reaction with BCG, IGRAs are the preferred tests in asymptomatic children older than 2 years of age who have been immunized against BCG.
- IGRAs may be useful to determine whether a BCG-immunized child with a reactive TST more likely has LTBI or has a false-positive TST reaction caused by the BCG. In general, if the IGRA result is negative and the TST result is positive in an asymptomatic child, the diagnosis of LTBI is unlikely.[9]
- IGRAs cannot be recommended routinely for use in children younger than 2 years of age or for immune-compromised children of any age because of a lack of published data about their utility with these groups.
- Indeterminate IGRA results do not exclude tuberculosis infection and should not be used to make clinical decisions.[10]

BCG Vaccine

BCG (bacille Calmette-Guérin) vaccine is a live virus vaccine prepared from attenuated strains of *Mycobacterium bovis*. BCG vaccine is widely used in many countries to protect infants and children against severe forms of TB disease, including miliary TB and TB meningitis. Use of BCG vaccine is recommended by the Expanded Programme on Immunizations of the World Health Organization (WHO) for administration at birth and is currently used in more than 160 countries.[11]

BCG vaccination has been shown to have relatively high protective efficacy (approximately 80%) against the severe forms of TB disease, meningeal and miliary tuberculosis, in children. The protective efficacy against milder forms of TB disease is less clear; for pulmonary TB, the measured efficacy varies significantly, from 0% to 50% in different studies.[12]

BCG is not generally recommended for use in the United States because of the low risk of infection with *M. tuberculosis*, the variable effectiveness of the vaccine against pulmonary TB, and the vaccine's potential interference with tuberculin skin test reactivity.[13]

BCG vaccination can produce a false-positive reaction to the TST. However, most children vaccinated in infancy show no reaction on subsequent TST testing and less than 10% of vaccinated children have a TST reaction ≥10 mm.[14] Children who receive BCG after infancy or those who receive more than one BCG immunization are more likely to have a positive TST.

Children born in countries with high rates of TB disease are likely to have received BCG immunization in infancy, but they are also more likely to have a positive TST from TB infection than from BCG immunization.[15]

Generally, interpretation of TST results in BCG recipients is the same as for children who have not received the BCG vaccine. A history of vaccination with BCG should not influence the interpretation of the TST reaction or clinical decisions regarding the management of children who are TST positive. Two possible exceptions are when BCG was given within the last 12 months and when the patient is from a low-incidence country.[16]

All children with a positive TST should be promptly evaluated, regardless of BCG immunization status. Tuberculosis disease should be suspected strongly in any symptomatic child with a positive TST result regardless of history of BCG immunization. TST-positive children from countries where TB is common are likely to be infected with TB and are at risk of developing active TB disease, even if they have been vaccinated with BCG.[17]

For some children, such as children recently immunized with BCG vaccine, children with documented multiple BCG immunizations or children who immigrated from a country with a low prevalence of TB, treatment for LTBI may not be indicated. In such cases follow up should include patient education and awareness of the signs and symptoms of tuberculosis disease.

Management of Children with a Positive TST or IGRA

The most efficient way to prevent pediatric TB is to evaluate and treat those children exposed to an infectious adult source case.

1. ALL infants, children, and adolescents with a newly positive TST or IGRA should promptly undergo clinical evaluation to rule out active TB disease.

The evaluation should include a history to determine the presence of symptoms of TB disease or coexisting medical conditions that could complicate medical therapy for LTBI or increase the risk of progression to TB disease; a physical examination, and a posterior-anterior (PA) chest radiograph. For children under 5 years of age, a lateral chest x-ray is also recommended for better visualization of hilar node enlargement.

Latent tuberculosis infection (LTBI) is defined as *M. tuberculosis* infection in a person who has a positive TST or IGRA test, no physical findings of disease, and chest radiograph findings that are normal or reveal evidence of healed infection (e.g. granulomas or calcification in the lung, hilar lymph nodes, or both).

2. ALL infants, children, and adolescents who have a positive TST or IGRA result but no evidence of TB disease should promptly receive treatment for LTBI.

Why treat children with latent TB infection (LTBI)? Children who have LTBI are the reservoir for future TB disease; hence, pediatric LTBI treatment is imperative to prevent TB disease and transmission in the future. Prompt treatment is especially important for children under 5 years of age who are at increased risk of rapid progression to active TB.

All infants, children, and adolescents who have a positive TST or IGRA result but no evidence of tuberculosis disease and who never have received antituberculosis therapy should receive treatment to prevent development of disease, unless a specific contraindication exists.

Treatment of Latent TB Infection (LTBI)

Do not start treatment for LTBI before ruling out TB disease.

Isoniazid (INH) for 9 months is the traditional regimen for children under 12 years without a known source case or with a source case whose *M. tuberculosis* isolate is susceptible to INH. Isoniazid can be administered daily, or twice weekly if directly observed therapy (DOT) is utilized. Twice weekly treatment by DOT is an excellent method for promoting adherence to treatment. However, recent studies have demonstrated the effectiveness of short-course LTBI regimens in children > 2 years of age. The CDC has recently (February 2020) updated its recommended LTBI regimens (see Table 4) and advocates for short-course treatments, when not contraindicated. The regimens are summarized on the CDC's LTBI webpage, https://www.cdc.gov/tb/topic/treatment/ltbi.htm, and are reviewed for recommendation "Grade" based on quality of evidence in the publication, "Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020"; Sterling TR, Njie G, Zenner D, et al. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep 2020;69(No. RR-1):1–11. DOI: http://dx.doi.org/10.15585/mmwr.rr6901a1.

Daily rifampin (RIF) for 4 months is a suitable alternative for children with LTBI who have been exposed to a source case whose *isolate is resistant to INH* but susceptible to rifampin, or for those who cannot tolerate INH.

