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

CONTENTS

Introduction

Purpose

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

- detect and diagnose latent tuberculosis infection (LTBI) in children
- detect and diagnose tuberculosis disease in children
- know when to report suspected or confirmed cases of tuberculosis in children
- follow basic treatment principles for latent tuberculosis infection and tuberculosis 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; and
- determine completion of therapy for pediatric patients

Pediatric patients are defined as those under 15 years of age.

Children, especially infants and young children under 5 years of age, are at increased risk to rapidly develop active and sometimes severe tuberculosis disease after they become infected because their immune systems are immature and not fully developed.

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

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

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

Call the Alaska TB Program at 907-269-8000 for consultation regarding the evaluation and treatment of pediatric patients with TB and LTBI.

For complicated pediatric tuberculosis cases, consult the Curry International Tuberculosis Center Warmline at 877-390- 6682. For more information see http://www.currytbcenter.ucsf.edu/consultation

Report suspected and confirmed cases of pediatric tuberculosis disease to the Alaska Division of Public Health, Section of Epidemiology at 907-269-8000.

Background

Pediatric tuberculosis is defined by the World Health Organization and the US Centers for Disease Control and Prevention as tuberculosis in children less than 15 years of age. Pediatric tuberculosis presents unique challenges. Infants and young children are at increased risk to progress to active disease if infected. Unlike adults and older adolescents who most commonly have reactivation disease, tuberculosis disease in infants and children is usually primary tuberculosis and may occur quickly after they become infected. Infants and children have fewer 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 tuberculosis medications to infants and children is often difficult. It is also important to remember that pediatric tuberculosis is a sentinel event, reflecting recent transmission 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, 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 tuberculosis 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 tuberculosis infection (LTBI). But in infants and young children under five years of age and 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 tuberculosis 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 tuberculosis disease, such as disseminated (miliary) tuberculosis or TB meningitis, sometimes quickly follows the primary infection, even in the weeks before development of a positive Mantoux tuberculin skin test (TST) or interferon gamma release assay (IGRA). This is the reason why "window period prophylaxis" with rifampin or isoniazid is recommended for exposed young children and immunocompromised children until infection can be excluded.

The risk of progression to tuberculosis 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 in immunocompromised children.[1] (Table 1). 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 and medical conditions, for example, 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 tuberculosis infection

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

The TST and the IGRA are the two methods for diagnosing tuberculosis infection in asymptomatic people.

Current guidelines recommend performing a TST rather than an IGRA in children under 2 years of age. IGRA testing is preferred for children 2 years and older, especially if the child has received BCG vaccination or is felt to be unlikely to return for TST reading, but TST is acceptable, especially if IGRA testing is not available, too costly, or too burdensome.[3]

It is important to remember that children (and adults) with active tuberculosis may have a negative TST or IGRA. This is especially true for infants under six months of age and for infants and children with immune disorders.

Remember: A negative TST or IGRA does not guarantee that a child does not have active tuberculosis.

Candidates for Testing for Tuberculosis Infection

Testing is recommended for children at high risk of tuberculosis infection or progression to tuberculosis disease. Some examples are children who are contacts of a person with active tuberculosis, children with suspected active tuberculosis 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 tuberculosis, and children who arrived in the United States within the previous two years from countries with a high tuberculosis incidence.

The American Academy of Pediatrics Committee on Infectious Diseases recommends testing of infants, children, and adolescents from several high-risk groups[4]:

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

Children for whom immediate TST or IGRA is indicated[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 (e.g., Asia, Middle East, Africa, Latin America, countries of the former Soviet Union), including international adoptees • Children with history of significant travel to countries with endemic infection who have substantial contact with the resident population [c]
Children who should have annual TST or IGRA • Children infected with HIV
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 epidemiological factors suggested 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.

