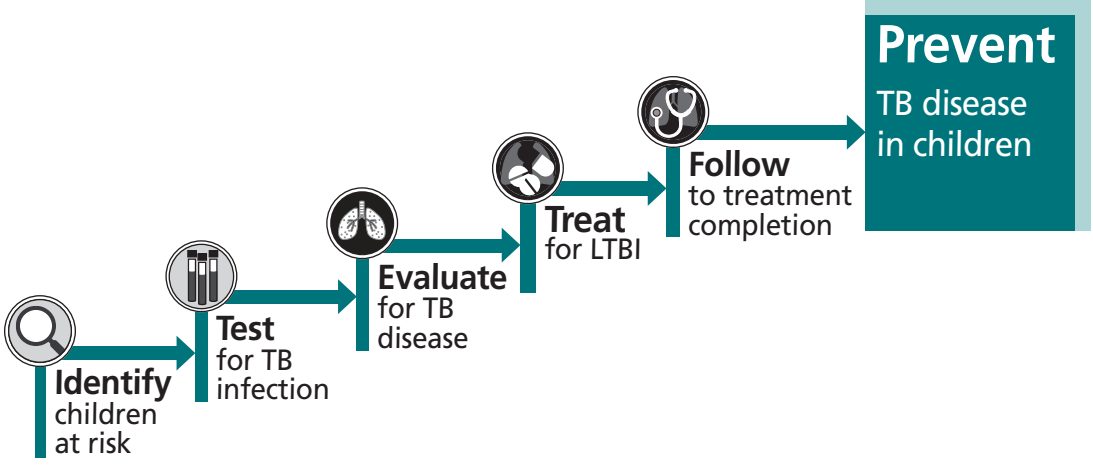
2022

Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI) in Children and Adolescents

Content based on the American Academy of Pediatrics (AAP) 2021 *Red Book: Report of the Committee on Infectious Diseases* with consideration for practical applications



RUTGERS HEALTH
New Jersey Medical School
Global Tuberculosis Institute

225 Warren Street
Newark, NJ 07103
(973) 972-3270
globaltb.njms.rutgers.edu

For additional resources

Identify, Test, and Treat Latent TB Infection (LTBI) in Children and Adolescents

Early diagnosis and appropriate treatment of children infected with *M. tuberculosis* prevents morbidity and mortality:

- Young children with LTBI (also called TB infection, or TBI) are at significant risk of progression to severe forms of TB disease (e.g., miliary or meningeal TB); recent post-pubertal adolescents are also at increased risk for progression
- Infection is likely to be recent in children; recent primary infection poses the greatest risk for progression to TB disease
- Medications for TB infection are well tolerated in children and have a low risk of toxicity
- Testing is not indicated in those without risk factors

Identify and Test Children with Risk Factors for Tuberculosis (TB)

An immediate test for TB infection is indicated for children:

- Who are contacts of persons with confirmed or suspected infectious TB - via a contact investigation (see Special Situations)
- With radiographic or clinical findings suggestive of TB disease
- Who are about to start immunosuppressive therapy (see below)
- Immigrating from countries with endemic infection (e.g., in Asia, Middle East, Africa, Latin America, Eastern Europe, and in the former Soviet Union), including international adoptees
- With a history of significant travel (e.g., >1 month) to endemic countries and substantial contact with the resident population[1]

Children with HIV infection should have an annual test for TB infection

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 special consideration is warranted. Conditions include diabetes mellitus, chronic renal failure, malnutrition, congenital or acquired immune deficiencies (including children receiving TNF alpha inhibitors), and Hodgkin disease and other lymphomas.

Providers should:

- Elicit information about potential TB exposure at each visit; if histories or local epidemiology suggest a possibility of exposure, immediate and periodic testing for TB infection should be considered[2]
- Test for TB infection in children **before** initiation of immunosuppressive therapy (e.g., prolonged systemic corticosteroid administration use equivalent to ≥2 mg/kg/day OR 15 mg of prednisone for ≥1 month, organ transplantation, biologic response modifiers, including TNF-alpha inhibitors)

Validated Questions for Determining Risk of LTBI in Children[3]

Has a family member or contact had TB disease?	Has a family member had a positive test for TB infection?
Was your child born in a high-risk country (other than the U.S., Canada, Australia, New Zealand, or western/northern Europe)?	Has your child traveled to a high-risk country? How much contact did they have with the resident population?