CDC guidelines published in 2018 updated the 12-week INH-Rifapentine (3HP) regimen recommendations to include use in children 2-12 years of age (previously, recommended ≥12 years of age). This regimen is for isoniazid and rifapentine once weekly by directly observed therapy (DOT) *recommended*, or parental administered self-administered therapy (SAT) for 12 weeks.[19]

The care and treatment of children exposed to a source case with a multidrug-resistant (MDR) *M. tuberculosis* strain should include consultation with an expert in the management of pediatric MDR TB, along with DOT for therapy management.

Before initiating therapy, it is important to educate patients and families regarding signs and symptoms of hepatotoxicity and other side effects and what to do should side effects be noted.

During treatment for LTBI, children should be evaluated monthly to reinforce adherence, evaluate for toxicities, and assess possible progression to TB disease.

LTBI Treatment Regimens

Table 4 **Dosages for Recommended Latent Tuberculosis Infection Treatment Regimens** [20]

Drug	Duration	Dose and age group	Frequency	Total doses
Isoniazid* and rifapentine†	3 mos	**Adults and *children aged ≥12 yrs***	Once weekly	12
		Isoniazid: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum		
		Rifapentine:		
		10–14.0 kg, 300 mg		
		14.1–25.0 kg, 450 mg		
		25.1–32.0 kg, 600 mg		
		32.1–49.9 kg, 750 mg		
		≥50.0 kg, 900 mg maximum		
		Children aged 2–11 yrs		
		Isoniazid*: 25 mg/kg; 900 mg maximum		
		Rifapentine†: see above		
Rifampin¶	4 mos	**Adults:** 10 mg/kg	Daily	120
		Children: 15–20 mg/kg**		
		Maximum dose: 600 mg		
Isoniazid* and rifampin¶	3 mos	**Adults**	Daily	90
		Isoniazid*: 5 mg/kg; 300 mg maximum		
		Rifampin¶: 10 mg/kg; 600 mg maximum		
		Children		
		Isoniazid*: 10–20 mg/kg††; 300 mg maximum		
		Rifampin¶: 15–20 mg/kg; 600 mg maximum		
Isoniazid*	6 mos	**Adults:** 5 mg/kg	Daily	180
		Children: 10–20 mg/kg††		
		Maximum dose: 300 mg		
		Adults:15 mg/kg	Twice weekly§	52
		Children: 20–40 mg/kg††		
		Maximum dose: 900 mg		
	9 mos	**Adults:** 5 mg/kg	Daily	270
		Children: 10–20 mg/kg††		
		Maximum dose: 300 mg		
		Adults: 15 mg/kg	Twice weekly§	76
		Children: 20–40 mg/kg††		
		Maximum dose: 900 mg		

Source: CDC, "Guidelines for Treatment of Latent Tuberculosis Infection, 2020." MMWR Recomm Rep 2020;69(No. RR-1):1–11. DOI: http://dx.doi.org/10.15585/mmwr.rr6901a1

* Isoniazid is formulated as 100-mg and 300-mg tablets.

† Rifapentine is formulated as 150-mg tablets in blister packs that should be kept sealed until use.

§ Intermittent regimens must be provided via directly observed therapy (i.e., a health care worker observes the ingestion of medication).

¶ Rifampin (rifampicin) is formulated as 150-mg and 300-mg capsules.

** The American Academy of Pediatrics acknowledges that some experts use rifampin at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers (**Source:** American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:829–53).

†† The American Academy of Pediatrics recommends an isoniazid dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice-weekly regimen.

TABLE 5. Summary of Evidence and Recommendations for regimens to treat latent tuberculosis infection[21]

Priority rank*	Regimen	Recommendation (strong or conditional)	Evidence (high, moderate, low, or very low)
Preferred	3 mos isoniazid plus rifapentine given once weekly	Strong	Moderate
Preferred	4 mos rifampin given daily	Strong	Moderate (HIV negative)†
		Conditional	Very low (HIV negative)
Preferred	3 mos isoniazid plus rifampin given daily	Conditional	Low (HIV positive)
		Strong§	Moderate (HIV negative)
Alternative	6 mos isoniazid given daily	Conditional	Moderate (HIV positive)
Alternative	9 mos isoniazid given daily	Conditional	Moderate

Abbreviation: HIV = human immunodeficiency virus.
* *Preferred:* excellent tolerability and efficacy, shorter treatment duration, higher completion rates than longer regimens and therefore higher effectiveness; *alternative:* excellent efficacy but concerns regarding longer treatment duration, lower completion rates, and therefore lower effectiveness.
† No evidence reported in HIV-positive persons.
§ Strong recommendation for those persons unable to take a preferred regimen (e.g., due to drug intolerability or drug-drug interactions).

Table 6: RECOMMENDATIONS AND CONSIDERATIONS FOR USING THE 12-WEEK ISONIAZID-RIFAPENTINE REGIMEN[22]

Consider the regimen for:	Regimen is NOT recommended for:	Comments:
▪ Healthy persons 12 years or older ▪ Recently exposed contacts of infectious TB and new TB converters ▪ Persons with radiographic findings of healed pulmonary TB ▪ HIV infected persons who are not taking antiretroviral medications	▪ Children younger than 2 years of age ▪ People with HIV/AIDS who are taking antiretroviral treatment ▪ People presumed to be infected with INH or RIF-resistant M. tuberculosis ▪ Pregnant women or women expecting to become pregnant within the 12–week treatment ▪ Individuals who had prior adverse events or hypersensitivity to rifampin	▪ Therapy may be considered in children ages 2-12 on a case by case basis

Source: CDC. Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection. MMWR 2011; 60(48); 1650

For consultation regarding the treatment of LTBI, call the local health authority in your county.