Adapted from 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. American Academy of Pediatrics; 2018; 829-853

a. Bacille Calmette-Guerin (BCG) immunization is not a contraindication to a TST
b. Beginning as early as 3 months of age for TST, 2 Years of age for IGRAs for LTBI and disease
c. 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.

Abbreviations: IGRA: indicated interferon-gamma release assay; HIV: human immunodeficiency virus; LTBI: latent *M tuberculosis* infection.

Testing is not recommended for children who are at low risk of tuberculosis infection and disease progression.

Administration and Interpretation of the Tuberculin Skin Test

TSTs should be administered and interpreted by experienced health care professionals who have been trained in the proper methods, because administration and interpretation by unskilled people and family members are unreliable.

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.

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.

Detailed information on the administration, measurement and follow-up of tuberculin skin testing can be found in Diagnosis of Latent Tuberculosis Infection Section **7.7**.

A TST can be administered or an IGRA can be drawn 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 possibly mumps, rubella, and varicella vaccines) may transiently suppress the TST or IGRA 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. However, if the live virus vaccine has already been administered, the TST or IGRA test should be deferred for four to six weeks.[5]

Approximately 10% to 15% of immunocompetent children with culture-documented disease do not react initially to a TST or show a positive IGRA. 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. Children and adults co-infected with HIV and *M. tuberculosis* may not react to a TST or show a positive IGRA. Control skin tests to assess cutaneous anergy are not recommended routinely.

Classification of TST results is 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: **POSITIVE TUBERCULIN SKIN TEST REACTIONS IN ALASKA**

Induration Size	Considered Positive For:
5 mm or more	▪ Recent contacts of a suspected or known case of tuberculosis (TB) disease ▪ Persons suspected to have tuberculosis disease ▪ Persons with human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) ▪ Persons with fibrotic lesions on chest radiograph consistent with healed TB ▪ Persons with organ transplants or other immunosuppressed persons (such as those receiving the equivalent of >15 mg/day of prednisone for >1 month) ▪ Persons receiving treatment with tumor necrosis factor-alpha (TNF-α) antagonists
10 mm or more	▪ All others

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 Alaska TB Program recommends prompt clinical and radiographic evaluation of all children and adolescents with positive TST reactions.

Interferon-Gamma Release Assays:

Interferon-gamma release assays (IGRAs) involve incubation of peripheral blood T-lymphocytes with antigens that are specific to *M. tuberculosis*. If an individual has had previous exposure to *M. tuberculosis,* his or her T-lymphocytes will respond to the antigens by releasing interferon gamma. Some examples are the QuantiFERON-TB Gold Plus test and the T-SPOT.*TB* test.

The sensitivity of IGRA tests is similar to that of TSTs for detecting TB infection in adults and children. 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 (e.g., are not found in *M avium* complex, but are found in *M kansasii, M szulgai,* and *M marinum*). 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 in even younger children.[6]

Testing with an IGRA is recommended for children 2 years of age and older who have a history of BCG vaccination or who are unlikely to return for reading of a TST. For other children 2 years or older, either an IGRA or a TST is acceptable for testing. For infants and children under 2 years of age, testing with a TST is recommended.[7]

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

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. 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.[8,9]

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.[10] The online BCG World Atlas is a useful resource for determining BCG vaccination policies in over 180 countries.

BCG vaccination has been shown to have relatively high protective efficacy (approximately 80%) against more severe forms of TB disease, including 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.[11]

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.[12]

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.[13] 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 tuberculosis infection than from BCG immunization.[14] The size of the TST after BCG immunization has been shown to correlate with the risk of developing TB disease.

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.[15]

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.[16]

For children 2 years and older who have received BCG vaccination, testing with an IGRA test is recommended, unless IGRA testing is not available or too costly.

Management of Children with a Positive IGRA or TST

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 positive IGRA or TST 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.

Latent tuberculosis infection (LTBI) is defined as *M. tuberculosis* infection in a person who has a positive IGRA or TST result, 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).

