

Management of Latent Tuberculosis Infection in Children and Adolescents

A GUIDE FOR THE PRIMARY CARE PROVIDER



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Table of Contents

4	PREFACE	
5	INTRODUCTION	
6	TESTING FOR TB INFECTION	
	Targeted testing recommendations.....	6
	Screening for risk of TB infection	7
	Epidemiology	8
	Tests for TB infection.....	9
	Tuberculin skin test (TST).....	9
	Interferon-gamma release assay (IGRA).....	11
	Recommendation for type of test.....	12
	Special considerations in TB testing and interpretation.....	13
	Live-virus vaccines.....	13
	BCG vaccine	13
	Contacts of persons with potentially infectious tuberculosis.....	15
	Evaluation of children and adolescents with a positive test for TB infection.....	17
19	TREATMENT OF LATENT TB INFECTION	
	Overview of treatment.....	19
	Treatment regimens for latent TB infection.....	20
	12 weeks of isoniazid and rifapentine (INH-RPT)	20
	4 months of rifampin (RIF).....	23
	9 months of isoniazid (INH).....	24
	Summary of regimens for latent TB infection in infants, children, and adolescents.....	27
	Completion of therapy.....	28
	Interruptions in therapy.....	28
	Monitoring during LTBI treatment.....	29
	Hepatotoxicity/liver function tests	30
	Treatment under special circumstances	31
	Children recently exposed to a person with TB disease.....	31
	Referring to a specialist.....	32
	Keys to successful treatment	32
	Selecting an appropriate regimen	32
	Education and communication with family members.....	32
	Techniques for medication administration.....	33
	Incentives.....	34
	Directly observed therapy.....	34
	Documenting completion of treatment.....	35
	Summary.....	36
37	APPENDIX A: Administration, measurement, and interpretation of the TST	
39	APPENDIX B: Adherence strategies for different age groups	
40	APPENDIX C: Sample letters for documenting testing and treatment for latent TB infection	
42	REFERENCES	
43	RESOURCES	



Preface

This document is a guide for pediatric primary care providers. It is not intended to provide complete information on all aspects of the management of latent tuberculosis infection (LTBI), but rather, is an overview of the current recommendations and suggestions for achieving the best patient outcome. The content is primarily based on recommendations from the American Academy of Pediatrics (AAP) as included in the *Red Book: 2018 Report of the Committee on Infectious Diseases*, though recommendations from the Centers for Disease Control and Prevention (CDC) have also been considered.

Recommendations for testing and treating children with LTBI differ from those for tuberculosis (TB) disease, which requires multiple drug therapy for an extended period of time. Since recommendations for management of both LTBI and TB disease change as new knowledge and treatment options become available, health care providers should refer to the reference list at the end, as well as other current literature. Updated CDC guidelines, educational materials, and other resources are available at CDC's LTBI Resources webpage: cdc.gov/tb/publications/tbi/tbiresources.htm. Updated information can also be found in the Red Book Online, which is available to AAP members.

Since TB is a public health concern, state and local health departments are integral to the prevention and control of the disease. These public health departments and TB programs can serve as a resource for information, consultation, and educational materials around TB disease and LTBI. Providers can consider accessing TB program resources or referring patients for consultation if needed. TB program contact information can be found at: tbcontrollers.org/community/statecityterritory. Consultation with a pediatric TB expert is strongly recommended in specific situations, which are described later in this guide.

The Global Tuberculosis Institute at Rutgers, The State University of New Jersey (GTBI) is one of four Tuberculosis Centers of Excellence (COEs) funded by the CDC to provide training, technical assistance, and medical consultation on TB in the United States. Physicians at the COEs have expertise in the management of children with latent TB infection, TB disease, and multidrug-resistant TB (MDR-TB). Providers should consult the TB COE in their region for additional information and medical consultation: cdc.gov/tb/education/tb_coe/default.htm. Information on GTBI's educational materials, trainings, and other resources can be accessed at: globaltb.njms.rutgers.edu.



Introduction

Latent tuberculosis infection (LTBI), also known as TB infection, is defined as infection with the tubercle bacilli without signs and symptoms or radiographic evidence of active tuberculosis (TB) disease, which requires therapy with multiple drugs. Since we know that LTBI is the precursor to TB disease, early diagnosis of children infected with *Mycobacterium tuberculosis* (*M. tuberculosis*) complex is a critical step in preventing morbidity and mortality in the pediatric population.

Currently, emphasis in the United States is on testing only those children identified as having risk factors for tuberculosis. “Targeted testing” places priority on groups at highest risk by identifying and testing those at the greatest risk for infection, as well as those at risk for developing TB disease if infected.¹

Appropriate treatment of LTBI in these children is equally important and should include development of a plan to ensure treatment completion. The rationale for treating LTBI in children includes the following:

- Young children are at significant risk of progression from latent infection to TB disease, including severe forms of TB such as miliary and meningeal disease. Infants are at an especially high risk of developing disease; infants have up to a 40% risk of developing active disease if infected²
- Recent post-pubertal adolescents are also at increased risk of progression from LTBI to TB disease
- Infection is likely to be recent in children and adolescents and recent primary infection poses the greatest risk for disease progression³
- Medications used to treat LTBI are well tolerated by children and have a low risk of toxicity
- Children have more years to potentially develop TB disease

Despite the importance of treatment, attempting to treat healthy children over an extended period of time can present challenges to providers, patients, and families. This guide and the additional resources listed will provide pediatric health care providers with information on testing, diagnosis, and treatment of LTBI in children from birth to adolescence, with a focus on identifying and treating these children to completion of therapy.



Testing for TB Infection

TARGETED TESTING RECOMMENDATIONS

Targeted testing is used to identify, evaluate, and treat children who are at high risk for LTBI or at high risk for developing TB disease once infected with *M. tuberculosis*. Because children and adolescents with LTBI represent the future reservoir for cases of TB, it is important that these children are promptly identified and treated. Children without TB risk factors should not be tested.

The following boxes contain a summary of the AAP recommendations on testing for TB infection in children from the *Red Book: 2018 Report of the Committee on Infectious Diseases*.⁴ Testing can begin as early as 3 months of age for the tuberculin skin test (TST) and generally 2 years of age for interferon-gamma release assays (IGRAs). Additional information on testing is included later in this guide.

Children for whom an immediate test for TB infection is indicated:

- Contacts of persons with confirmed or suspected infectious TB (via a contact investigation)
- Children with radiographic or clinical findings consistent with TB disease
- Children immigrating from countries with high prevalence of TB (e.g., Asia, Middle East, Africa, Latin America, Eastern Europe, and countries of the former Soviet Union), including international adoptees
- Children with significant travel histories to endemic countries and substantial contact with people who live in these countries*
- Children who are about to start immunosuppressive therapy (see next page)

Children who should have an annual test for TB infection:

- Children with HIV infection

* If the child is well and has no known TB exposure, the test for TB infection should be delayed for up to 10 weeks after returning.

Children at increased risk for progression of infection to disease:

- Underlying immune deficiencies associated with certain medical conditions can increase the possibility of progression to severe TB disease, thus, children in these categories deserve special consideration. *Without TB exposure, these children are not at risk of acquiring TB infection.*
- Other medical conditions that increase the possibility of progression from TB infection to TB disease include:
 - Hodgkin disease
 - Lymphoma
 - Diabetes mellitus
 - Chronic renal failure
 - Malnutrition
 - Congenital or acquired immune deficiencies
 - Use of tumor necrosis factor (TNF) alpha-antagonists or blockers, or other immunosuppressive therapy
- At each visit, information regarding potential exposure to TB should be elicited from parents of these children; if histories or local epidemiological factors suggest a possibility of exposure, immediate and periodic TB testing should be considered*
- A test for TB infection should be performed in any child *before* initiation of immunosuppressive therapy including use of TNF-alpha antagonists or blockers, prolonged systemic steroid administration, organ transplantation, or other immunosuppressive therapies

* Some experts recommend annual testing in children on dialysis or who are receiving immunosuppressive therapy, including use of TNF-alpha antagonists or blockers, prolonged systemic steroid administration, or organ transplantation.

SCREENING FOR RISK OF TB INFECTION

The most effective strategies for finding children with LTBI and preventing TB disease are centered on timely and thorough contact investigations, rather than widespread testing of the general population. Universal testing, such as at schools, day care, or camps is discouraged because the yield of true positive results is low, leading to an ineffective use of resources.⁴ However, using a risk assessment tool in health care settings helps identify children with risk factors for LTBI who should be prioritized for testing.

This approach suggests that providers screen children on a regular basis by taking a TB-focused health history. The AAP suggests that a risk assessment for TB be performed at the provider's first encounter with the child and then annually. Testing for TB infection should be performed *only* if one or more risk factors are present.