Expert consultation with a pediatric TB specialist should be obtained for children judged to be infected with a multidrug-resistant strain of *M. tuberculosis* or infected with HIV.

Children who are at especially **high risk for progression to TB disease**, and either are suspected of nonadherence or, are on an intermittent (e.g. twice weekly) dosing regimen, should be **treated using DOT**. This method of treatment is especially appropriate when a household member is on DOT for TB disease, or the child attends institutions or facilities (schools) where a staff member can observe treatment. DOT is highly recommended for 12-week INH-Rifapentine (3HP) regimen.

Dosages for LTBI Treatment Regimens

Once the appropriate regimen has been identified, refer to Table 6 for instructions on dosages for each drug. The information in Table 6 is taken from ATS, CDC, and Infectious Diseases Society of America (IDSA) guidelines.

Table 7: **RECOMMENDED DOSAGES[23,24]**

Drug	Preparation	Adults/ Children*	Daily	Twice a Week
INH	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 ml)	Adults (max.)	5 mg/kg (300 mg)	15 mg/kg (900 mg)
		Children (max.)	10–15 mg/kg (300 mg)	20–30 mg/kg (900 mg)
RIF	Capsule (150 mg, 300 mg); powder may be suspended for oral administration	Adults (max.)	10 mg/kg (600 mg)	10 mg/kg (600 mg)
		Children (max.)	10–20 mg/kg (600 mg)	10–20 mg/kg (600 mg)
Definitions of abbreviations; INH = isoniazid; RIF = rifampin.				

*Children weighing >40 kg (88 pounds) should be dosed as adults

Source: ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):4; CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):28–29.

Table 8: **RECOMMENDED DOSAGE FOR THE NEW COMBINATION INH/RPT 12 WEEK REGIMEN FOR TREATMENT OF LTBI BY DOT[25].**

Drug	Preparations	Dosages (≥12 years of age)	Once a Week Maximum dose
INH (Isoniazid)	Tablets (100mg, 300mg)	15 mg/kg rounded up to the nearest 50 or 100 mg	900 mg (max.)
RPT (Rifapentine)*	Rifapentine Tablets 150mg	10.0-14.0 kg= 300 mg 14.1-25.0 kg= 450 mg 25.1-32.0 kg= 600 mg 32.1-49.9 kg= 750mg ≥50.0 kg= 900 mg	900mg (max.)
Children aged 2–11 yrs **			
Isoniazid		25 mg/kg; 900 mg maximum	
Rifapentine		see above ≥ 12 years dosages	

Source: Source: CDC. Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection. MMWR 2011; 60(48); 1650-1653.

** CDC. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep 2020;69(No. RR-1):1–11. DOI: http://dx.doi.org/10.15585/mmwr.rr6901a1

DOT is strongly recommended for INH/RPT 12-week regimen.
Doses must be administered at least 72 hours apart to be counted.

The use of INH elixir is discouraged, as it commonly causes diarrhea and cramping in children. If children have difficulty taking medications, open capsules and crush tablets, and then hide the drugs in soft foods or liquids. Possible foods are maple syrup, peanut butter, spinach baby food, and chocolate whipped cream. Layer the food and drug on a spoon, and teach the child to take the contents of the spoon without chewing.

Monitoring

Children should be seen in the clinic monthly, and questions should be asked about symptoms of toxicity, symptoms of active TB, adherence to therapy, and results of skin testing of family members and other contacts.

Antituberculosis drug doses should be adjusted in accordance with the weight of the child. Monthly monitoring of body weight is therefore especially important in pediatric cases with adjustment of doses as children gain weight.

Children taking anti-epileptic drugs and either INH or rifampin should be monitored closely because both of these drugs can affect the metabolism and serum levels of anti-epileptics.

Side Effects and Adverse Reactions

Families should be educated on symptoms of hepatotoxicity, for example, vomiting, loss of appetite, abdominal pain, or jaundice, and instructed to stop the therapy and return to the clinic if they note any symptoms which may be consistent with drug toxicity. Untoward effects of isoniazid therapy, including severe hepatitis in otherwise healthy infants, children, and adolescents, are rare. Monitoring of liver function is not routinely recommended for asymptomatic children who do not have underlying liver disease and are not taking other hepatotoxic drugs.

Pyridoxine (Vitamin B6):

Routine administration of pyridoxine (vitamin B6) is not recommended for all children taking isoniazid. Pyridoxine supplementation is recommended for:

- exclusively breastfed infants,
- children on a milk- and meat-deficient diet,
- children with nutritional deficiencies,
- HIV-infected children,
- pregnant adolescents,
- children who experience paresthesia while taking isoniazid.[27]

The recommended dose is 6.25 mg (1/4 of a 25 mg tablet) for infants), 12.5 mg (1/2 of a 25 mg tablet) for toddlers, and 25 mg (1 tablet) for school age children. For infants and small children, the tablet portions can be crushed and placed in an agreeable liquid or soft food for administration[28].

Window-Period Prophylaxis

Young children and children with HIV infection and other immunocompromising conditions are more likely to become ill with TB disease if they are infected and more likely to develop severe forms of TB disease. Because of their increased risk, they are candidates for window-period prophylaxis, which is treatment for presumptive TB infection during the interval between infection and detectable TB screening test reactivity. The National Tuberculosis Controllers Association (NTCA) and the CDC recommend that the window period be estimated at 8 to 10 weeks after last contact with the infectious source case or 8 to 10 weeks after the infectious source case has become non-infectious.[29]

The most efficient way to prevent pediatric TB is to evaluate and treat those children exposed to an infectious adult source case. **ALL** children and adolescents exposed to an infectious case of tuberculosis disease should have a TB screening test (TST or IGRA) and an evaluation for tuberculosis disease. A chest radiograph (PA and lateral) should be performed on all exposed children under 5 years of age and all exposed children with HIV infection or other immunosuppressive conditions, regardless of their initial TST or IGRA result.