1. If the child is well and has no known TB exposure, the test for TB infection should be delayed for 8 to 10 weeks after returning.
2. Some experts recommend annual testing in children on dialysis or who are receiving immunosuppressive therapy.
3. Based on the AAP 2021 *Red Book;* may ask additional questions based on local epidemiology.

Diagnosis of LTBI in Children and Adolescents

Available Tests

- Two types of tests are available: blood-based interferon gamma release assays (IGRAs) and the tuberculin skin test (TST)
- Neither test can distinguish between LTBI and TB disease
- Negative results from either or both tests cannot exclude LTBI or TB disease
- Negative test results are unreliable in infants <3 months of age
- Results may remain positive for the child's lifetime, even after LTBI treatment

Recommendation for Type of Test

- TST is recommended in children <2 years of age
- IGRAs are generally preferred in children ≥2 years, though TST is acceptable; selection may depend on availability, logistics, and resources
- IGRAs are strongly preferred in BCG-vaccinated children and those unlikely to return for TST interpretation
- Testing with TST **and** IGRA is **not** routinely recommended, but may be considered in some circumstances (e.g., negative result in a young child who has a high risk of infection, progression, or poor outcomes), including test results that are inconsistent with the clinical picture when there is a suspicion for TB disease; **expert consultation is strongly recommended**

IGRAs Available in the United States

QuantiFERON®-*TB* Gold Plus (QFT-Plus)

- Results reported as positive, negative, or indeterminate*

T-SPOT®.*TB*

- Results reported as positive, negative, borderline, or invalid*
- Borderline results: Quantitative values near but not reaching the threshold for positivity; interpretation depends on patient risk factors. In general, the test should be repeated

TSTs

- Requires two visits
- Interpretation (after 48-72 hours) is based on size of induration (not redness) in mm, risk of infection, and risk for progression
- See Additional Resources for more information on interpretation

**Indeterminate and invalid results do not have diagnostic interpretation; may be a result of testing/laboratory issues, improper specimen handling, or patient health (e.g., immunosuppression). Repeat IGRA or administer TST.*

Evaluation of Children with a Positive TST or IGRA Result

- The diagnostic criteria for LTBI includes a positive TST or IGRA result, absence of signs or symptoms of disease, and chest radiograph (CXR) findings that are normal[1] or reveal evidence of healed infection (e.g., calcification in the lung, lymph nodes, or both)
- Evaluation should include detailed health history, physical exam (PE), symptom screen, and CXR
  - Experts recommend both posterior-anterior (PA) and lateral views in children <5 to better evaluate for intrathoracic lymphadenopathy; in older children a single PA chest radiograph may be considered adequate, though clinicians may opt to obtain additional views to aid in decision making, as two-view CXRs are always more sensitive (ideally, films should be obtained and interpreted by a pediatric radiologist)
- Early signs and symptoms of TB disease in children can be non-specific and may include poor appetite, failure to gain weight, and malaise (less playful), as well as classic adult signs and symptoms (e.g., cough, fever, and weight loss). Young children with TB disease may be mildly symptomatic or asymptomatic and have a normal PE
- **Consult a pediatric TB expert if TB disease is suspected or if there are questions about interpreting a TB test result**

1. Asymptomatic lymphadenopathy is considered and treated as TB disease.

Treatment of LTBI in Children

All children with a positive test for TB infection should be evaluated for TB disease before initiating LTBI treatment. Regimens can be provided by self-administered therapy (SAT) or directly observed therapy (DOT)

COMMONLY USED PEDIATRIC TREATMENT REGIMENS[1]

(for those infected with presumed drug-susceptible *M.tb*); consult an expert for exposure to drug-resistant TB)

<table>
<tr><th>REGIMEN</th><th colspan="2">DOSAGE</th><th>COMMENTS</th></tr>
<tr><td rowspan="2">12 Weeks of Once-Weekly Isoniazid (INH) Plus Rifapentine

Administration:
DOT or SAT[2]