The following validated questions for determining risk of TB infection in children in the United States are recommended by the AAP:⁴

- Has a family member or contact had TB disease?
- Has a family member or close contact had a positive test for TB infection?
- Was your child born in a high-risk country (countries other than U.S., Canada, Australia, New Zealand, or Western and Northern European countries)?
- Has your child traveled to a high-risk country? How much contact did your child have with the resident population?*

* If the child is well and has no history of TB exposure, the test for TB infection should be delayed for up to 10 weeks after returning.

In addition to the above questions for determining risk of infection, providers may consider that exposure may have occurred in the home as a result of significant contact with visitors from high-risk countries. Special considerations for screening children with HIV or those on or about to start immunosuppressive therapy are noted in the previous section.

EPIDEMIOLOGY

Local epidemiology and immigration patterns should be considered when making testing and treatment decisions. Providers should become familiar with the incidence of TB in the countries from which their patients and families are emigrating. Recent data from CDC indicates that 70% of TB cases in the United States occurred among non-US born individuals. Fifty-five percent of those cases occurred in people from five countries; Mexico, the Philippines, India, Vietnam, and China.⁵

The World Health Organization (WHO) has developed separate lists of high-burden countries for TB, TB/HIV coinfection, and MDR-TB. Each list contains 30 countries: 20 countries with the highest number of cases in absolute terms, as well as 10 countries with the largest per capita case rate that do not already appear among the first 20 countries and that meet a minimum threshold in terms of absolute numbers of cases. These lists are available at stoptb.org/countries/tbdata.asp.

TESTS FOR TB INFECTION

Two methods of testing for *M. tuberculosis* infection are available. These include the Mantoux tuberculin skin test (TST) and blood-based interferon-gamma release assays (IGRAs). Important considerations for these tests include the following:

- Neither the TST nor the IGRA can distinguish between latent TB infection and TB disease
- Neither method of testing can be considered the “gold standard”
- A negative result from either test does not exclude LTBI or TB disease
- A negative result from either test is considered especially unreliable in infants younger than 3 months of age

Children exposed to a person with infectious TB whose initial test is negative should be retested 8-10 weeks after their last exposure, since it can take this amount of time for an immune response to develop.

Tuberculin Skin Test (TST)

- Delayed type hypersensitivity test
- Uses Mantoux method, which is an intradermal injection of purified protein derivative (PPD)
- Response to antigen is measured in millimeters of induration (erythema alone at TST site does not indicate positive test result; measure induration, not erythema)
- Requires a second visit to read and interpret results 48-72 hours after administration
- Should be administered, read, and interpreted by experienced and trained staff to avoid unreliable results (see Appendix A for more information)
- May have decreased sensitivity as a result of host factors including young age, poor nutrition, immunosuppression, viral infections (especially measles, varicella, and influenza), recent infection, and disseminated TB disease
- May have cross-reactivity in persons with a history of BCG vaccination (see page 13 for additional information)

Definition of positive TST results in infants, children, and adolescents

The interpretation of the TST is based on a person's risk of TB infection and risk of progression to TB disease if infected. The definitions below apply regardless of previous immunization with bacille Calmette-Guérin (BCG) vaccine, which is discussed in further detail on page 13.

The AAP offers the following guidelines for defining positive TST results in infants, children, and adolescents:⁴

Induration of 5 mm or greater

- Children in close contact with persons with known or suspected infectious TB disease
 - Children suspected to have TB disease
 - Findings on chest radiograph consistent with active or previous TB disease
 - Clinical evidence of TB disease^a
 - Children receiving immunosuppressive therapy^b or with immunosuppressive conditions, including HIV infection
-

Induration of 10 mm or greater

- Children at increased risk of disseminated TB disease:
 - Children younger than 4 years of age^c
 - Children with other medical conditions such as Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition
 - Children with likelihood of increased exposure to TB disease
 - Children born in regions of the world with a high prevalence of TB
 - Children who travel to regions of the world with a high prevalence of TB
 - Children frequently exposed to adults who are HIV-infected, homeless, users of illicit drugs, residents of nursing homes, or incarcerated
-

Induration of 15 mm or greater

- Children 4 years of age or older without any risk factors; however, children without risk factors should not be tested

a Evidence by physical examination or laboratory assessment that would include TB in the working differential diagnosis (e.g., meningitis).

b Includes immunosuppressive doses of corticosteroids or tumor necrosis factor-alpha antagonists or blockers.

c CDC considers a 10 mm induration positive in children younger than 5 years of age.

Interferon-Gamma Release Assay (IGRA)

- Blood test that measures ex-vivo interferon-gamma production by T-lymphocytes in response to stimulation with antigens specific to *M. tuberculosis* complex
- Whole blood is mixed with TB antigens and analyzed in a laboratory
- Requires a single patient visit
- Approved products include QuantiFERON®-TB Gold Plus and T-SPOT®.TB

In many clinical settings, IGRAs have a higher specificity than the TST because the antigens used are not present in BCG nor found in many nontuberculous mycobacterial species, including *M. avium* complex; therefore, there is no cross-reactivity. False positive results may be caused by *M. kansasii*, *M. marinum*, *M. szulgai*, and *M. leprae* infection.^{4,6} False positive results may also be caused by wild-type *M. bovis* infection.

QuantiFERON®-TB Gold Plus

- Results are based on the amount of interferon-gamma released by white blood cells
- Results are reported as positive, negative, or indeterminate based on a defined cut point
 - May also include numerical values
 - An indeterminate result represents a test failure

T-SPOT®.TB

- Results are based on the relative number of specifically sensitized cells
- Results are reported as positive, negative, invalid, or borderline
 - May also include numerical values
 - An invalid result represents a test failure
 - Borderline results are considered equivocal, neither negative nor positive

Interpretation of IGRA results:^{*}

- Children with positive IGRA results should be considered infected with *M. tuberculosis* complex
- Negative IGRA results 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 tests should not be used to make clinical decisions
- Providers should take the child's risk of infection and risk of progression into account when interpreting quantitative and qualitative IGRA results, particularly in interpreting borderline results from T-SPOT[®].TB or results near the cut point for QuantiFERON[®]-TB Gold Plus
 - A repeat test can be considered in the case of borderline results

^{*} Consult package inserts or contact laboratory for additional information on interpreting IGRA results.

Recommendations for type of test

The AAP states that either the TST or IGRA is acceptable in children 2 years of age and older and notes that published data indicates that IGRAs consistently perform well in children 2 years of age or older (and that some data supports their use in even younger children).⁴

- TST is preferred in children younger than 2 years of age
- IGRA is preferred in children 2 years of age or older who have been previously vaccinated with BCG (to avoid a false-positive TST)
- IGRAs are recommended for children unlikely to return for TST interpretation

Considerations such as cost, test availability, prevalence of BCG exposure in the target population, ability to re-evaluate the patient 2-3 days after testing, and the training and expertise of health workers may all affect the decision about which test to use.⁶

Use of more than one test

Routine testing with both TST and IGRA is not recommended, but may be considered in some circumstances:

- **The initial IGRA result is indeterminate or invalid**
 - A TST may be used or the IGRA repeated
- **The initial TST is negative, but there is:**
 - A high risk of infection, progression, or poor outcome *and/or*
 - A high clinical suspicion for TB disease* and additional evidence is sought to support the diagnosis
- **The initial TST is positive, but:**
 - Additional evidence is needed to ensure adherence to treatment, *and/or*
 - The child is healthy and at low risk *and/or*
 - Infection with nontuberculous mycobacteria (NTM) is suspected
- **There is a concern for TB disease in children of any age *and* the initial test (either IGRA or TST) is negative;**
 - Both an IGRA and a TST should be performed, as either test being positive is of clinical utility*

* Empiric treatment for TB disease should be provided until TB disease is ruled out.

In the above circumstances, an IGRA may be used in children younger than 2 years of age, although the body of evidence on IGRA performance in this age group is limited (see page 14).

As outlined in the targeted testing section of this chapter, testing for TB infection is *only* recommended for children who are at increased risk of infection (exposure), children with HIV, and, in some cases, for children with other medical conditions associated with underlying immune deficiencies. Children without any risk factors should not be tested.

SPECIAL CONSIDERATIONS IN TB TESTING AND INTERPRETATION

Live-virus vaccines

Measles vaccine can temporarily suppress tuberculin reactivity. The TST should be administered before the measles, mumps, rubella vaccine (MMR) vaccine, simultaneously with the MMR vaccine, or at least 4-6 weeks after the vaccine. The effect of other live-virus vaccines (varicella, yellow fever, and live attenuated influenza) on tuberculin reactivity is not known, though the same spacing recommendations apply. Although the effects of live-virus vaccines on IGRAs have not been determined experimentally, a similar approach should be used.

BCG vaccine

BCG is not part of the vaccine schedule in the United States, but is used extensively throughout the world as a neonatal vaccine, especially in countries where TB is endemic, for the specific purpose of reducing the risk of infants developing serious complications of TB, such as TB meningitis or miliary disease. Its effectiveness wanes over time.