The following contacts with initially **negative** TST results should receive treatment for LTBI (window-period prophylaxis) after TB disease has been ruled out by clinical examination and chest radiograph:

1. Contacts younger than 5 years of age (with highest priority given to those under 3 years)
2. Contacts with human immunodeficiency virus (HIV) infection or who are otherwise immunocompromised

If a second TST or IGRA test is done 8 to 10 weeks after last exposure is negative (<5 mm induration) and the contact is immunocompetent (including immunocompetent young children) and no longer exposed to infectious TB, treatment for LTBI (window-period prophylaxis) may be discontinued, and further follow-up is unnecessary.

For young infants, less than one year of age consult with a pediatric tuberculosis expert, (Curry International Tuberculosis Center Warmline 877-390-6682)

If the second test is negative but the contact is immunocompromised (e.g., with human immunodeficiency virus [HIV] infection), a full course of therapy for LTBI should be completed.[30]

If the second TST or IGRA test is positive (5mm or greater induration), a full course of therapy for LTBI should be completed.

Infants and children on window period prophylaxis should be closely monitored for signs and symptoms of active TB disease.

Immunocompromised contacts to an infectious TB case, such as HIV-infected contacts, should be given full treatment for LTBI regardless of the TST reaction.[31]

Diagnosis of Tuberculosis Disease

Medical History

The symptoms and signs of pulmonary tuberculosis in children are usually minor and are more common in infants and young children. More than half of infants and children with radiographic evidence of moderate to severe pulmonary tuberculosis have no symptoms or findings and are often only discovered by contact tracing. Nonproductive cough and mild dyspnea are the most common symptoms in infants. Fever, night sweats, anorexia, weight loss or poor weight gain, and irritability may also be noted.

It is important to also identify underlying medical conditions, for example HIV infection or other immunosuppressive conditions, that increase risk for progression to active TB. Because most children become infected by inhaling droplet nuclei containing *M. tuberculosis* bacteria that have been expelled by coughing persons with infectious pulmonary or laryngeal TB, any possible contacts with adults with confirmed tuberculosis or symptoms of active tuberculosis should be explored.

Physical Examination

Children with primary pulmonary disease often have radiographic abnormalities but are clinically asymptomatic. The chest x-ray findings often have no correlation with signs and symptoms. Physical examination should include an assessment of vital signs including temperature, respiratory rate, and growth parameters. Tachypnea, localized wheezing, or decreased breath sounds can occur with bronchial obstruction, but respiratory distress is rare.

About one-third of children with TB have extrapulmonary disease. Disease of extra-thoracic lymph nodes, especially lymph nodes of the neck (scrofula), is the most common non-pulmonary presentation. TB disease can also occur in many other parts of the body, including the pleura, pericardium, meninges, abdomen and gastrointestinal and genitourinary systems, skin, the larynx, and bone and joints.

TABLE 9: **SIGNS AND SYMPTOMS OF PULMONARY TB IN CHILDREN**[32]

Sign	Infants	Children	Adolescents
Rales	Common	Uncommon	Rare
Wheezing	Common	Uncommon	Uncommon
Fremitus	Rare	Rare	Uncommon
Dullness to percussion	Rare	Rare	Uncommon
Decreased breath sounds	Common	Rare	Uncommon

Symptom	Infants	Children	Adolescents
Fever	Common	Uncommon	Common
Night sweats	Rare	Rare	Uncommon
Cough	Common	Uncommon	Common
Productive cough	Rare	Rare	Common
Hemoptysis	Never	Rare	Rare
Dyspnea	Common	Rare	Rare

Adapted from slides in a presentation on Pediatric Tuberculosis by Dr. Ann Loeffler, Francis Curry National TB Center, http://www.currytbcenter.ucsf.edu/products/pediatric-tuberculosis-online-presentation

Radiology

Chest radiography is an important part of the diagnostic workup of pediatric TB. Because the results may be difficult to interpret, especially if there has been inadequate inspiration or over penetration, films should be reviewed by a radiologist experienced in reading pediatric chest radiographs.

To increase the chances of discerning intrathoracic adenopathy, a common radiographic feature of primary pulmonary TB in children, **both posterior-anterior (PA) and lateral chest radiographs are required**, especially in children under 5 years of age.

A variety of radiographic findings can be seen in children with TB disease, ranging from normal to diverse abnormalities, such as lymphadenopathy of the hilar, subcarinal, paratracheal, or mediastinal nodes; atelectasis or infiltrate of a segment or lobe; pleural effusion; cavitary lesions; or miliary disease.

With primary TB disease, lung parenchymal lesions may be anywhere. With reactivation TB disease, parenchymal lesions are typically, but certainly not always, in the apical regions.

Table 10: **A COMPARISON OF RADIOGRAPHIC FINDINGS NOTED IN ADULT AND PEDIATRIC PATIENTS WITH PULMONARY TB**[33]

	Adults	Infants and Children
Location	Apical	Anywhere (25% multilobar)
Adenopathy	Rare (except HIV)	Usual (30-90%)
Cavitation	Common	Rare (except adolescents)
Signs and symptoms	Consistent	Relative paucity

Adapted from slides in a presentation on Pediatric Tuberculosis by Dr. Ann Loeffler, Francis Curry National TB Center, http://www.currytbcenter.ucsf.edu/products/pediatric-tuberculosis-online-presentation

Radiologic abnormalities in children with active TB may, in the short term, worsen on treatment before they improve. Usually there has been some response by two months, but even at the end of a satisfactory course of treatment there may be residual lymphadenopathy or scarring.