Completion Criteria:
12 doses within 16 wks.</td><td>2-11 Years
INH: 25 mg/kg; rounded up to the nearest 50 or 100 mg (max 900 mg)</td><td>≥12 Years
INH: 15 mg/kg rounded up to the nearest 50 or 100 mg (max 900 mg)</td><td rowspan="2">• Preferred by most experts for treatment of LTBI in children ≥2 years of age
Not indicated for:
➢ Children <2 years of age
➢ Children with M.tb infection that is presumed resistant to INH and/or RIF
➢ Children who had prior adverse events or hypersensitivity to INH, RIF, or rifapentine
➢ Pregnant adolescents
• Pill burden is substantial for young children and sometimes is not well tolerated
• Should take with food containing fat, if possible
• Rifapentine may not be readily available</td></tr>
<tr><td colspan="2">Rifapentine:
10-14.0 kg: 300 mg
14.1-25.0 kg: 450 mg
25.1-32.0 kg: 600 mg
32.1-49.9 kg: 750 mg
≥50.0 kg: 900 mg</td></tr>
<tr><td>4 Months of Daily Rifampin (RIF)
Administration: SAT[2]
Completion Criteria:
120 doses within 6 mos.</td><td colspan="2">15-20 mg/kg; max 600 mg</td><td>• Widely used in children and adolescents
• Continuous daily therapy is required
• Consider drug-drug interactions (see next column)</td></tr>
<tr><td>6 or 9 Months of Daily INH[3]
Administration: SAT[2]
Completion Criteria:
6 mo. regimen: 180 doses within 9 mos.
9 mo. regimen: 270 doses within 12 mos.</td><td colspan="2">10-15 mg/kg; max 300 mg</td><td>• Many providers use the INH regimen only when a rifamycin-based regimen cannot be used; long duration can result in poor adherence and lower completion rates
• Although 9 mos. duration is recommended for children (including those with HIV or other immunosuppression), CDC and many experts accept 6 consecutive mos. of uninterrupted daily therapy as adequate</td></tr>
</table>

PATIENT EDUCATION AND ADHERENCE

Including Families/Caregivers as Partners

Consider all caregivers (e.g., both parents or other relatives as appropriate):

- Clearly explain the benefits of LTBI treatment and the importance of treatment adherence at the initial encounter and throughout treatment; share anecdotal stories of children with TB and provide educational materials to help parents understand the importance of treatment; provide information on patient groups (e.g., we are TB: wearetb.com) to connect with others affected by TB
- Discuss treatments options, including pill burden and treatment duration when developing a treatment plan in coordination with parents and families
- Consider input from older children and adolescents; encourage parents of these children to discuss the importance of taking medication and potential consequences of non-adherence and to monitor children taking medication
- 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
- Explain possible side effects and adverse drug reactions and provide patients with written information; **advise to promptly seek medical evaluation for adverse reactions and provide guidance for when to stop medications in the case of serious adverse reactions**

Supporting Adherence to Ensure Successful Completion of Treatment

- Use a patient-centered approach to identify and address possible barriers to treatment completion, providing educational messages relevant to patients, and offering opportunities to bring up concerns or questions
- Work with schools/community agencies for incentives/enablers, case management, or in-person or video-based DOT

Tips for Medication Administration

Administering medications for an extended time can be challenging, especially for very young children. Strategies include:

- Crushing pills or opening capsules and mixing with food for children unable to swallow pills[4]
  - Mix with food the child likes, such as mashed bananas, applesauce, pudding, or yogurt (the latter three should be sugar-free if child is receiving INH)
  - Dissolve crushed pills in a few drops of warm water to create a slurry before mixing with food
  - Use the smallest amount of food possible to ensure that the entire dose is consumed
  - Give medication promptly after mixing with food
  - Offer a spoonful of food without medication once the medication has been ingested
  - Vary food periodically so that child does not develop an aversion to any specific food
- Administering medication when the child is likely to be hungry and is less likely to refuse
- Providing RIF and/or INH at bedtime or with a small snack to children who complain of an upset stomach or mild nausea, the 12-dose INH-rifapentine regimen should ideally be taken with a meal
- Establishing a routine (e.g., taking the medication at mealtime or before brushing teeth)

Treatment of LTBI in Children

ADVERSE DRUG REACTIONS & TREATMENT CONSIDERATIONS

Adverse Drug Reactions (ADRs)

Medications for LTBI are generally safe and well tolerated in children and ADRs are rare. In case of possible severe ADRs, discontinue treatment and provide supportive medical care as indicated.