If a child is at risk for tuberculosis, a test for TB should be performed regardless of BCG vaccine history. Important considerations for testing BCG-vaccinated children include:

- TST may have cross-reactivity in persons with a history of BCG vaccination. However, if BCG vaccination does cause a positive TST result, the reaction generally becomes negative by about 5 years of age
- It is not possible to distinguish a reaction caused by infection with *M. tuberculosis* and one that is a result of the BCG vaccine
- Cross-reactivity in BCG-vaccinated individuals does not occur with IGRAs

Testing BCG-Vaccinated Children for TB Infection	
<2 years of age	2 years of age or older
TST preferred*	IGRAs preferred

* Some data support IGRA use in even younger children; see page 13 for circumstances where IGRAs may be considered in children <2 years of age.

BCG-vaccinated children tested with the TST

Although IGRAs are preferred in BCG-vaccinated children, history of BCG vaccine is not a contraindication for the TST. Some children who have been vaccinated with BCG still receive a TST either because they are younger than 2 years of age or due to availability, access, or local policies or practices around IGRA use.

- IGRAs can help assess whether positive TST results are the result of TB infection or previous BCG vaccination
- Use the criteria on page 13 to determine when an IGRA should be performed in children initially tested using the TST
- While a negative IGRA cannot be universally interpreted as absence of infection, in general, if the IGRA is negative and the TST result is positive in a BCG-vaccinated, unexposed, asymptomatic child 2 years and older, LTBI is unlikely

The body of evidence on IGRA performance is limited in children younger than 2 years of age, though some data supports their use in this age group. Since the risk of progression to severe disease is significant in these children, IGRA use can be considered in some situations.

- Performing an IGRA can increase sensitivity in children younger than 2 years of age whose *initial* TST is negative but for whom there is a high clinical suspicion of TB and/or a high risk for infection, progression, or poor outcome
- Children in this age group with a positive TST result should be carefully evaluated for TB disease; treatment for TB disease should not be delayed in any child for whom there is a high clinical suspicion for TB disease
- Except in the specific circumstances noted on page 13 (additional evidence needed to ensure adherence, the child is healthy and at low risk, and/or NTM is suspected), the positive TST result should be relied upon in BCG-vaccinated children younger than 2 years of age, and the child should be treated for LTBI or TB disease accordingly

Educating parents

Providers should educate parents of BCG-vaccinated children diagnosed with LTBI on the importance of treatment. This is especially important for young children who received a TST.

- Acknowledge the difficulty of distinguishing a reaction caused by infection with *M. tuberculosis* and one that is a result of BCG vaccine
- Emphasize that the TST is the preferred test in children younger than 2 years of age because there is limited data on IGRA use in this age group and testing in this age group is critical given the significant risk of progression to TB disease
- Explain that for children older than 2 years of age who have a positive TST result, a positive IGRA can be used as additional evidence of TB infection and to support the diagnosis and treatment of LTBI; this may help ensure adherence to treatment

Contacts of persons with potentially infectious tuberculosis

Contact investigation is a systematic process used to identify persons (contacts) who were exposed to someone with infectious TB disease and provide appropriate treatment if necessary. Contact investigations are conducted by the jurisdictional health authority, generally the state or local health department.

- Persons who are **contacts** of patients with infectious tuberculosis are at risk of infection with *M. tuberculosis* and the subsequent development of disease
- A person with infectious TB disease who has transmitted infection with *M. tuberculosis* complex to another person or persons is known as a **source case**
- A person who has had recent contact with someone with presumed or confirmed infectious TB disease but has a negative test for TB infection and no physical or radiograph findings consistent with TB is known as an **exposed person**. Some exposed persons become infected and later develop a positive TST or IGRA test result

Although many years can elapse between initial infection and disease, the risk of developing disease is greatest within six months of infection and remains high for two years. Thus, when an adult has been diagnosed with confirmed or presumed infectious TB disease, children who have been in contact with that individual should be identified and evaluated as soon as possible to rule out TB disease, since infection is likely to have been recent and the risk of progression to TB disease is high.

Contact investigation allows for the potential early identification of TB disease; often children with TB disease identified during a contact investigation are asymptomatic or minimally symptomatic. See page 17 for more information on evaluating children to exclude TB disease.

Evaluation of pediatric contacts

The AAP recommends that children or adolescents who have recently been exposed to a person with infectious pulmonary TB disease should be evaluated with a TST or IGRAs, chest radiography (regardless of the TST or IGRAs result), and a history and physical examination. In practice, some providers only routinely obtain chest radiographs on children younger than 5 years of age, in keeping with CDC contact investigation guidelines.⁷ However, chest radiographs should be obtained in children of any age based on the individual history, physical exam and local epidemiology (for example, children with signs and symptoms consistent with TB disease, immunosuppressed children, or contacts to a highly infectious person).

- If the initial TST or IGRAs is positive and there is no evidence of disease, treatment for LTBI should be initiated. (See Treatment of Latent TB Infection, page 19 and Treatment Under Special Circumstances, page 31 for information on treatment of children recently exposed to a person with TB disease)
- If the initial test for TB infection is negative, a repeat test should be administered 8-10 weeks after exposure to the source case has ended or after the source case has been deemed to be non-infectious, since it can take this amount of time for an immune response to develop
- Children with a positive result on the repeat TST or IGRAs should also be re-evaluated (with a history, physical exam, and chest radiographs) and treated accordingly

Window prophylaxis for pediatric contacts

If the child is younger than 5 years of age or has impaired immunity, treatment for presumptive LTBI with INH should be initiated as soon as TB disease is excluded, even if the initial TST or IGRAs result is negative. This treatment, known as **window prophylaxis**, is indicated because of the high risk of progression to TB disease if infected and because these children are more likely to develop disseminated disease or TB meningitis. In addition, recently infected children younger than 5 years of age or immunosuppressed children can have a negative TST or IGRAs because a cellular immune response has not yet developed or because of anergy.⁴

A repeat test should be administered 8-10 weeks after contact with the infectious patient has ended; this is known as the **window period**.

- If the repeat TST or IGRAs is still negative, treatment can be discontinued in immunocompetent children. In immunosuppressed children, treatment for LTBI should be continued for the full course, regardless of the results of the repeat test, after an evaluation for TB disease (see Treatment Under Special Circumstances, page 31). Some experts may also choose to continue treatment in very young infants, based on the individual circumstance

- If the repeat TST or IGRA is positive in a child receiving window prophylaxis, the child should be re-evaluated for TB disease with a history, physical exam, and chest radiograph. In the absence of disease, the child should complete 9 months of treatment with isoniazid or be switched to an appropriate shorter-course regimen, such as 4 months of rifampin or 12 once-weekly doses of isoniazid and rifapentine (the latter regimen for children 2 years of age and above). While full courses of the shorter regimen would be needed, either regimen would still result in a shorter overall duration of treatment than if they completed treatment with 9 months of isoniazid

Evaluation of children and adolescents with a positive test for TB infection

The evaluation of individuals with positive TST or IGRA results includes a detailed health history, a physical assessment, and a chest radiograph. By focusing on the presence of symptoms, radiographic findings, risk of progression to TB disease, and co-existing medical conditions, the practitioner can identify or exclude TB disease.

Children suspected of having active TB disease should be referred to a specialist with expertise in management of pediatric TB.

The diagnostic criteria for LTBI includes a positive test for TB infection, the absence of symptoms or physical findings suggestive of TB disease, and a chest radiograph with no evidence of TB disease (isolated calcified granulomata or calcified hilar lymph nodes without other abnormalities are considered evidence of healed infection and are consistent with LTBI not TB disease). However, hilar adenopathy is evidence of TB disease.⁴

Early symptoms of TB disease in children, if they are present, may be non-specific and may include:

- Poor appetite
- Failure to gain weight or poor weight gain
- Growth delays
- General malaise
- Classic symptoms such as cough, fever, and weight loss. Night sweats and hemoptysis are less frequent in young children
- Neurological symptoms including decreased activity or playfulness, lethargy or irritability, somnolence, vomiting, headache, or seizures. (Later in the illness course, children can develop cranial nerve palsies and become obtunded)

Chest radiographs are used as a diagnostic tool to evaluate a child with a positive TST or IGRA.

- Two views, posterior-anterior (PA)* and lateral, are recommended for children younger than 5 years of age to better evaluate for presence of intrathoracic lymphadenopathy that may be obscured in the frontal view
- A single PA chest radiograph is usually sufficient for diagnostic purposes in children 5 years of age or older. However, clinicians may opt to obtain additional views to aid in decision making, as two-view chest radiographs are always more sensitive
- Films may have to be repeated if the child is crying during the X-ray, as expiratory films can result in crowding of the mediastinum and can make a normal radiograph appear abnormal
- Films should be obtained and ideally interpreted by a radiologist experienced in interpreting pediatric chest radiographs

* In small children, if a PA is not possible, radiologists may obtain an anterior-posterior (AP) view.