Magnetic resonance (MR) or computed tomography (CT) scans are generally not necessary unless there is a questionable abnormality on the plain film and further definition is required. MR and CT imaging may be very helpful in the evaluation of suspected active Central Nervous System (CNS) disease or bone and joint disease. MR and CT imaging can also be helpful in the evaluation of endobronchial disease and disease in other sites, such as the intra or extra-thoracic lymph nodes, pericardium and peritoneum.[34]

Bacteriologic Testing

The gold standard for diagnosing TB disease in children is isolation of *M. tuberculosis* by culture from specimens of gastric aspirates, sputum, bronchial washings, pleural fluid, cerebrospinal fluid (CSF), urine, other body fluids, or a biopsy specimen.

For many children with pulmonary TB, culture confirmation is not needed. Diagnosis is made on the basis of a positive TST or IGRA, clinical and radiographic findings suggestive of TB, and history of contact with an identified adult source case. The drug-susceptibility test (DST) results from the source case's TB isolate can be used to guide the optimal treatment for the child. However, cultures should be obtained from the child if the source patient is unknown or has a drug-resistant organism and if the child is immunocompromised or has extrapulmonary TB.

Gastric Aspirates

For infants and young children with suspected pulmonary TB, the best specimen to obtain for culture is an early morning gastric aspirate obtained using a naso-gastric tube before the child arises and before peristalsis empties the stomach of the respiratory secretions swallowed overnight. Three consecutive morning gastric aspirates yield *M. tuberculosis* in 30% to 50% of cases; the yield from infants is as high as 70%.

Curry International Tuberculosis Center has guidelines for the collection of gastric aspirates, available at http://currytbcenter.ucsf.edu/products/product_details.cfm?productID=ONL-10

Sputum Collection

For older children collection of spontaneously produced or induced sputum is often possible. The combination of sputum induction and gastric aspirate has yielded the organism in up to 90% of cases. In older children or adolescents, sputum induction is preferable to bronchoscopy.

Bronchoscopy

The culture yield is lower from bronchoscopy specimens than from properly obtained gastric aspirates. Most children do not need flexible fiber optic bronchoscopy; but the procedure may be useful in diagnosing endobronchial TB and excluding other causes of pulmonary abnormality, particularly in immunocompromised children, such as those with HIV infection in whom other opportunistic infections may coexist with or mimic TB.

Treatment of Tuberculosis

Basic principles

The goal of treatment is to achieve sterilization of 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.

Evaluation and treatment of children with TB disease requires a coordinated team approach, including clinicians, public health nurses, and often a social worker and an interpreter. The team should always include a clinician experienced in the management of pediatric TB. Expert consultation is especially important for any pediatric patient with drug-resistant TB or co-infected with HIV.

Successful treatment of a child with TB requires that they swallow each dose of all their medications. All children with TB disease should be treated by directly observed therapy (DOT). Parents, and in general, family members, should not be relied on to supervise DOT.

The Nevada TB Program welcomes consultation regarding treatment of pediatric patients with TB.

TB Consultation For complicated TB cases, for example, children with multi-drug resistant TB and HIV co-infection, an excellent resource of pediatric TB expertise is the Curry International Tuberculosis Center Warmline
http://www.currytbcenter.ucsf.edu/consultation
Telephone: 415-502-4700 or 877-390-6682

Treatment Regimens and Dosages

In general, the recommended drug-treatment regimens and duration of treatment for children with TB are similar to those for adults. Initial treatment should start with daily dosing by DOT, with four drugs for the initial two-month phase and two drugs for the continuation phase of treatment**.**

If the child or the child's source case is known to have a fully-sensitive TB isolate, it is acceptable to start with a three-drug regimen of isoniazid, rifampin, and pyrazinamide.

Otherwise, ethambutol is always included in the initial treatment regimen until drug sensitivities are known, to minimize the emergence of drug-resistant strains.

The Curry International TB Center has a brochure of helpful tips on administration of TB medications to infants and children. These are listed in Appendix A and are available online at: http://currytbcenter.ucsf.edu/pediatric_tb/resources.cfm

Antituberculosis drug doses should be adjusted in accordance with the weight of the child**.** Monthly monitoring of body weight is therefore especially important in pediatric cases with adjustment of doses as children gain weight.

Duration of Treatment

Drug-sensitive pulmonary disease and hilar adenopathy disease: After treatment for two months with three or four drugs (ethambutol may be discontinued when it becomes known that the child or source case has a fully sensitive TB isolate), treatment is continued with isoniazid and rifampin for a minimum of four additional months. The minimum duration of treatment for fully-sensitive pulmonary TB disease is six months. If the chest radiograph shows a cavitary lesion or lesions and sputum or gastric aspirate specimens remains culture positive after two months of therapy, the duration of therapy should be extended to nine months. And if pyrazinamide is not used in the regimen (in the instance of *M. bovis,* which is usually resistant to PZA) the treatment is extended to nine months.

Drug-sensitive extra-pulmonary TB: Extrapulmonary TB in children is treated with the same regimens as pulmonary disease, with the exception of CNS TB, disseminated/miliary TB, and bone and joint TB, for which the recommended minimum duration of treatment is nine to twelve months.