Isoniazid: Hepatotoxic effects (rare in children and largely reversible when found early; early symptoms include nausea, vomiting, abdominal pain, malaise) rash, peripheral neuropathy (see below)

Rifampin and rifapentine: GI intolerance, hepatotoxic effects (rare), flu-like symptoms, rash, pruritus, polyarthralgia, myelosuppression, and hypersensitivity reaction[5]

Considerations for Treatment

- Rifamycin-based regimens should be used whenever possible, based on patient attributes and preferences, including potential for drug-drug interactions, local practice, and drug susceptibility results of the presumed source case, if known
- Rifamycin-associated drug interactions include, but are not limited to, hormonal contraceptives, certain HIV antiretrovirals, anticonvulsants, methadone, oral hypoglycemics, anticoagulants, and some psychotropic medications
- Hepatitis risk increases with alcohol use and/or use of other hepatotoxic drugs
- Adolescents who become pregnant should consult their provider

Patients on INH-containing regimens

- Counsel parents that prolonged use of acetaminophen with INH treatment may result in hepatotoxicity
  - Alternatives such as NSAIDs should be used when anti-pyretic or pain relief is needed
- Supplement with pyridoxine in selected patients
  - Peripheral neuritis or seizures caused by the inhibition of pyridoxine metabolism are rare; most children do not need supplementation
  - Add vitamin B6 at a daily dose of up to 1-2 mg/kg/day; usually 25-50 mg/day (maximum 50 mg) for children in these situations:
    - Meat/milk-deficient diets
    - Nutritional deficiencies
    - HIV infection
    - Exclusively breast-fed infants
    - Pregnant/ breastfeeding adolescents
    - Existing peripheral neuropathy or paresthesias (or if symptoms develop)

Patients on rifamycin containing regimens

- Inform patients that temporary orange discoloration of urine, sweat, tears, and other bodily fluids is a normal and expected side effect
- Instruct adolescents who use hormonal birth control to add, or switch to a barrier method

1. Other regimens are available, consult AAP *Red Book* for additional information; CDC indicates that short course rifamycin-based regimens are preferred over INH monotherapy.
2. DOT is considered a priority for some health departments for children <5, immunosuppressed children, recent contacts, adolescents, contacts to those with MDR-TB, and those with evidence of non-adherence, though this may not be possible outside of public health settings. Consult your local health department, which *may* have resources to assist in these cases.
3. If daily therapy is not possible, twice-weekly may be used but must be provided by DOT; medication doses differ.
4. Although a liquid INH preparation is available and INH and RIF can be compounded by a pharmacy, these preparations contain sorbitol, which can cause diarrhea, cramping, and abdominal pain and is generally not recommended; the technique of mixing with food is generally very successful and can be used in most children.
5. Hypersensitivity reactions (e.g., hypotension or thrombocytopenia and hematologic toxicity) have been more commonly associated with 12-dose isoniazid-rifapentine regimen, however, hypersensitivity reactions, which have been reported more frequently in adults, are rare in children and adolescents.

MONITORING & EVALUATION FOR ALL CHILDREN

Children on LTBI treatment should be monitored monthly. Discuss monitoring plan with parents at treatment initiation. Monitoring visits allow providers to perform a PE and check for sign/symptoms of TB disease and/or ADRs, address concerns of parent/ child, emphasize importance of adherence, reinforce educational messages, and ask about status of TB testing/evaluation for other family members. Telehealth may be an option for some visits.

Clinical Monitoring

Monthly monitoring visits should include and document:

- Adherence to the prescribed regimen
- Symptoms of TB disease
- Presence of adverse reactions (based on regimen used), including:
  - Decreased appetite, malaise, GI upset/ abdominal complaints (e.g., nausea, vomiting, or pain), peripheral neuropathy, hypersensitivity reactions (e.g., hypotension or thrombocytopenia), flu-like symptoms, hematologic toxicity, rash
- Weight and percentile (compare to previous weight)
- Findings of PE including signs of TB disease and indications of drug toxicity (icterus, jaundice, etc.)
- All other prescription and non-prescription medications
- Alcohol/substance use
- Oral contraceptive use and dates of last menstrual period

If adverse reactions occur, a prompt clinical evaluation is necessary with treatment changes as indicated.

Laboratory Monitoring

Routine monthly monitoring of liver function tests (LFTs) is not generally indicated as monthly clinical evaluation to identify signs and symptoms of hepatotoxicity is considered appropriate follow up.