If there is a question of TB disease, consultation with a pediatric TB specialist should be considered before initiation of LTBI treatment. If the initial chest radiograph is normal and the child remains asymptomatic and completes treatment for latent TB infection, no further radiographs are required.



Treatment of Latent TB Infection

OVERVIEW OF TREATMENT

As noted previously, treatment is recommended for all children and adolescents who have been diagnosed with LTBI. Medications used to treat LTBI are generally safe and well tolerated in children. There are currently several regimens available for treatment of LTBI in children and adolescents. All of these regimens are considered adequate, depending on the circumstance of the individual patient, since some regimens should not be used in certain situations.

In conjunction with the patient and family, providers should select the most appropriate regimen based on patient history, clinical characteristics, and other factors that may affect treatment completion. Shorter regimens have been shown to have increased adherence and completion rates, as compared to 9 months of daily isoniazid.^{8,9}

Directly observed therapy (DOT), which is defined as a health care worker observing the administration of medication, is not routinely provided for treatment of LTBI. However, many TB programs and health departments prioritize DOT for treatment of LTBI for those at high risk of progression from infection to severe forms of TB disease. This includes children younger than 5 years of age, immunosuppressed children, adolescents, children who were contacts to a person with infectious TB, those who were contacts to a person with MDR-TB, and those with evidence of non-adherence. Availability of DOT for LTBI in children through health departments will depend on program policies and available resources. (See page 34 for additional information on collaborating with health departments for provision of DOT in children and adolescents.)

The AAP guidelines outline three regimens for treatment of LTBI in children:⁴

- Isoniazid and rifampine once weekly for 12 weeks (currently for children 2 years of age and older)
- Rifampin daily for 4 months
- Isoniazid daily for 9 months (or twice weekly under DOT, if adherence to daily therapy cannot be ensured)

The AAP also notes two additional regimens that are considered adequate for treatment of LTBI in children; 1) three months daily isoniazid and rifampin and 2) two months of daily rifampin and pyrazinamide (only when given as part of four-drug therapy for suspected TB disease that is subsequently determined to be *M. tuberculosis* infection only).⁴

The following pages provide details on each of the three main regimens included in the 2018 Red Book. The table on page 27 summarizes all five regimen options, including recommended dosage. Providers should refer to current literature or consult a TB expert for complete information and considerations for use of these regimens. For children taking other medications, a drug-drug interaction check is suggested prior to regimen selection.

TREATMENT REGIMENS FOR LATENT TB INFECTION

Isoniazid and Rifapentine 12-dose regimen (INH-RPT)^{4,10, 11}

This once-weekly regimen provided for 12 weeks may be used in children as young as 2 years of age since it has been shown to be safe, well-tolerated, and at least as efficacious as 9 months of INH in these children, with higher completion rates.⁸

- Many experts prefer this regimen for treatment of LTBI in children 5 years of age and older, and some prefer this regimen in children 2 years of age and older
- This regimen should *not* be used for children younger than 2 years of age (because of the lack of pharmacokinetic data or an established dose for rifapentine in this population), pregnant adolescents or those expecting to become pregnant while on treatment, patients who have known exposure to a person with infectious TB disease that is INH or RIF resistant, and HIV-infected children receiving certain antiretroviral (ARV) medications
- Rifapentine interacts with some ARV medications; thus, HIV-infected children on ARV treatment who have LTBI should be referred for specialty care or consultation with a pediatric TB/HIV specialist
- The regimen can be provided to children through self/family administration (SAT) or, as preferred by many experts, through DOT in coordination with state or local health departments or school nurses. Some providers use a combination of SAT and DOT, where DOT is provided at monthly monitoring visits at weeks 4, 8, and 12

Many health departments prioritize DOT for treatment of LTBI in children younger than 5 years of age, immunosuppressed children, adolescents, children who are contacts to a person with infectious TB, and those with evidence of non-adherence

- Providers should choose the method of administration based on local practice, individual patient attributes or preferences, and other considerations, including risk for progression to severe forms of TB disease
- Based on current formulation, the pill burden for this regimen can be high (see table on page 27). However, new RPT formulations are in development and crushing of tablets (as described on the next page) can assist in masking the pill burden

As this regimen becomes more widely utilized for treatment of LTBI in children and adolescents, additional information on best practices will be available; referral to updated CDC and AAP resources is recommended.

Formulation

Isoniazid (INH): 100 mg and 300 mg tablets

A liquid preparation is also available or can be compounded by a pharmacy, but contains sorbitol which can cause diarrhea, abdominal pain, or cramping and, therefore, is generally not recommended.

Rifapentine (RPT): 150 mg tablets packed in blister packs

- Packs should be kept sealed until use
- May not be readily available at commercial pharmacies

Techniques for administration

Isoniazid

- For children unable to swallow tablets, the INH tablets should be crushed and dissolved in a few drops of warm water to create a slurry, then mixed with a small amount of semi-soft food the child likes (e.g., mashed bananas, or sugar-free applesauce, pudding, or yogurt)
- The crushed medication slurry should be mixed with the smallest amount of food possible to ensure the child consumes the entire dose
- Afterwards, a spoonful of food without medicine should be given, followed by liquid to wash down the INH. For accurate dosing, do not add crushed medication to a full glass of water or milk, as the drug will sink to the bottom
- The technique of crushing and mixing with food is generally successful and can be used in most children

Rifapentine

- Methods of administration for RPT in children have not been standardized, however, the above process of crushing, creating a slurry, and mixing medication with the smallest amount of food possible (that the child likes) may be used
- Administering RPT with food increases bioavailability,⁸ although current recommendations do not address whether the INH-RPT regimen should be given with food

Adverse effects and drug interactions

For severe adverse reactions in children, including hepatotoxicity, treatment should be discontinued and supportive medical care provided as needed. Consultation with a pediatric TB specialist is recommended for restarting and managing treatment.

Report adverse events from LTBI treatment to FDA Medwatch at

www.accessdata.fda.gov/scripts/medwatch/index.cfm or 1-800-FDA-1088 and the CDC Division of Tuberculosis Elimination at ltbidrugevents@cdc.gov.

Isoniazid:

- Hepatotoxic effects in children are rare, but life threatening; parents should be educated about early signs of hepatotoxicity. Parents should also be counseled that prolonged use of acetaminophen with INH treatment may result in hepatotoxicity. Alternatives such as nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended when anti-pyretic or pain relief is indicated
- INH should be stopped immediately if the patient develops significant nausea, vomiting, anorexia, abdominal pain, or jaundice (see monitoring section for additional information)
- Baseline liver function tests are not recommended unless there are conditions that might increase the risk of hepatotoxicity (see page 30)
- Peripheral neuritis or seizures caused by the inhibition of pyridoxine metabolism are rare in children and adolescents who receive the recommended doses of INH; most do not need supplementation

Pyridoxine (vitamin B6) supplementation at a daily dose of up to 1 mg/kg/day; usually 25-50 mg/day (maximum 50 mg/day)^a is recommended for the following patients receiving INH:⁴

- Children on meat and milk-deficient diets
 - Children with nutritional deficiencies
 - Children with symptomatic HIV infection
 - Adolescents who are pregnant or breastfeeding
 - Exclusively breast-fed infants^b
 - Patients with existing peripheral neuropathy or paresthesias (or those who develop symptoms on INH)
- INH is a CYP3A inhibitor. INH may increase concentrations of certain cytochrome P450 substrates, including carbamazepine, phenytoin, and valproate; therefore, doses of these medications should be adjusted in collaboration with a clinical pharmacist if INH is to be used

a Common vitamin B6 formulations are 25, 50 or 100 mg tablets; for infants, infant vitamin drops as recommended by the child's pediatrician will provide the proper amount of vitamin B6 needed for supplementation.

b Infants taking INH who receive a combination of breastmilk and commercial infant formula do not require vitamin B6 supplementation as commercial infant formulas contain sufficient vitamin B6.

Rifapentine:

- Hepatotoxic effects are rare; the most common side effect is gastrointestinal upset
- Temporary orange discoloration of urine, sweat, tears, and other bodily fluids is a normal and an expected side effect. Patients should be warned that it may cause permanent orange discoloration of contact lenses; this has been best described in patients wearing permanent hard contact lenses, and is unlikely to occur for patients who use disposable contact lenses
- Rifamycin-associated drug interactions, include but are not limited to, hormonal contraceptives, antiretrovirals, anticonvulsants, methadone, oral hypoglycemic agents, anticoagulants, and psychotropic medications
- Adolescents using hormonal contraceptives should be advised to use additional forms of birth control, such as a barrier method, while on treatment
- Other possible adverse reactions include hypersensitivity reaction (e.g., hypotension or thrombocytopenia), flu-like symptoms, rash and pruritis, polyarthralgia, and myelosuppression. Hypersensitivity reactions, which have been reported more frequently in adults, are rare in children and adolescents

4 Months of Rifampin (RIF)⁴

Daily rifampin for 4 months* is an acceptable regimen for treatment of LTBI in children and adolescents. Extensive published and unpublished experience with this regimen in children demonstrate the effectiveness, safety, and tolerability (in addition to much higher completion rates) as compared to 9 months of INH.