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

Why treat children with latent tuberculosis infection (LTBI)? Children who have LTBI are the reservoir for future tuberculosis disease, hence the importance of LTBI treatment to prevent TB disease and transmission in the future. Treatment of LTBI in children has been demonstrated to provide substantial protection against future development of active TB disease. Prompt treatment is especially important for children under 5 years of age because they are at increased risk of rapid progression to active TB.

Isoniazid given to adults who have LTBI (e.g., no clinical or radiographic abnormalities suggesting tuberculosis disease) provides substantial protection (54%–88%) against development of tuberculosis disease for at least 20 years. Among children, efficacy approaches 100% with appropriate adherence to therapy. All infants, children, and adolescents who have a positive IGRA or TST result but no evidence of tuberculosis disease and who never have received antituberculosis therapy should receive treatment for latent tuberculosis infection.

Treatment of Latent Tuberculosis Infection (LTBI)

Do not start treatment before ruling out tuberculosis disease.

Several regimens are available. Any of these options is considered adequate, depending on the circumstances for individual patients. Recommended regimens for treatment of latent tuberculosis infection currently include:

- 4 months of daily rifampin
- 3 months of once-weekly isoniazid plus rifapentine (for children 2 years and older)
- 3 months of daily isoniazid plus rifampin
- 9 months of daily isoniazid

Studies find completion rates are higher for short rather than long LTBI treatment regimens.

Shorter, rifamycin-based treatment regimens generally have a lower risk of hepatotoxicity than isoniazid for 9 months.

Isoniazid-rifapentine should not be used in children younger than 2 years because of a lack of pharmacokinetic data and an established dose for rifapentine in this age group.[17]

Any of these regimens may be used for children without a known source or with a source that has a fully susceptible *M. tuberculosis* isolate. All of these regimens are usually well-tolerated by most children.

Rifampin for 4 months would be appropriate for children with LTBI who have been exposed to a source case whose isolate is resistant to INH but susceptible to rifampin.

Similarly, isoniazid for 9 months would be appropriate for children with LTBI who have been exposed to a source case whose isolate is resistant to rifampin but susceptible to isoniazid or for children who cannot tolerate rifampin.

For the isoniazid regimen, daily treatment is preferable. If daily therapy is not possible, directly observed two-times-per week treatment can be used on a case-by-case basis.

Daily treatment can be administered by a parent or caregiver or by DOT. DOT should be used for children on intermittent (2 times per week) treatment. The once weekly isoniazid and rifapentine regimen may be by DOT or self-administered therapy (SAT) by a parent or guardian. The decision to treat by DOT or SAT should be determined by the provider and the public health nurse.

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

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 if side effects are noted.

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

For consultation regarding the treatment of LTBI, call the Alaska TB Program at 907-269-8000.

Expert consultation with a pediatric TB specialist should be obtained for children suspected to be infected with a multidrug-resistant strain of *M. tuberculosis* or HIV. Call the Curry International Tuberculosis Center at 877-390-6682 or visit their website: http://www.currytbcenter.ucsf.edu/consultation

Children who are at especially high risk for TB and either at risk for nonadherence, or on an intermittent (for example, 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 in institutions and facilities (schools) where a staff member can observe treatment.

LTBI Treatment Regimens and Dosages[18]

The four treatment regimens for latent TB infection (LTBI) use rifampin (RIF) alone, isoniazid (INH) plus rifampin (RIF), isoniazid (INH) plus rifapentine (RPT), or isoniazid (INH) alone. Treatment must be modified if the patient is a contact of an individual with drug-resistant TB disease. Consultation with a TB expert is advised if the known source of TB infection has drug-resistant TB.