- **Monitoring LFTs at baseline and during treatment (at monthly visits) is indicated in those:**
  - With underlying (or history of) hepatic or biliary disease
  - Who are pregnant or <3 months postpartum
  - With symptoms/clinical evidence suggestive of hepatotoxicity *(prompt physician evaluation is indicated)*
  - Taking other potentially hepatotoxic drugs (e.g., anti-convulsants, HIV agents, or acetaminophen)
  - With HIV infection
  - Who are regular alcohol users or injection drug users
  - With risks for hepatic disease

Some experts would also consider LFTs in morbidly obese adolescents

Management of hepatotoxic effects

- Medications should be withheld, and patients evaluated promptly if:
  - Transaminase levels ≥3 times upper limit of normal with symptoms
  - Transaminase levels ≥5 times upper limit of normal, even if asymptomatic
- **If hepatitis develops, treatment should be discontinued, and cause evaluated**

When LFTs have returned to normal, consider an alternate regimen, with close clinical and laboratory monitoring.

Consult a TB expert for management options and/or approaches for re-challenging with medications.

Report adverse events to CDC Division of Tuberculosis Elimination by sending an email to ltbidrugevents@cdc.gov and to FDA MedWatch at accessdata.fda.gov/scripts/medwatch/index.cfm or 1-888-INFO-FDA).

Special Circumstances

Indications for Expert Consultation: State TB programs (cdc.gov/tb/php/tb-programs/index.html) and TB Centers of Excellence (cdc.gov/tb-programs/php/about/tb-coe.html) can provide consultation with pediatric TB experts; consider consultation for:

- Children with signs or symptoms of TB disease
- Infants or immunosuppressed children (including with HIV) being evaluated for LTBI or TB disease
- Children exposed to a person with drug-resistant TB
- Children who develop hepatitis or other severe adverse drug reactions while on treatment for LTBI

Children Recently Exposed to a Person with Suspected or Confirmed Infectious TB Disease (Contacts)

- Contact investigations are conducted by state/local health departments; coordination is required for evaluation and treatment of contacts
  - Children, especially those <5 years of age are a priority due to increased risk of progression to severe disease; thus, all pediatric contacts should promptly receive a TST or IGRA and be evaluated for TB disease with a history and PE (and CXR if symptomatic or positive test results)
  - Children with TB disease identified during contact investigations are often asymptomatic or minimally symptomatic
- If the initial test result is negative, the test should be repeated 8-10 weeks after exposure has ended (or the source is no longer infectious), as it can take this amount of time for an immune response to develop; certain children should be treated for LTBI regardless of initial result (see next column)
- All pediatric contacts whose initial or repeat TST or IGRA is positive should be carefully evaluated for TB disease (see Diagnosis of LTBI)
- Children with a positive initial or repeat TST or IGRA should be treated for LTBI after TB disease is excluded
- If there is concern for TB disease and testing is negative, refer urgently to a pediatric TB specialist for further evaluation and treatment

Window Period Treatment for Certain Children

- For exposed contacts with **impaired immunity** (e.g., HIV infection) **or those <5 years of age,** treatment for presumptive LTBI (also called window prophylaxis) should be initiated in consultation with the health department, *even if the initial TST or IGRA is negative,* once TB disease has been excluded

After testing has been repeated (8-10 weeks after exposure has ended):

- Discontinue treatment in immune-competent children if the repeat test is negative
- Continue LTBI treatment to completion in those with a positive repeat test, after TB disease is excluded
- Continue LTBI treatment to completion in immunosuppressed children, *regardless of test result,* after a careful evaluation for TB disease; some experts may continue treatment in very young infants based on the individual circumstances

Treatment Interruptions: Consider the child's schedule, such as planned extended vacations/absences or time spent with relatives (e.g., weekends or holidays) when starting LTBI treatment. If treatment is interrupted, try to assess and address underlying causes (e.g., side effects, difficulty giving/taking medications, etc.). For children on DOT, video DOT may be used during absences.

If treatment interruptions occur:

- Treatment may need to be restarted from the beginning if there are substantial interruptions, **after** a careful history and PE (including CXR, if indicated) has ruled out TB disease
  - Consider length of interruption, risk of progression to severe disease (including very young age), presence of symptoms, and abnormal findings on the PE when deciding if a CXR is indicated
- If the appropriate number of doses cannot be completed within the required time-frame, recommendations are available for some situations:
  - Treatment with RIF: interruption ≥2 months ▶ **restart** treatment
  - Treatment with INH: interruption ≥3 months ▶ **restart** treatment
  - Specific recommendations are not available for interruptions in the 12-dose INH-rifapentine regimen. Many experts would recommend restarting LTBI treatment when 12 doses cannot be completed within 16 weeks. Expert consultation is suggested