* Continuous daily therapy is required; intermittent therapy, even by DOT, is not recommended.

Formulation

Rifampin (RIF): 150 mg and 300 mg capsules

Rifampin can be compounded into a suspension by a pharmacy. Administration may be difficult due to taste and quantity (though many compounding pharmacies can add flavoring).

Techniques for administration

- For children unable to swallow capsules, the capsules can be opened and contents mixed with a small amount of semi-soft food the child likes to mask the bitter taste (e.g., applesauce, mashed bananas, pudding, or yogurt) or suspended in a small amount of flavored syrup
- The medication should be mixed with the *smallest* amount of food possible to ensure the child consumes the entire dose
- Afterwards, a spoonful of food without medicine should be given, followed by liquid to wash down the RIF. For accurate dosing, *do not* add contents of the capsule to a full glass of water, milk, or other liquid
- The technique of opening capsules and mixing with food is generally successful; a compounded suspension may be used for infants when the correct dose cannot be achieved with 150 mg capsules

Adverse effects and drug interactions

For severe adverse reactions in children, including hepatotoxicity, treatment should be discontinued and supportive medical care provided as needed. Consultation with a pediatric TB specialist is recommended for restarting and managing treatment. Report adverse events from LTBI treatment to FDA Medwatch at www.accessdata.fda.gov/scripts/medwatch/index.cfm or 1-800-FDA-1088 and the CDC Division of Tuberculosis Elimination at ltbidrugs@cdc.gov.

- Hepatotoxic effects are rare; the most common side effect is gastrointestinal upset
- Temporary orange discoloration of urine, sweat, tears, and other body fluids is a normal and an expected side effect. Patients should be warned that it may cause permanent orange discoloration of contact lenses; this has been best described in patients wearing permanent hard contact lenses and is unlikely to occur for patients who use disposable contact lenses
- Rifamycin-associated drug interactions, include, but are not limited to, hormonal contraceptives, antiretrovirals, anticonvulsants, methadone, oral hypoglycemics, anticoagulants, and psychotropic medications
- Adolescents using hormonal contraceptives should be advised to use additional forms of birth control, such as a barrier method, while on treatment
- Other possible adverse reactions include hypersensitivity reaction (e.g., hypotension or thrombocytopenia), flu-like symptoms, rash and pruritis, polyarthralgia, and myelosuppression

9 Months of Isoniazid (INH)⁴

Daily INH for 9 months has efficacy approaching 100 percent when adherence is high, but adherence and completion rates are generally low (<50%) when medication is self-administered.

- INH should *not* be used in children who have previously been treated for TB disease or when the source case has suspected or proven INH resistance
- Twice-weekly dosing for 9 months may be considered when adherence to daily therapy cannot be ensured but *must* be administered via DOT

Formulation

Isoniazid (INH): 100 mg and 300 mg scored tablets

A liquid preparation is also available or can be compounded by a pharmacy, but contains sorbitol which can cause diarrhea, abdominal pain, or cramping and, therefore, is generally not recommended.

Techniques for administration

- For children unable to swallow tablets, the INH tablets should be crushed and dissolved in a few drops of warm water to create a slurry, then mixed with a small amount of semi-soft food the child likes (e.g., mashed bananas, or sugar-free applesauce, pudding, or yogurt)
- The crushed medication slurry should be mixed with the smallest amount of food possible, to ensure the child consumes the entire dose
- Afterwards, a spoonful of food without medicine should be given, followed by liquid to wash down the INH. For accurate dosing, do not add crushed medication to a full glass of water or milk, as the drug will sink to the bottom
- For infants, the tablet should also be crushed and dissolved in a few drops of warm water, then mixed with approximately 10 ccs (about 2 teaspoons) of breast milk or formula and placed in a nipple for administration
- The technique of crushing and mixing with food is generally successful and can be used in most children. However, liquid INH formulations may be used for small infants (<5 kg) if an accurate dose cannot be obtained using tablets

Adverse effects and drug interactions

For severe adverse reactions in children, including hepatotoxicity, treatment should be discontinued and supportive medical care provided as needed. Consultation with a pediatric TB specialist is recommended for restarting and managing treatment. Report adverse events from LTBI treatment to FDA Medwatch at www.accessdata.fda.gov/scripts/medwatch/index.cfm or 1-800-FDA-1088 and the CDC Division of Tuberculosis Elimination at tbidrugs@cdc.gov.

- Hepatotoxic effects in children are rare, but life threatening; parents should be educated about early signs of hepatotoxicity. Parents should also be counseled that prolonged use of acetaminophen with INH treatment may result in hepatotoxicity. Alternatives such as nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended where anti-pyretic or pain relief is indicated
- INH should be stopped immediately if the patient develops significant nausea, vomiting, anorexia, abdominal pain, or jaundice (see monitoring section for additional information)
- Baseline liver function tests are not recommended unless there are conditions that might increase the risk of hepatotoxicity (see page 30)

- Peripheral neuritis or seizures caused by the inhibition of pyridoxine metabolism are rare in children and adolescents who receive the recommended doses of INH; most do not need supplementation

Pyridoxine (vitamin B6) supplementation at a daily dose of up to 1 mg/kg/day; usually 25-50 mg/day (maximum 50 mg)^a is recommended for the following patients receiving INH:⁴

- Children on meat and milk-deficient diets
 - Children with nutritional deficiencies
 - Children with symptomatic HIV infection
 - Adolescents who are pregnant or breastfeeding
 - Exclusively breast-fed infants^b
 - Patients with existing peripheral neuropathy or paresthesias (or those who develop symptoms on INH)
- INH is a CYP3A inhibitor. INH may increase concentrations of certain cytochrome P450 substrates, including carbamazepine, phenytoin, and valproate; therefore, doses of these medications should be adjusted in collaboration with a clinical pharmacist if INH is to be used

^a Common vitamin B6 formulations are 25, 50 or 100 mg tablets; for infants, infant vitamin drops as recommended by the child's pediatrician will provide the proper amount of vitamin B6 needed for supplementation.

^b Infants taking INH who receive a combination of breastmilk and commercial infant formula do not require vitamin B6 supplementation as commercial infant formulas contain sufficient vitamin B6.

Summary of regimens for latent TB infection treatment in infants, children, and adolescents

See section on each regimen for specific information including contraindications, medication preparation, and administration.

Drug(s)	Formulation	Duration / Total Doses	Frequency	Dose
Isoniazid (INH) and Rifapentine (RPT)	100 or 300 mg tablets 150 mg tablets in a blister pack ^a	3 months/ 12 doses	Once weekly ^b	Children aged 12 years and older: INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; max. 900 mg RPT: 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 Max. 900 mg Children aged 2-11 years: INH: 25 mg/kg; rounded up to the nearest 50 or 100 mg; max. 900 mg RPT: same as above
Rifampin (RIF)	100 or 300 mg capsules	4 months/ 120 doses	Daily	<u>Infants, children, and adolescents:</u> 15-20 mg/kg ^c ; max. 600 mg
Isoniazid (INH)	100 or 300 mg tablets	9 months/ 270 doses	Daily	<u>Infants, children, and adolescents:</u> 10 (range 10-15) mg/kg; max. 300 mg
		9 months/ 76 doses	Twice weekly ^d	<u>Infants, children, and adolescents:</u> 20-30 mg/kg; max. 900 mg
Additional possible regimens for treatment of LTBI				
Isoniazid (INH) and Rifampin (RIF)	100 or 300 mg tablets 100 or 300 mg capsules	3 months/ 90 doses	Daily	<u>Infants, children, and adolescents:</u> INH: 10 (range 10-15) mg/kg; max. 300 mg RIF: 15-20 mg/kg ^c ; max. 600 mg
Rifampin (RIF) and Pyrazinamide (PZA)	100 or 300 mg capsules 500 mg tablets	2 months/ 60 doses	Daily	RIF: 15-20 mg/kg ^c ; max. 600 mg PZA: 30-40 mg/kg; max. 2g
When given as part of 4-drug therapy for suspected TB disease later found to be TB infection only. Due to an increased risk of hepatotoxicity with a regimen consisting of only RIF and PZA, this option should <u>NOT</u> be used outside of a four-drug regimen.				

^a Blister pack should be kept sealed until use.
^b The INH-RPT regimen can be provided via directly observed therapy (DOT) or self/family administration. The choice is based on local practice, individual patient attributes and preferences, and other considerations, including risk for progression to TB disease, especially severe forms such as disseminated TB or TB meningitis. Because of this risk, many experts prefer to collaborate with health departments to provide this regimen to children using DOT.
^c The AAP notes that many experts recommend using a daily RIF dose of 20-30 mg/kg/day for infants and toddlers.⁴
^d The INH twice weekly regimen must be provided via DOT.