Table 4: **LATENT TB INFECTION TREATMENT REGIMENS**

Drugs	Duration	Interval	Comments
Rifampin	4 months	Daily	Preferred treatment for persons who are contacts of patients with INH-resistant, RIF-susceptible TB or for persons who cannot tolerate isoniazid therapy. Continuous daily therapy is required for rifampin. Intermittent rifampin therapy even by DOT is not recommended.[19]
Isoniazid plus Rifapentine	12 weeks (3 months)	Once weekly	Treatment for: • Current recommendations are to use this regimen for persons 2 years of age and older. Not recommended for persons who are: • Younger than 2 years old, • Living with HIV/AIDS taking antiretroviral agents with clinically significant or unknown drug reactions with rifapentine, • Presumed infected with INH or RIF-resistant M. tuberculosis, and • Women who are pregnant or expect to become pregnant within the 12–week regimen course.
Isoniazid plus Rifampin	3 months	Daily	
Isoniazid	9 months	Daily	Preferred treatment for: • Persons with HIV taking HIV medications with clinically significant drug interactions with rifamycins. • Persons who do not tolerate rifampin therapy
		Twice weekly by DOT	• If daily therapy is not possible, DOT two times a week can be used for 9 months.

Source: Adapted from CDC's Treatment Regimens for Latent TB Infection (LTBI). Available at: https://www.cdc.gov/tb/topic/treatment/ltbi.htm , and AAP Committee on Infectious Diseases 2018 Red Book, personal communication with Dr. Ann Loeffler, Pediatric Tuberculosis Consultant, Curry International Tuberculosis Center.

Dosages

Once the appropriate regimen has been identified, refer to Table 5 for instructions on dosages for each drug. The information in Table 5 is taken from ATS, CDC, and Infectious Diseases Society of America (IDSA) guidelines, the 2018 AAP Red Book, and CDC Latent TB Infection Treatment Regimens.

The following drugs are available from the Alaska TB Program for treating LTBI. These drugs are provided free of charge upon approval of the Alaska TB Program.

- Isoniazid (INH)
- Rifampin (RIF)
- Rifapentine (RPT)

Table 5: RECOMMENDED DOSAGES FOR TREATMENT OF LATENT TUBERCULOSIS INFECTION IN CHILDREN

Drug	Preparation	Daily	Two times a Week	Once Weekly Isoniazid + Rifapentine by DOT
Isoniazid (INH)	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 ml)	10–15 mg/kg (Maximum dose 300 mg)[20]	20–30 mg/kg **by DOT** (Maximum dose 900 mg) [21]	15 mg/kg rounded up to the nearest 50 or 100 mg in patients 12 years and older 25 mg/kg rounded to the nearest 50/100 mg in patients 2-11 years[22] (Maximum dose 900 mg)
Rifampin (RIF)	Capsule (150 mg, 300 mg); powder may be suspended for oral administration	15–20 mg/kg for children 2 years and older 20-30 mg/kg for children under 2 years (Maximum dose 600 mg)	Not recommended	
Rifapentine (RPT)	Tablets (150 mg) Rifapentine tablets can be crushed and administered with semi-solid food for children unable to swallow pills			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 750 mg ≥*50.0 kg* 900 mg (max dose)

Source: Adapted from CDC's Treatment Regiments for Latent TB Infection (LTBI). Available at: https://www.cdc.gov/tb/topic/treatment/ltbi.htm , and AAP Committee on Infectious Diseases 2018 Red Book[23]

The use of INH elixir is discouraged, as it commonly causes diarrhea and cramping in children. If children have difficulty taking medications, open capsules or crush tablets and then hide them in soft foods or liquids. Possible foods include maple syrup, chocolate syrup, Nutella, 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.[24]

Monitoring

Children should be seen in the clinic at least monthly, and questions should be asked about symptoms of toxicity as well as 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 these drugs can affect the metabolism and serum levels of anti-epileptics.