Drug-Resistant Tuberculosis or HIV Co-infection: For the treatment of children proven to have or suspected of having drug-resistant TB or HIV co-infection, consultation with a pediatric TB specialist experienced in the management of drug-resistant TB should be obtained. An excellent resource for pediatric TB expertise is the Francis J. Curry National TB Center Warmline; telephone: 415-502-4700 or 877-390-6682

The Curry International Tuberculosis Center and California Department of Health Services have an excellent reference on drug resistant TB: *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians*, 2nd edition. Available online at http://currytbcenter.ucsf.edu/products/product_details.cfm?productID=WPT-11CD

First-Line TB Drugs

The first-line drugs commonly used in the treatment of pediatric TB diseases, their regimens are summarized in Table 11, and their doses and side effects are summarized in Table 12.

Table 11: **DRUG REGIMENS FOR DRUG SUSCEPTIBLE TUBERCULOSIS**

Initial Phase			**Continuation Phase**				
Regimen	Drugs[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b] (Minimum Duration) [c]	Range of Total Doses	Comments [c] [d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182-130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110-94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse and acquired drug resistance	
4	INH RIF PZA EMB	7 d/wk for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice weekly regimens in HIV infected patients or in patients with smear positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.	Lesser

Abbreviations: DOT, directly observed therapy; EMB, ethambutol; HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.
a Other combinations may be appropriate in certain circumstances; additional details are provided in the section "Recommended Treatment Regimens."
b When DOT is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice. DOT should be used when drugs are administered <7 days per week.
c Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.
d Pyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (eg, pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.
e Alternatively, some US tuberculosis control programs have administered intensive-phase regimens 5 days per week for 15 doses (3 weeks), then twice weekly for 12 doses.

Source: Payam Nahid, Susan E. Dorman, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines. Treatment of Drug-Susceptible Tuberculosis. Clinical Infections Diseases® 2016 DOI:10.1093/cid/ciw376 downloaded from http://cid.oxfordjournals.org/ on August 25, 2016

Table 12: **DOSES[a] OF FIRST-LINE ANTITUBERCULOSIS DRUGS FOR ADULTS AND CHILDREN[b] †35**

			Doses (maximum)			
Drug	**Preparation**	**Adult/Child***	**Daily**	**1 x weekly**	**2 x weekly**	**3 x weekly**
Isoniazid	Tablets (50, 100, 300 mg); Elixir (50 mg/5 ml); Aqueous IV/IM solution (100 mg/ml)	Adults	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
		Children	10-15 mg/kg (300 mg)	----	20-30 mg/kg (900 mg)	----[b]
Rifampin	Capsule (150, 300 mg); suspend powder for PO; Aqueous IV solution	Adults[c]	10 mg/kg (600 mg)	----	10 mg/kg (600 mg)	10 mg/kg (600 mg)
		Children	10-20 mg/kg (600 mg)	----	10-20 mg/kg (600 mg)	----[b]
Rifabutin	Capsule (150 mg)	Adults[d] Children	5 mg/kg (300 mg) Appropriate dosing for	children is unknown. _	Not recommended Estimated at 5 mg/kg	Not recommended Daily. Intermittent Dosing is not recommended
Rifapentine	Tablet (150 mg)	Adults	----	10-20 mg/kg (600 mg);[e] continuation phase only	---	---
		Children	Active tuberculosis: for children ≥ 12 yrs of age, same dosing as for adults, administered once weekly. Rifapentine is Not FDA approved for treatment of active tuberculosis in children <12 yrs. Of age.			
Pyrazinamide	Tablet (500 mg)	Adults	40-55 kg → 1,000 mg 56-75 kg → 1,500 mg 76-90 kg → 2,000 mg	----	40-55 kg → 2,000 mg 56-75 kg → 3,000 mg 76-90 kg → 4,000 mg	40-55 kg → 1,500 mg 56-75 kg → 2,500 mg 76-90 kg → 3,000 mg
		Children	20-40 mg/kg (2,000 mg)	----	50 mg/kg (2,000 mg)	----[b]
Ethambutol	Tablet (100 and 400 mg)	Adults	40-55 kg → 800 mg 56-75 kg → 1,200 mg 76-90 kg → 1,600 mg	----	40-55 kg → 2000 mg 56-75 kg → 2,800 mg 76-90 kg → 4,000 mg	40-55 kg → 1,200 mg 56-75 kg → 2,000 mg 76-90 kg → 2,400 mg
		Children[f]	15-25 mg/kg (1000 mg)	----	50 mg/kg (2,500 mg)	----[b]

Abbreviations: FDA, US Food and Drug Administration; HIV, human immunodeficiency virus; IM, intramuscular; INH, isoniazid; IV, intravenous.

[a] Dosing based on actual weight is acceptable in patients who are not obese. For obese patients (>20% above ideal body weight [IBW]), dosing based on IBW may be preferred for initial doses. Some clinicians prefer a modified IBW (IBW + [0.40 actual weight – IBW)]) as is done for initial aminoglycoside doses. Because tuberculosis drug dosing for obese patients has not been established, therapeutic drug monitoring may be considered for such patients.

[b] For purposes of this document, adult dosing begins at age 15 years or at a weight of >40 kg in younger children. The optimal doses for thrice-weekly therapy in children and adolescents have not been established. Some experts use in adolescents the same doses as recommended for adults, and for younger children the same doses as recommended for twice-weekly therapy.

[c] Higher doses of rifampin, currently as high as 35 mg/kg, are being studied in clinical trials.

[d] Rifabutin dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

[e] TBTC Study 22 used rifapentine (RPT) dosage of 10 mg/kg in the continuation phase of treatment for active disease [9]. However, RIFAQUIN and PREVENT TB safely used higher dosages of RPT, administered once weekly [164, 210]. Daily doses of 1200 mg RPT are being studied in clinical trials for active tuberculosis disease.