COMPLETION OF THERAPY

Allowing for short gaps, the total number of doses over a specified period is what determines completion of treatment, as defined by CDC:^{1,10}

- **Once weekly INH-RPT regimen:** CDC defines completion as 11 or 12 doses within 16 weeks, though many experts prefer to achieve 12 doses within 16 weeks
- **4-month regimen of daily RIF:** 120 doses within 6 months
- **9-month regimen of daily INH:** 270 doses within 12 months
 - **9-month regimen of twice weekly dosing of INH (must be provided by DOT):** 76 doses within 12 months

INTERRUPTIONS IN THERAPY

Providers should ask parents or caregivers about planned extended vacations or absences and take this into consideration when starting treatment for LTBI. In situations where treatment for LTBI is provided by DOT, one way to avoid interruptions in therapy is to be sure that the family will not be traveling for an extended period of time while the child is on treatment, as this can make the logistics of arranging DOT challenging. If available, video-based DOT may be an option for treatment administration. In some cases, treatment initiation may be delayed in order to avoid interruptions. When interruptions in treatment do occur, providers should attempt to determine and address the reason for these lapses, including the regimen itself (e.g., intermittent versus daily therapy).

If there is an interruption in treatment for more than 3 months during treatment with INH^a or 2 months during treatment with RIF, the treatment regimen should be restarted from the beginning after a careful history and physical examination (including chest radiograph if indicated) has ruled out TB disease.^b When deciding if a chest radiograph is indicated, providers should consider the length of the treatment interruption, the risk of progression to severe disease (including very young age), presence of symptoms, and abnormal findings on the physical exam.

Specific recommendations are not available for interruptions in the 12-dose INH-RPT regimen which result in a situation where the recommended number of doses cannot be completed within 16 weeks. Many experts would recommend restarting LTBI treatment in this case, after TB disease has been ruled out. Consultation with a pediatric TB expert is suggested.

a In limited situations, when a child has completed 6 consecutive months of uninterrupted daily therapy with INH as part of a 9-month regimen, some experts may consider this to be adequate treatment. This is consistent with World Health Organization recommendations¹² and restarting and completing therapy (either with a 9-month course of INH or a shorter rifamycin-based regimen) may not be acceptable for children and families.

b Early symptoms of TB disease in children can be non-specific and may include poor appetite, failure to gain weight, and general malaise, as well as classic signs such as cough, fever, and weight loss. Children may also be asymptomatic and have a normal physical exam.

MONITORING DURING LATENT TB INFECTION TREATMENT

Children on LTBI treatment should be monitored monthly by a health care provider. This regular contact is an important aspect of management and allows for ongoing evaluation of the treatment plan and development of a relationship with the child and caregiver. When a monthly physician visit is not feasible, an evaluation should be performed by a nurse with knowledge of TB. Additional visits may be required intermittently if questions or problems arise. Visits should be as convenient and brief as possible. Adherence to monthly follow-up visits is especially important for children whose medication is being administered by families or self-administered.

Regular patient-provider contact, including monthly monitoring, offers the opportunity to:

- Stress the importance of adherence
- Perform a physical examination, checking for any signs and symptoms of TB disease or possible adverse reactions
- Address concerns the patient or caregiver may have regarding treatment
- Educate the patient and family about expected medication side effects (e.g., temporary orange discoloration of bodily fluids) and possible adverse effects
- Inquire about status of TB testing for family and other contacts, as well as identification of a source case

Monthly assessment should include a history and physical examination and should document the following:

- Adherence to medication regimen, including pill count for children not on DOT
- Presence of adverse reactions (based on regimen used) such as: decreased appetite, malaise, abdominal complaints (nausea, vomiting, pain), peripheral neuropathy, hypersensitivity reactions (including hypotension or thrombocytopenia), flu-like symptoms, or hematologic toxicity
- Child's weight (compare to previous weight)
- Indications of drug toxicity such as icterus, or jaundice
- All other prescription and non-prescription medications
- Alcohol/substance use
- Oral contraceptive use and date of last menstrual period in adolescent girls

In some cases, DOT and monitoring can be provided in coordination with the local health department or TB program. Screening for adverse reactions should occur prior to each dose for children on any regimen receiving DOT. When the 12-dose INH-RPT regimen is provided through DOT at a health department clinic or other health care facility, a monthly assessment can be performed when the medications are administered.

For severe adverse reactions in children, including hepatotoxicity (which is discussed in more detail below), treatment should be discontinued, and supportive medical care provided as needed. Conservative management and continuation of therapy under direct observation may be considered for mild to moderate adverse reactions as determined by the health care provider.

Parents should be provided written educational material and instructed to stop medications and contact the provider immediately when they first note any symptoms of possible adverse reactions, in particular hepatotoxicity (i.e., nausea, vomiting, abdominal pain, jaundice). For parents of children and adolescents on the 12-dose INH-RPT regimen, providers should mention the symptoms of adverse reactions including drug hypersensitivity reactions, rash, hypotension, or thrombocytopenia.

Hepatotoxicity/liver function tests (LFTs)

Routine monitoring of serum transaminase concentrations is not recommended. The monthly clinical evaluation to identify signs and symptoms of hepatotoxicity (described on the previous page) is considered to be appropriate follow-up for children receiving treatment for LTBI. However, monitoring of serum transaminase levels before and during treatment is indicated in children being treated for LTBI in the following situations:^{1,4,11}

- Underlying (or history of) hepatic or biliary disease, including prior elevation of transaminases
- Pregnant or in the first 3 months postpartum
- Clinical evidence of hepatotoxic effects
- Concurrent use of other hepatotoxic drugs (e.g., anticonvulsants or HIV agents)
- HIV infection
- Regular alcohol use
- Injection drug use
- Risks for hepatic disease

Additionally, some experts would consider liver function tests in morbidly obese adolescents, who may have increased risk of transaminitis due to nonalcoholic steatohepatitis. When hepatic blood chemistry tests are indicated during treatment for LTBI, they should be repeated at subsequent monthly clinical encounters.

Management of symptoms consistent with hepatotoxicity

- Patients who develop symptoms consistent with hepatotoxicity should be evaluated promptly by a physician, with treatment changes as indicated
- Medication should be withheld and patients evaluated if:
 - Transaminase levels ≥ 3 times upper limit of normal in the presence of symptoms
 - Transaminase levels ≥ 5 times upper limit of normal in asymptomatic patients
- If children taking LTBI treatment develop hepatitis, treatment should be discontinued and an evaluation done to determine the cause of the hepatitis

When LFTs have returned to normal, consider an alternative regimen, with close clinical and laboratory monitoring. Consultation with a pediatric TB specialist is recommended for management, options for continued treatment, and/or approaches for re-challenging with medications.

Report adverse events from LTBI treatment to FDA Medwatch at www.accessdata.fda.gov/scripts/medwatch/index.cfm or 1-800-FDA-1088 or the CDC Division of Tuberculosis Elimination at ltbidrugevents@cdc.gov.

TREATMENT UNDER SPECIAL CIRCUMSTANCES

Children recently exposed to a person with TB disease

The following recommendations apply to children who are **contacts** to persons with confirmed or suspected infectious pulmonary TB disease.

When the source case has drug-susceptible TB:

- Children with a positive initial TST or IGRA should be treated for LTBI after TB disease is ruled out
- Immunosuppressed children and those younger than 5 years of age should be started on treatment with INH once TB disease is excluded, even if the initial test for TB infection is negative; this is known as **window prophylaxis**
- The TST or IGRA should be repeated 8-10 weeks after exposure to the source case has ended or after the source case has been deemed to be non-infectious, since it can take this amount of time for an immune response to develop
 - Treatment for those on window prophylaxis can be stopped in immunocompetent children if the repeat TST or IGRA is negative; treatment should continue until the completion of therapy for immunosuppressed children after an evaluation for TB disease. Some experts may also continue treatment in very young infants, based on the individual circumstance
 - All pediatric contacts whose repeat TST or IGRA is positive should be carefully re-evaluated for the presence of TB disease including a history, physical exam, and chest radiograph
 - For children already on window prophylaxis, if no disease is found, the child should complete the recommended regimen of INH for a total of 9 months, or be switched to an appropriate shorter course regimen, such as 4 months of rifampin or 12 once-weekly doses of isoniazid and rifapentine. While full a course of these regimens would be required, either would result in a shorter overall treatment period as compared to 9 months of INH
 - Children whose repeat test for TB infection is positive, who are not already on window prophylaxis should begin treatment with any acceptable regimen after TB disease is ruled out

When the source case has isoniazid-resistant/rifampin-susceptible TB:

- Consult a specialist with experience in treating pediatric TB
- Treatment of choice is daily rifampin as monotherapy for 4 months

When the source case has multidrug-resistant TB (MDR-TB; resistant to at least INH and RIF):

- Consult a specialist with experience in treating pediatric MDR-TB
- Treatment for LTBI should be guided by the in-vitro susceptibility test results from the isolate of the source case
- The most commonly used regimens are fluoroquinolone-based regimens (moxifloxacin or levofloxacin) of 6-12 months duration

Referring to a specialist

Consider consultation with an expert in management of pediatric tuberculosis if the child with LTBI:

- Exhibits any signs or symptoms of TB disease such as abnormal chest radiograph, cough, weight loss, anorexia, or change in activity level
- Is living with HIV or immunosuppressed
- Has a history of liver disease
- Is a contact to a person with INH-resistant or multidrug-resistant TB
- Develops hepatitis or other severe adverse drug reactions
- Has significant interruptions in treatment, particularly with the INH-RPT 12-dose regimen

State TB Programs or the TB Centers of Excellence can arrange consultations with a pediatric TB expert (see Resources on page 44). Referral to the TB or health department clinic may also be helpful if the family requires additional counseling and/or has financial concerns that would benefit from health department involvement.