Side Effects and Adverse Reactions

Before starting treatment, parents and other caregivers should be taught the possible side effects of the recommended treatment and what to do if their child has any side effects during treatment. Most persons tolerate these medications without problems, but on rare occasion, some persons can have side effects. Routine liver function testing is not indicated for asymptomatic children who do not have underlying liver disease and are not taking other hepatotoxic drugs, although some clinicians recommend checking baseline liver function before starting treatment. Parents and other caregivers should be instructed to stop the medicine immediately and notify their healthcare provider if they note problems, for example

- Loss of appetite, tiredness, weakness, gastric pain, nausea, vomiting
- Numbness or tingling of fingers or toes
- Yellow skin or eyes or dark colored urine
- Fever or chills
- Rashes, hives, bruising, or blistering

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 paresthesias – numbness, tingling, prickling --while taking isoniazid[25]

The recommended daily 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.[26]

Window-Period Prophylaxis

Infants and young children and children with HIV infection and other immunocompromising conditions are more likely to become ill with tuberculosis disease if they become infected with tuberculosis. They are also more likely to develop severe forms of tuberculosis disease. Because of their increased risk, they are candidates for window-period prophylaxis, which is treatment for presumptive tuberculosis infection during the interval between exposure and the development of detectable tuberculin skin test or IGRA 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.[27]

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 tuberculin skin test or IGRA test and an evaluation for tuberculosis disease. Tuberculin skin testing is recommended for children under 2 years of age; TST or IGRA can be used for children 2 years of age and older. A chest radiograph 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 tuberculin skin test or IGRA result, to be sure that there are no radiographic findings of active tuberculosis before starting window prophylaxis treatment.

Window prophylaxis helps to prevent rapid progression to TB soon after infection. The following contacts with initially negative tuberculin skin test or IGRA results should receive treatment for presumptive latent tuberculosis infection (window prophylaxis) after tuberculosis 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 other immunocompromising condition

For children over 6 months of age -- If a second skin test or IGRA test done 8 to 10 weeks after last exposure is negative (TST <5 mm induration or IGRA negative) and the contact doesn't have HIV or another immunosuppressive condition and is no longer exposed to infectious TB, treatment for LTBI (window-period prophylaxis) may be discontinued, and no further follow-up is necessary.

Young infants (under 6 months) may be unable to manifest a tuberculin skin test reaction due to their immature immune systems. For young infants the Curry International Tuberculosis Center recommends continuing window period prophylaxis until the infant is at least 6 months of age and at least 8 to 10

weeks after last exposure or 8 to 10 weeks after the source case becomes non-infectious. At that point, a second tuberculin skin test should be done, and the decision made whether to continue or stop treatment.[28]

If the second test is negative but the contact is immunocompromised (for example, with human immunodeficiency virus [HIV] infection), a full course of therapy for LTBI should be completed after active disease has been ruled out.[29]

Contacts to an infectious TB case who are immunocompromised (due to HIV infection or other conditions) should be given full treatment for LTBI regardless of their TST/IGRA reaction.[30]

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 and are 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, fatigue, reduced playfulness, 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 the risk for progression to active TB. Because most children become infected by inhaling droplet nuclei containing *M. tuberculosis* bacteria expelled by persons with infectious pulmonary or laryngeal TB, any possible contacts with adults with confirmed or suspected 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 tuberculosis have extrapulmonary disease. Disease of extra-thoracic lymph nodes, especially lymph nodes of the neck (scrofula), is the most common non-pulmonary presentation. Tuberculosis disease can also occur in many other parts of the body, including the pleura, pericardium, meninges, abdomen and gastrointestinal and genitourinary systems, skin, larynx, bone, and joints.

TABLE 6: **SIGNS AND SYMPTOMS OF PULMONARY TB IN CHILDREN**[31]

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

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 recommended, especially in children under 5 years of age.

A variety of radiographic findings can be seen in children with tuberculosis 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 disease, lung parenchymal lesions may be anywhere. With reactivation disease, parenchymal lesions are typically, but not always, in the apical regions.