[f] As an approach to avoiding ethambutol (EMB) ocular toxicity, some clinicians use a 3-drug regimen (INH, rifampin, and pyrazinamide) in the initial 2 months of treatment for children who are HIV-uninfected, have no prior tuberculosis treatment history, are living in an area of low prevalence of drug-resistant tuberculosis, and have no exposure to an individual from an area of high prevalence of drug-resistant tuberculosis. However, because the prevalence of and risk for drug-resistant tuberculosis can be difficult to ascertain, the American Academy of Pediatrics and most experts include EMB

Sources: Payam Nahid, Susan E. Dorman, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines. Treatment of Drug-Susceptible Tuberculosis. Clinical Infections Diseases® 2016 DOI:10.1093/cid/ciw376 downloaded from http://cid.oxfordjournals.org/ on August 25, 2016

American Academy of Pediatrics. [Tuberculosis] In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases.* 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:[pp 805-831]

NOTE: Pyridoxine (vitamin B6), 25-50mg/day, is given with INH to all persons at risk of neuropathy (eg, pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition; or chronic renal failure; or patients with advanced age),. For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

Pharmacology and Adverse Reactions

Isoniazid is bactericidal, rapidly absorbed and well tolerated and penetrates into body fluids, including Cerebral Spinal Fluid (CSF). Isoniazid is metabolized in the liver and excreted primarily through the kidneys. Hepatotoxic effects are rare in children but can be life threatening.

In children and adolescents given recommended doses, peripheral neuritis or seizures caused by inhibition of pyridoxine metabolism are rare, and most do not need pyridoxine supplements. Pyridoxine is recommended for exclusively breastfed infants and for children and adolescents on meat- and milk-deficient diets; children with nutritional deficiencies, including all symptomatic HIV-infected children; and pregnant and breastfeeding adolescents and women.[36] For these infants and children, the recommended dose is 6.25 mg (1/4 of a 25 mg tablet) for infants, 12.5 mg (1/2 of a 25 mg tablet) for toddlers, and 25 mg (1 tablet) for school age children. For infants and small children, the tablet portions can be crushed and placed in an agreeable liquid or soft food for administration.[37]

Rifampin is a bactericidal agent that is absorbed rapidly and penetrates into body fluids, including CSF. Rifampin is metabolized by the liver and can alter the pharmacokinetics and serum concentrations of many other drugs. Hepatotoxic effects, influenza-like symptoms, and pruritus may occur rarely. Rifampin is excreted in bile and urine and can cause orange urine, sweat, and tears and discoloration of soft contact lenses. Rifampin can make oral contraceptives ineffective, so other birth control methods should be adopted when rifampin is administered to sexually active adolescent women.[38]

Pyrazinamide attains therapeutic CSF concentrations, is detectable in macrophages, is administered orally, and is metabolized by the liver. Administration of pyrazinamide with isoniazid and rifampin allows for 6-month regimens in patients with drug-susceptible tuberculosis. In doses of 30 mg/kg per day or less, pyrazinamide seldom has hepatotoxic effects and is well tolerated by children. Some adolescents and many adults develop arthralgia and hyperuricemia because of inhibition of uric acid excretion. Pyrazinamide must be used with caution in people with underlying liver disease.[39]

Ethambutol is well absorbed after oral administration, diffuses well into tissues, and is excreted in urine. However, concentrations in the cerebrospinal fluid are low. At 15 mg/kg per day, ethambutol is bacteriostatic only, and its primary therapeutic role is to prevent emergence of drug resistance.[40]

A common question is whether the first-line drug ethambutol (EMB) can be safely administered to children. EMB can cause retro bulbar neuritis, a side effect that is dose-dependent and renal-function dependent. It manifests as decreased visual acuity or decreased red-green color discrimination and is usually reversible upon discontinuation of the drug. Monitoring of vision is recommended monthly in older children and adults. Past guidelines have advised against the use of EMB or have advised caution when using EMB in children who cannot verbalize symptoms of optic neuritis, but recent studies have not found evidence of visual toxicity in young children treated with recommended ethambutol dosing.[41] In young children in whom toxicity cannot be monitored use of EMB in a dose of 15 to 20 mg/kg per day is acceptable and carries a very low risk of optic neuritis.

Monitoring Response to Treatment

Children on TB treatment should be monitored closely for response to treatment and for medication side effects and adverse reactions, especially hepatitis and allergic and non-allergic drug reactions.

Parents and other caregivers should be educated on the TB medications being given to their child and the potential side effects and adverse reactions to watch for and to promptly report if noted while their child is on TB treatment.

A baseline complete blood count with platelet count, chemistry panel with liver function and creatinine, and an HIV screen are recommended for all persons starting treatment for active TB disease.

Follow-up liver function testing should be done at least monthly on children with abnormal baseline liver function and on children co-infected with HIV; some clinicians routinely monitor liver function on all pediatric TB patients.

Liver function testing should also be done if a child develops loss of appetite, malaise, jaundice, or other symptoms of possible hepatitis while on TB treatment.

For children on a TB treatment regimen that includes ethambutol, baseline and periodic follow-up testing of visual acuity and color vision is recommended for children who are able to do these tests.

Antituberculosis drug doses should be adjusted in accordance with the weight of the child. Monthly monitoring of body weight is therefore especially important in pediatric cases with adjustment of doses as children gain weight.

Children taking anti-epileptic drugs and either INH or rifampin should be monitored closely because both of these drugs can affect the metabolism and serum levels of anti-epileptics.