KEYS TO SUCCESSFUL TREATMENT

Completion of treatment for LTBI can be challenging for a variety of reasons: treatment duration can be long, children are not currently ill, and parents may have concerns about the safety and efficacy of treatment. Additionally, the administration of medications to children can be challenging. However, there are strategies and approaches that can be used to ensure adherence and successful treatment completion. Some specific suggestions for adherence strategies based on the age of the child can be found in Appendix B.

Selecting an appropriate regimen

Multiple studies have shown that shorter regimens for treatment of LTBI have higher completion rates as compared to 9 months of daily INH. Utilizing the 12-dose INH-RPT regimen or the 4-month RIF regimen in children and adolescents who are eligible for these regimens may be more acceptable for families and, thus, improve adherence and treatment completion.

Education and communication with family members

Parents and guardians of children with LTBI should be viewed as partners in care. Ongoing dialogue, education, and encouragement for the parent and patient is an

important aspect of management of LTBI in children. Providers should:

- Clearly explain the benefits of treatment for LTBI at the first encounter and throughout the course of therapy, particularly when there are concerns about the length of therapy
- Remind the patient and family that when treatment is completed, the child will likely never need future testing or treatment
- Encourage parents to discuss the importance of taking medication and potential consequences of non-adherence with older children and adolescents *and* to monitor children taking medication
- Share anecdotal stories of children with TB and provide educational materials to help parents realize the importance of treatment (see resources on page 43)
- Emphasize that it may take a few days before children, especially young children, start taking the medications well, but that after some practice for both parents and children, the process will go more smoothly and become routine

Written materials should also include instructions to stop medications and contact the provider immediately if the parent notes any of the signs of medication intolerance or toxicity.

Techniques for medication administration

Administering medications to children, especially very young children, can be challenging and stressful for both parents and children. This can be especially true for treatment of LTBI, which may require taking medications over a long time period. However, utilizing some specific strategies can improve this process:

- Instruct parents on proper medication administration techniques. As previously noted, medications used to treat LTBI can be crushed (or capsules opened) and then placed in food to make swallowing easier and more palatable. Consult specific instructions for administration of each drug or regimen
- If medications are to be mixed with food, tell parents to utilize foods that children like such as mashed bananas, applesauce, pudding, or yogurt (the latter three should be sugar-free if child is receiving INH)
 - Once the medication is ingested, a spoonful of food without medication should be offered
 - Food should be varied periodically so that child does not develop an aversion to any specific food
 - If possible, schedule medication administration when the child is likely to be hungry and is less likely to refuse
- If children complain of an upset stomach or nausea after taking medication, parents can offer a small snack to relieve the discomfort, or in cases of mild nausea, advise parents to try administering medicines at bedtime
- Describe the benefits of establishing a routine for medication administration to the family, for example, taking the medication at mealtime, bedtime, or before brushing teeth

Incentives

Incentives can help encourage a child to take medications appropriately. Parents should provide positive feedback, encouragement, and incentives that they feel are reasonable, appropriate, and attractive to their child, while considering the age and developmental level of the child. Some examples of small tangible rewards include stickers, books, games, or special experiences or outings.

Directly observed therapy

Directly observed therapy (DOT) is the term used to describe the observation of TB medication ingestion by a member of the health care team. State and local health departments and TB programs can provide expert consultation on TB as well as other resources. While DOT is the standard of care for patients with TB disease, it can also improve adherence in children with LTBI. Depending on their policies and resources, health departments and TB programs may collaborate with providers to provide DOT for LTBI in those at risk for progression to severe forms of TB. Many TB programs consider DOT to be a priority for children younger than 5 years of age, immunosuppressed children, adolescents, recent contacts to a person with infectious pulmonary TB disease, contacts to those with MDR-TB, and those with evidence of non-adherence. Primary care providers treating children for LTBI should be aware of community resources for DOT and can utilize these resources where available.

Schools can also be asked to collaborate in LTBI treatment by providing DOT. The school nurse may be able to dispense medication, observe and document ingestion, and report any adverse reactions.

Some important consideration while administering medication for LTBI in the school setting include:

- Ongoing communication and collaboration between the school and health care provider are necessary to achieve success in a school DOT program
- Due to the potential stigma of TB, patient confidentiality must be ensured in the school setting
- Alternate methods of providing medications can be developed in advance for planned school vacations or absences; the treatment period can be extended if doses are missed for illness or other unplanned absences
- Parental consent is needed for administration of medication in school
- Communication with the parent during the course of treatment is essential

For information on establishing a school DOT program, refer to the *Tuberculosis Handbook for School Nurses from the Global Tuberculosis Institute*: globaltb.njms.rutgers.edu/educationalmaterials/productfolder/tbedusn2.php.

DOCUMENTING COMPLETION OF TREATMENT

When treatment for LTBI is completed, written documentation should be provided to the family (see Appendix C for sample letters). There may be instances when this information will be necessary, such as entrance to college, armed services, or employment in the health care industry. This document should be reviewed with the family and should summarize the child's diagnosis and treatment. The following information must be recorded:

- The dates when the TST or IGRA was administered, read, and interpreted and results (expressed in millimeters of induration for TST)
- The date and findings of the chest radiograph
- The diagnosis and treatment given, including the medication, dosage, and duration of treatment (number of doses within specific time frame)
- A statement that the patient is not infectious
- A statement that no further testing for TB infection should be performed and no chest radiograph is required unless symptoms suggestive of TB (e.g., unexplained/prolonged cough, weight loss, or fever) are noted
- Contact information for the provider/facility

The provider should ensure that the family understands both the child's diagnosis of LTBI and that treatment has been completed. The family should be instructed to keep the original documentation/letter in their possession and to provide a copy when requested. After treatment completion, the patient can be discharged from care with a final reminder that if the child or a family member develops symptoms of TB such as persistent cough, fever, or weight loss, the possibility of TB should be considered and medical care should be sought.

SUMMARY

Pediatric primary care providers have an important role in the prevention and elimination of tuberculosis. Early identification and management of LTBI in children and adolescents involves the following:

- Assessing each individual child for risk of LTBI
- Testing children when one or more risk factors are present
- Evaluating all children with a positive TB test to rule out TB disease, and referring those with suspected TB disease to a pediatric TB specialist
- Educating the patient and family about TB, LTBI treatment, medication side effects, possible adverse reactions, and the importance of adherence
- Initiating appropriate treatment, monitoring children while on therapy, managing minor side effects, and seeking expert consultation as needed for severe adverse reactions
- Coordinating with the local health department as needed for access to potential resources including medications and provision of DOT
- Providing appropriate follow up to ensure completion of therapy and providing the patient and family with documentation of treatment completion



Appendix A

ADMINISTRATION, MEASUREMENT, AND INTERPRETATION OF THE TST

The Mantoux test is the recommended TST. It is administered by injecting 0.1 ml of 5 TU of purified protein derivative (PPD) solution intradermally into the volar surface of the forearm using a 27-gauge needle with a tuberculin syringe.* The TST should be administered and interpreted by a trained health care professional.

Administration of the TST

- Store purified protein derivative (PPD) solution at 36-46° F and separate from other biologics, for example DTaP
- Avoid fluctuations in temperature. Do not store PPD solution in the refrigerator door shelf
- Label the vial with date it was opened and discard unused portion within 30 days
- Fill syringes immediately prior to administration
- Select the injection site; avoid areas of skin with veins, rashes, or excess hair
- Cleanse the area with alcohol swab and inject PPD solution just below the surface of the skin, forming a 6-10 mm wheal (a pale, raised area with distinct edges)
- Measure the wheal using a TST ruler. If no wheal forms or if it is less than 6 mm, the test should be repeated immediately at a site that is approximately 2 inches from the original site or on the opposite arm
- Clean the ruler with an alcohol swab after each use
- Dab the injection site with cotton if minor bleeding occurs
- Do not cover the area with a bandage
- Record the date, time, and site of the intradermal injection
- Record the brand name of the PPD solution, the lot number, manufacturer, and expiration date
- Instruct the parent and child that the site should not be covered with a bandage and that the child should not scratch the injection site
- Tell the parent and child of the importance of returning within 48-72 hours (2-3 days) for interpretation
- Give written confirmation of appointment to return for TST interpretation

* Controls (anergy panels) are never recommended.