Table 7. **A COMPARISON OF RADIOGRAPHIC FINDINGS NOTED IN ADULT AND PEDIATRIC PATIENTS WITH PULMONARY TB**[32]

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

Radiologic abnormalities in children with active tuberculosis 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) imaging or computed tomography (CT) imaging for pulmonary tuberculosis is generally not necessary unless there is a questionable abnormality on the plain film and further definition is required. MR and CT imaging may be helpful in the evaluation of suspected CNS, bone, joint, peritoneal, or pericardial disease.[33]

Bacteriologic Testing

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

New guidelines recommend collecting and testing respiratory specimens for mycobacterial culture on all children with suspected pulmonary tuberculosis, even when a likely source case has been identified and drug susceptibility results are available for the source case's tuberculosis isolate. Studies have found on occasion that the child's *M. tuberculosis* isolate's genotype and drug susceptibility results may differ from those of the identified source case.[34] Collecting respiratory specimens, especially gastric aspirates, from very young children in remote and rural communities across Alaska may be difficult due to lack of access to services, logistics and associated travel costs.

In the absence of culture confirmation, diagnosis of active tuberculosis may be made on the basis of a positive tuberculin skin test or IGRA, clinical and radiographic findings suggestive of TB, and history of contact with an identified adult source case. In this case, the drug-susceptibility test results from the source case's *M. tuberculosis* isolate can be used to guide optimal treatment for the child.

Specimens for AFB smear, TB PCR, and TB culture should always be obtained from the child if the source case 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 highest-yielding specimen to obtain for culture is an early morning gastric aspirate obtained using a nasogastric tube before the child arises and peristalsis empties the stomach of the respiratory secretions swallowed overnight. Gastric aspiration usually requires a child to be admitted for up to 3 days and has to be undertaken in the early morning while the child is recumbent and fasted overnight. Three consecutive morning gastric aspirates yield *M. tuberculosis* in 40% to 50% of cases; the yield is as high as 90% in infants and up to 77% in symptomatic children with extensive disease.[35]

The Curry International Tuberculosis Center has guidelines for the collection of gastric aspirates, available at http://www.currytbcenter.ucsf.edu/products/pediatric-tuberculosis-online-presentation/resources

Sputum Collection

Children older than 2 years and adolescents frequently can produce sputum spontaneously or by induction with aerosolized hypertonic saline; nasopharyngeal suctioning can also be used to obtain respiratory specimens. The combination of sputum induction and gastric aspirate yields the organism in up to 90% of cases. In older children or adolescents, sputum induction is preferable to bronchoscopy. Sputum collected from children by nasopharyngeal aspiration or sputum induction with a bronchodilator has a yield of 20%–30%.[36]

Bronchoscopy

The culture yield is lower from bronchoscopy specimens than from properly obtained gastric aspirates. Most children do not need flexible fiberoptic 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 lesions 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. Directly observed therapy decreases the rates of relapse, treatment failure, 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 tuberculosis. Expert consultation is especially important for any pediatric patient with drug-resistant tuberculosis or co-infection with HIV.

Successful treatment of a child with tuberculosis requires that they swallow each dose of all their medications. All children with tuberculosis disease should be treated by directly observed therapy (DOT). Parents, and in general, family members, should not be relied on to supervise DOT. DOT is the standard of care for all persons diagnosed with active tuberculosis in Alaska.

The Alaska TB Program at the Section of Epidemiology (907-269-8000) can provide consultation regarding treatment of pediatric patients with tuberculosis.

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

Treatment Regimens and Dosages

Regimens

In general, the recommended treatment regimens and duration of treatment for children with tuberculosis are like those for adults. Initial treatment should start with daily dosing by DOT, commonly with four drugs for the initial two-month phase and two drugs for the continuation phase of treatment for children with fully susceptible tuberculosis.

If the child or the child's source case is known to have a fully susceptible tuberculosis 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 susceptibilities are known, to minimize the emergence of drug-resistant strains.