Pyridoxine (Vitamin B6):

Routine administration of pyridoxine (vitamin B6) is not recommended for all children taking isoniazid. Pyridoxine supplementation is recommended for:

- exclusively breastfed infants
- children on a milk- and meat-deficient diet
- children with nutritional deficiencies
- HIV-infected children
- pregnant adolescents
- children who experience paresthesia while taking isoniazid[42]

The recommended dose is 6.25 mg (1/4 of a 25 mg tablet) for infants), 12.5 mg (1/2 of a 25 mg tablet) for toddlers, and 25 mg (1 tablet) for school age children. For infants and small children, the tablet portions can be crushed and placed in an agreeable liquid or soft food for administration.[43]

Response to Treatment:

In most children, response to treatment is assessed primarily clinically and by x-ray. In children, weight loss or, more commonly, failure to gain weight adequately is of particular concern and is often one of the first (or only) signs of treatment failure. For children able to produce sputum, follow-up sputum cultures are helpful, especially if there is a concern of treatment failure. Similarly, follow-up gastric aspirates may be of benefit in infants and young children, especially for those with severe or drug resistant TB disease.

Completion of Treatment

The date of completion of treatment is determined by the total doses administered by DOT. If therapy has been interrupted, the date of completion should be extended. Decisions about the completion of treatment should be made in consultation with the Nevada TB Program.

See *Treatment of Tuberculosis Disease*, Chapter 4, of this manual for more information about determining completion of treatment.

Special Issues

Isolation of Children with TB Disease

Most children with tuberculosis disease are not infectious and do not require airborne isolation and negative pressure rooms in the hospital, although hospital infection control policies may require otherwise. Airborne precautions with isolation in a negative pressure room are indicated for (1) children with cavitary pulmonary tuberculosis; (2) children with positive sputum AFB smears; (3) children with laryngeal involvement; (4) children with extensive pulmonary infection; and (5) children with congenital tuberculosis undergoing procedures that involve the oropharyngeal airway (e.g., endotracheal intubation); until effective therapy has been initiated, sputum smears demonstrate a diminishing number of organisms, and cough is abating. [44]

The major concern in hospital infection control relates to adult household members and contacts who may be the source case to a child with TB. Household members and other contacts should be managed with tuberculosis precautions when visiting until they are demonstrated not to have infectious tuberculosis. Nonadherent household contacts should be excluded from hospital visitation until their evaluation is complete and tuberculosis disease is excluded or treatment has rendered source cases noninfectious. [45]

Child Care and Schools

Children with tuberculosis disease can attend school or child care if they are receiving therapy. 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 substantially.[46]

Source Case Investigations

A diagnosis of LTBI or tuberculosis disease in a young child is a sentinel event representing recent transmission of *M. tuberculosis* in the community. Health care providers should assist state and local health department personnel in the search for a source case and others infected by the source case. Members of the household, such as relatives, babysitters, au pairs, boarders, domestic workers, and frequent visitors or other adults, such as child care providers and teachers with whom the child has frequent contact, potentially are source cases.

See *Contact Investigation*, Chapter 8, of this manual for more information about source case investigations.

In children less than 5 years of age, LTBI, in addition to TB disease, is a reportable condition under Nevada state law. Please contact your local health department if you require assistance reporting LTBI in children less than 5 years of age. Prompt reporting assists health departments in initiating effective source case investigations.

Drug Delivery Options [47]

Drug delivery to children can be very difficult. Prepare the family for the challenge and encourage them not to be discouraged if it takes a week or two to get into a comfortable routine. It is better to get the child into a good pattern than to set up a power struggle.

All children with tuberculosis disease (TB) require treatment with directly observed therapy (DOT). With DOT, a healthcare worker, teacher, or other non-family member observes administration of the TB drugs.

Drugs should be taken all at once, not throughout the day, and they should be given close to the same time each day.

Methods to deliver the drugs:

1) Pills and capsules taken intact or in halves: This is the easiest way! Tip the head back to swallow pills and tip the head forward to swallow capsules. If the child can swallow capsules, but not tablets, crush the pills and place the powder in commercially available empty capsules.

2) Pills fragmented (with a knife or commercial pill cutter) or crushed (by commercial pill crusher, mortar and pestle, spoon against spoon or bowl); capsules can be opened.

a) Put a thin layer of soft food onto a spoon. Place the pill fragments or powder on top of the food layer and top with more yummy food. Give the child the dose of medication in this "sandwich."
Teach them to swallow it without chewing by practicing without the medication in place first.
- Chocolate sauce, pudding, fudge sauce, ice cream, etc.
- Jelly or marmalade (the texture hides the powder granularity)
- Apple sauce or berry-sauce (better to hide the red rifampin color)
- Nutella or peanut butter
- Cream cheese or chili con carne

The crushed pills have a strong flavor; small fragments of the pill taste better.

OR

b) Suspend in a SMALL AMOUNT of liquid. Water is best.
Sugary liquids may interact with INH and should be avoided.
Dispense with:
- Syringe (it is difficult to get the pulverized INH through regular tip syringe; other drugs crush finer and solubilize better)
- Medicine dropper with larger tip; available at many pharmacies
- Baby bottle (may need to make nipple hole larger)
- Special Rx MediBottle - with internal sleeve for syringe; available at many pharmacies.

Pulverized INH is very difficult to get through this syringe. Give the other meds with this bottle and then give INH separately or by the liquid product if it is tolerated by the baby.

- Medicine delivering pacifier; available at many pharmacies (holes will need to be enlarged)

3) Liquids:
   - INH suspension is available commercially in sorbitol. The large osmotic load is poorly tolerated by most children, but may be better tolerated by babies.

   - Other TB medications are not commercially available as liquids. Medications may be suspended by local pharmacies but the stability and homogeneity are not guaranteed.

For more information on delivering TB medications to children consult *Tuberculosis Medication Delivery Tips*, by Dr. Ann Loeffler, Pediatric TB Specialist, Curry International Tuberculosis Center
http://currytbcenter.ucsf.edu/pediatric_tb/resources.cfm

Resources and References

Resources

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