Measurement of TST reactions

- Locate the skin test site, verify from the record which arm was tested, and confirm with patient/family
- Inspect and palpate the area with fingertips to identify areas of induration rather than erythema
- Measure the area of induration perpendicular to the long axis of the arm
- Using a ballpoint pen, mark the edges of induration
- Measure the distance between the two edges of induration using a TST ruler or ruler with millimeter calibration (measure only induration, not erythema)

Recording/documentation

- Record the date TST was administered
- Record the results in millimeters of induration (00 mm if there is no induration) rather than as 'positive' or 'negative'
- Record the date and time of reading
- Interpret TST results based on established cut points (see page 10)

Patient education

- Explain the significance of a positive TST result, answer questions, and explain the next steps in evaluation (e.g., chest X-ray for patients with positive test results)
- Provide the patient/parent with appropriate educational materials
- Provide documentation of TST reaction
- Instruct patients who had no reaction at 48-72 hours to return for evaluation if induration occurs later
- Inform the family of possibility that TB program personnel will test other household members in search of a source case, especially for children younger than 5 years of age with a positive TB test
- Advise the family that there is no need for further TB skin testing if the child has a positive TST result



Appendix B

ADHERENCE STRATEGIES FOR DIFFERENT AGE GROUPS*

AGE	ADHERENCE STRATEGY
Infant Birth-1 year	Parents and caregivers must understand the need for treatment. To promote adherence, offer medication when baby is hungry. Tablet can be crushed and dissolved in small amount of warm water, then mixed with milk. Mix with approximately 10 cc of breast milk or formula. INH liquid contains sorbitol, which can cause diarrhea, therefore, it is not recommended. Crushed INH can also be mixed with a small amount of baby food such as cereal or fruit and given by spoon.
Toddler 1-3 years	Use distraction. Disguise taste by mixing with a small amount of food of the child's choice. Expect difficulty at first but be persistent, most toddlers will eventually learn to take medications. Give simple explanations. Use incentives for each daily dose if needed.
Preschooler 3-5 years	Give simple explanations. Allow some negotiation for time of medication administration or vehicle used. Offer rewards and verbal praise, but be consistent and assertive.
School age 5-12 years	Discuss treatment plan with child. Provide simple and accurate information. Child may be able to swallow tablets whole. School-based DOT can be used, if available.
Adolescent 12-18 years	Use a calendar to document adherence. Involve adolescent in decision making wherever possible to avoid the potential for poor adherence. School-based DOT is an excellent option, if available. Peer support may also be beneficial.

* Many TB programs consider DOT for LTBI to be a priority for children younger than 5 years of age, immunosuppressed children, adolescents, recent contacts to a person with infectious pulmonary TB disease, contacts of those with MDR-TB, and those with evidence of non-adherence.

Appendix C

SAMPLE LETTERS FOR DOCUMENTING TEST FOR TB INFECTION AND LTBI TREATMENT

Test for TB Infection Record

To Whom it May Concern:

The following is a record of a test for TB infection:

Name: _____ Date of birth: _____

Type of Test and Results

Mantoux tuberculin skin test (TST)	<input type="checkbox"/> Interferon-gamma release assay (IGRA)	
Date and time administered: _____ Date and time interpreted: _____	Type of IGRA Performed: <input type="checkbox"/> QuantiFERON®-TB Gold Plus <input type="checkbox"/> T-SPOT®.TB Date test performed: _____	
Results: _____ mm of induration	QuantiFERON®-TB Gold Plus result	T-SPOT®.TB result
	Interpretation: <input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Indeterminate	Interpretation: <input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Invalid <input type="checkbox"/> Borderline

Signature of Provider: _____ Date: _____

Treatment Completion Letter

To Whom it May Concern:

This letter is to document that (NAME) has successfully completed treatment for latent tuberculosis infection:

Date of birth: _____

TST or IGRA results

<input type="checkbox"/> Mantoux tuberculin skin test (TST)	<input type="checkbox"/> Interferon-gamma release assay (IGRA)	
Date and time administered: _____ Date and time interpreted: _____	Type of IGRA Performed: <input type="checkbox"/> QuantiFERON®-TB Gold Plus <input type="checkbox"/> T-SPOT®.TB Date test performed: _____	
Results: _____ mm of induration	QuantiFERON®-TB Gold Plus result	T-SPOT®.TB result
	Interpretation: <input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Indeterminate	Interpretation: <input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Invalid <input type="checkbox"/> Borderline

Chest X-ray: Date: _____ Results: _____

Date LTBI treatment initiated: _____

Medication(s): _____

LTBI regimen completed: Yes No

Date of completion: _____ Total number of doses: _____

Comments: _____

This person is not infectious. He/she will always have a positive TB test and should not be re-tested for TB infection. Annual or serial chest radiographs are not necessary for follow up and are only indicated in the presence of serious or chronic respiratory illness or other symptoms suggestive of TB disease. If you need any further information, please contact this office.

Signature of Provider: _____ Date: _____



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Resources

Latent TB Infection Resources (Recommendations, resources, and fact sheets for providers and patients), Centers for Disease Control and Prevention:

cdc.gov/tb/publications/tbi/tbiresources.htm

Pediatric Toolbox, Heartland National TB Center:

heartlandntbc.org/pedi-toolkit/

Diagnosis and Treatment of Latent Tuberculosis Infection pocket card, Rutgers Global Tuberculosis Institute:

globaltb.njms.rutgers.edu/educationalmaterials/productfolder/lbtidrugcard.php

LTBI Videos for Primary Care Providers, Rutgers Global Tuberculosis Institute:

globaltb.njms.rutgers.edu/educationalmaterials/productfolder/lbtimulti.php

NTCA Provider Guidance - Using the Isoniazid/Rifapentine Regimen to Treat Latent Tuberculosis Infection (LTBI), National Tuberculosis Controllers Association:

tbcontrollers.org/resources/tb-infection/3hp/

Tuberculosis. In: American Academy of Pediatrics Textbook of Pediatric Care, 2nd Edition. Loeffler A.M., Lobato M.N. Eds: McInerney T.K., Adam H.M., Campbell D.E., Foy J.M., Kamat D.M. Elk Grove Village, IL: American Academy of Pediatrics; 2016.

What You Need to Know About Tuberculosis patient education flipbook, English and Spanish versions, Rutgers Global Tuberculosis Institute:

English:

globaltb.njms.rutgers.edu/educationalmaterials/productfolder/whatyouneedtoknow.php

Spanish:

globaltb.njms.rutgers.edu/educationalmaterials/productfolder/spanish_flipbook.php

ADDITIONAL TB RESOURCES

Centers for Disease Control and Prevention (CDC)

Division of Tuberculosis Elimination

The CDC Division of Tuberculosis Elimination's website contains information on TB in the United States and provides TB education and training materials and resources.

cdc.gov/tb

Find TB Resources Website

This website includes a searchable database of materials from numerous national and international organizations. The site also includes information about other TB organizations, how to order materials, and funding opportunities.

findtbresources.cdc.org

TB Centers of Excellence (COEs)

CDC funds four regionally-assigned COEs to provide training, education and medical consultation services to TB health care workers. The COE all-products page provides COE produced TB educational materials.

sntc.medicine.ufl.edu/rtmccproducts.aspx

Curry International Tuberculosis Center

CITC serves: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming, and the U.S. Pacific Island Territories.

2001 Center Street, Suite 700, Berkeley, CA 94704

510-238-5100 (Phone)

currytbcenter.ucsf.edu

Global Tuberculosis Institute

GTBI serves: Connecticut, District of Columbia, Delaware, Indiana, Massachusetts, Maryland, Maine, Michigan, New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia, and the U.S. Pacific Island Territories.

225 Warren Street, Newark, NJ 07103

973-972-3270 (Phone)

globaltb.njms.rutgers.edu

Heartland National Tuberculosis Center

HNTC serves: Arkansas, Iowa, Kansas, Louisiana, Missouri, Nebraska, North Dakota, Oklahoma, South Dakota, Texas, and the U.S. Pacific Island Territories.

2303 SE Military Drive, San Antonio, TX 78223

800-839-5864 (Phone)

heartlandntbc.org

Southeastern National Tuberculosis Center

SNTC serves: Alabama, Florida, Georgia, Illinois, Kentucky, Minnesota, Mississippi, North Carolina, South Carolina, Tennessee, Wisconsin, Puerto Rico, the U.S. Virgin Islands, and the U.S. Pacific Island Territories.

Physical Address: 2055 Mowry Road, Suite 250, Gainesville, FL 32611

Mailing Address: PO Box 103600, Gainesville, FL 32610-3600

888-265-7682 (Phone)

sntc.medicine.ufl.edu

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