Daily directly observed therapy at least 5 days per week is recommended for both the intensive and continuation phases of treatment. If the child is doing well after completion of the intensive phase of treatment and if continued daily dosing is not feasible, consideration may be given to changing to thrice-weekly dosing, also by DOT, during the continuation phase. This alternative regimen is not preferred and should be managed by a specialist in pediatric tuberculosis.[40]

The Curry International Tuberculosis 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-susceptible 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 susceptible *M. tuberculosis* isolate), treatment is continued with isoniazid and rifampin for a minimum of four additional months. The minimum duration of treatment for fully susceptible pulmonary tuberculosis disease is six months. If the chest radiograph shows a cavitary lesion or lesions and sputum or gastric aspirate specimens remain culture positive after two months of therapy, the duration of therapy should be extended to nine months.

Drug-susceptible extra-pulmonary tuberculosis: Extrapulmonary tuberculosis in children is treated with the same regimens as pulmonary disease, except for CNS tuberculosis, for which the recommended minimum duration of treatment is nine to twelve months. Some experts favor 9 months of treatment for children with disseminated tuberculosis and bone and joint tuberculosis, while others feel that 6 months of treatment is adequate.[37]

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 tuberculosis and TB/HIV coinfection should be obtained. An excellent resource for pediatric TB expertise is the Curry International Tuberculosis Center Warmline Consultation Service 877-390-6682 http://www.currytbcenter.ucsf.edu/consultation

The Curry International Tuberculosis Center and the Tuberculosis Control Branch of the California Department of Public Health have an excellent reference on drug resistant tuberculosis: *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians*, 3rd[d] edition. Available online at http://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition

Table 8: **DRUG REGIMENS FOR MICROBIOLOGICALLY CONFIRMED PULMONARY TUBERCULOSIS CAUSED BY DRUG-SUSCEPTIBLE ORGANISMS**[38]

NOTE: Daily dosing in both the intensive and continuation phases (Regimen 1) is preferred for pediatric patients

Intensive Phase			Continuation Phase				
Regimen	**Drug***	**Interval and Dose† (Minimum Duration)**	**Drugs**	**Interval and Dose†,±(minimum Duration)**	**Range of Total Doses**	**Comments±,****	**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 does (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††	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior	Lesser

Source: ATS, CDC, IDSA. Treatment of Drug-Susceptible Tuberculosis. *Clinical Infectious Diseases 2016*; 63(7):147-95.

Abbreviations: DOT: directly observed therapy; EMB: ethambutol; HIV: human immunodeficiency virus; INH: isoniazid; PZA: pyrazinamide; RIF: rifampin

* Other combinations may be appropriate in certain circumstances; additional details are provided in the section "Recommended Treatment Regimens."

† 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.

± 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

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

†† 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.

First-Line TB Drugs

The first-line drugs commonly used in the treatment of pediatric tuberculosis, their doses and side effects are summarized in Table 9.

Table 9: **COMMONLY USED DRUGS FOR THE TREATMENT OF TUBERCULOSIS IN INFANTS, CHILDREN, AND ADOLESCENTS**[39][40]

Drugs	Dosage Forms	Daily Dosage,* mg/kg	Thrice Weekly Dosage, mg/kg**	Adverse Reactions
Isoniazid	Scored tablets 100 mg 300 mg	10–15 (Maximum 300 mg)	20-30 (Maximum 900 mg)	Mild hepatic enzyme elevation, hepatitis, peripheral neuritis, hypersensitivity
Rifampin	Capsules 150 mg 300 mg	15-20 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.[41] (Maximum 600 mg)	15-20 (Maximum 600 mg)[42]	Orange discoloration of secretions or urine, staining of contact lenses, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus; oral contraceptives may be ineffective
Pyrazinamide	Scored tablets 500 mg	30-40 (Maximum 2,000 mg)	50 (Maximum 2,000 mg)	Hepatotoxic effects, hyperuricemia, arthralgias, gastrointestinal tract upset, rash
Ethambutol	Tablets 100 mg 400 mg	15–25 (Maximum 1,600 mg)	50 (Maximum 2,400 mg)	Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity

Source: ATS, CDC, IDSA. Treatment of Drug-Susceptible Tuberculosis. *Clinical Infectious Diseases 2016*; 63(7):147-95 and AAP 2018 Red Book

* For children unable to receive daily dosing at least 5 days per week, DOT three times weekly can be considered during the continuation phase. Daily dosing is preferred.

** 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.

Pharmacology and Adverse Reactions

Isoniazid is bactericidal, rapidly absorbed, and well-tolerated and penetrates well into body fluids, including 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.[43] 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.[44]

Rifampin is a bactericidal agent that is absorbed rapidly and penetrates well 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 added when rifampin is administered to sexually active adolescent women on hormonal contraceptives.[45]

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. Pyrazinamide seldom has hepatotoxic effects in children and is usually well tolerated. Some adolescents and adults develop arthralgia and hyperuricemia because of inhibition of uric acid excretion. Pyrazinamide must be used with caution in people with underlying liver disease.[46]

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.[47]

A common question is whether the first-line drug ethambutol (EMB) can be safely administered to children. EMB can cause retrobulbar 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 studies have not found evidence of visual toxicity in young children treated with recommended ethambutol dosing.[48] 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, the potential side effects and adverse reactions to watch for, and to promptly report any adverse reactions 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.

Medication Side Effects and Adverse Reactions

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.

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

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

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 paresthesias while taking isoniazid.[49]

The recommended daily 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[50].

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 concern as it may be a sign of treatment failure. For children with pulmonary tuberculosis who can produce sputum, obtaining follow-up sputum cultures at one, two, and three months after starting treatment is recommended, and is also recommended if there is a concern for 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 and the number of weeks of treatment. 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 Alaska TB Program.

See the Treatment of Tuberculosis section of this manual for more information about determining completion of treatment **6.2**2.

Special Issues

Isolation of Children with TB Disease

Most children with tuberculosis disease are not highly infectious. However, as with older tuberculosis patients, airborne isolation and negative pressure rooms are appropriate in the hospital setting until testing shows they are not infectious. Airborne precautions with isolation in a negative pressure room are especially important for (1) children with cavitary pulmonary tuberculosis; (2) children with positive sputum AFB smears or positive GeneXpert TB PCR testing; (3) children with laryngeal involvement; (4) children with extensive pulmonary infection; or (5) children with congenital tuberculosis undergoing procedures that involve the oropharyngeal airway (e.g., endotracheal intubation). Precautions should be continued until effective therapy has been initiated, sputum smears are negative, and cough is abating. [51]

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. [52]

Childcare and Schools:

Children with tuberculosis disease can attend school or childcare if they are receiving therapy. They can return to school, childcare, and regular activities as soon as effective therapy has been instituted, adherence to therapy has been documented, and clinical symptoms have diminished substantially, usually a minimum of 2 weeks after starting treatment. [53]

Source Case Investigations

A diagnosis of latent tuberculosis infection or tuberculosis disease in a young child is a sentinel event representing recent transmission of *M tuberculosis* in the community. Healthcare 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 childcare providers and teachers with whom the child has frequent contact, are potential source cases.

See the Contact Investigation section of this manual for more information about source case investigations **11.10**.

Drug Delivery Options

Appendix A [54] by Dr. Ann Loeffler, Pediatric Tuberculosis Consultant, Curry International Tuberculosis Center:

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 groove. It is better to get the child into a good pattern than to set up a power struggle.

All children with tuberculosis disease (TB) should be treated with directly observed therapy (DOT). With DOT, a health department 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
   - Whatever the family can make work

   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 hole larger)
   - Special Rx MediBottle - with internal sleeve for syringe; available at many pharmacies. Pulverized INH is very difficult to get through this syringe. I suggest giving the other meds with this bottle and then giving 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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