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Tuberculosis Infection in Children

Rebekah J. Stewart [epidemiologist and nurse practitioner],
Centers for Disease Control and Prevention, Atlanta, Georgia,

Jonathan Wortham,
Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia.

Farah Parvez,
Bureau of Tuberculosis Control, New York City Department of Health and Mental Hygiene, New York, New York.

Sapna Bamrah Morris,
Division of Tuberculosis Elimination,

Hannah L. Kirking,
Division of Global HIV and TB, Centers for Disease Control and Prevention, Atlanta, Georgia.

Lindsay Hatzenbuehler Cameron,
Division of Pediatric Infectious Diseases, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas.

Andrea T. Cruz
Section of Infectious Diseases and Emergency Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, TX.

Abstract

Globally, tuberculosis (TB) is the leading cause of infectious disease mortality; however, clinicians in the United States are increasingly unfamiliar with TB and the recommended tests and treatment for latent TB infection. Compared with adults, children who develop TB more often develop severe disease, and children < 2 years are particularly susceptible to developing TB disease after initial infection. Nurse practitioners who work in primary care are on the front lines of identifying children at high risk and obtaining testing and treatment. This article reviews the clinical course for identifying children at risk for TB and provides updated guidelines for testing and treatment.

Keywords

children; infection; latent; pediatric; tuberculosis

contacted at rstewart@cdc.gov.

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Case Study

A 14-year-old girl, who emigrated from India to the United States 1 year ago, would like to volunteer at a local children's hospital. Tuberculosis (TB) testing is required before the start of the volunteer opportunity. Her nurse practitioner (NP) places a tuberculin skin test (TST). Two days later, her TST has 10 mm of induration. Her parents recall that she received the bacille Calmette-Guérin (BCG) vaccine in her birth country and ask if that could be the reason for her positive TST.

Her NP is unsure but remembers an interferon-γ release assay (IGRA) may help distinguish between BCG immunization and latent TB infection (LTBI). He orders an IGRA test, which is reported as positive. The patient reports feeling completely healthy, but to rule out the possibility of TB disease, the NP obtains a chest radiograph, which shows no abnormality. After excluding TB disease, he decides to treat her for LTBI due to her risk factors and the risk of progression to TB disease. Because LTBI is noninfectious and asymptomatic, he sends a letter to clear her for participation in the volunteer opportunity.

Epidemiology

In 2017, approximately 10 million people, including 1 million children, developed TB disease (ie, active TB with clinical signs or symptoms of TB, or both) worldwide, and 1.3 million died, including at least 233,000 children.[1] TB is the ninth leading cause of death worldwide and the leading cause of death from a single infectious agent, ranking above HIV/AIDS.[1] TB is curable with antibiotic treatment. In most regions of the world, LTBI is not a reportable condition to public health authorities, making prevalence estimates challenging. Estimates suggest that > 50 million children worldwide have LTBI.[2]

In the US, 9105 cases of TB disease were reported in 2017, with 5% occurring in children.[3] TB is distributed inequitably, with the highest burden of disease worldwide occurring in resource-limited settings where confirming TB diagnoses in children is challenging.

Population-based studies using IGRAs have estimated a prevalence of 5%, with wide disparities between persons born outside the US (15.9%) and US-born persons (2.8%).[4,5] Similarly, in children 6 to 14 years, prevalence estimates based on IGRA results in the US suggest 0.7% of US-born and 2.6% of noneUS-born children may be infected.[5]

Pathogenesis

Mycobacterium tuberculosis is a rod-shaped, nonmotile, slow-growing, and small (2–4 μm 0.2–0.5 μm) acid-fast bacillus. *M tuberculosis* is carried in airborne particles, called droplet nuclei. Infectious droplet nuclei are generated when a person who has pulmonary or laryngeal TB coughs, sneezes, shouts, or sings. Droplets containing infectious mycobacteria can remain viable in the air for approximately 4 hours. Other persons sharing airspace become infected when they inhale those infectious particles into their lungs. Although infection usually requires prolonged sharing of airspace, rare instances of *M tuberculosis* transmission have been documented after short exposures to persons with active TB disease.[6,7]

After inhalation, the bacilli will be eliminated by the immune system (>90% of exposed adults), be contained by a granuloma, or will begin rapidly multiplying. These processes can occur at any site in the body after bacillus deposition; however, infection most commonly occurs in the lungs. If the bacilli remain contained, that person has LTBI only. Persons progress to TB disease if the bacilli do not remain contained and begin multiplying. Children younger than age 2 are particularly susceptible to experiencing rapid progression to TB disease after initial infection (Table 1)[8]; this is termed primary disease. Primary disease develops in up to 50% of exposed infants, with 10% to 20% developing disease that includes central nervous system involvement. Persons with TB disease often develop symptoms, such as cough, weight loss, and signs of disease, such as lymphadenopathy or cavitary disease that is visible on a chest radiograph or other diagnostic examinations. The most common radiologic findings of TB disease in children are intrathoracic (hilar, mediastinal) lymphadenopathy.[9]

Children often have fewer organisms than adults (termed paucibacillary disease) but develop a pronounced inflammatory reaction to the organisms. Children can have disease outside of the lungs, and miliary (disseminated) and central nervous system involvement is more common in children than adults. Children lack a tussive force (profound cough) to transmit bacilli to others. However, adolescents can develop contagious, adult-like TB (including cavitary) disease. Most children who develop TB disease are otherwise healthy; their only risk factor for progression from infection to disease is their age (Table 1).[9]

Children rarely are the source of infection for another child or adult, but their infection usually follows a recent exposure to an adult or adolescent with disease. A TB diagnosis in a child is a sentinel event that frequently points to recent transmission of *M tuberculosis* within a community.[9]

Testing for TB Infection

The US Preventative Services Task Force (USPSTF) recommends testing persons at increased risk for LTBI (Table 2).[10] While the USPSTF recommendation does not include children, it does endorse the American Academy of Pediatrics' Bright Futures program, which outlines risk factors for children between 2 and 17 years old (Table 3).[11]

Immediate testing for TB infection should be performed for children who are contacts of persons with contagious TB disease, those with clinical or radiographic findings suggestive of TB disease, and children with certain high-risk medical conditions, such as HIV infection, that confer an increased risk for progression to TB disease once infected. Additionally, children living with HIV and those receiving immunosuppressive therapy should be tested annually. For severely immunocompromised children, a negative TB test result might represent an anergic response due to immunosuppression[12]; therefore a negative test result in this population does not rule out TB. TB experts may recommend treatment for infection in young children who are recent contacts of a person with active TB, even with a negative test, given their risk of progression once infected. Treatment decisions during contact investigations should be made in concert with local health department staff.

Testing Methods

Two types of tests for TB infection are currently available in the US: the Mantoux TST and IGRA blood tests. Either type is acceptable for the diagnosis of TB infection; however, IGRAs have several advantages over TSTs. An IGRA test involves a blood draw that can be conducted in 1 office visit. In contrast, the TST requires a precise intradermal placement technique, patient compliance with a return visit 2 to 3 days later, and cross-referencing induration measurement with risk stratification to interpret the result (Table 4).[13,14]

A meta-analysis demonstrated that IGRAs have superior specificity compared with TSTs for the diagnosis of TB infection among children ≥ 2 years old from high-burden TB countries due to false-positive TST results in children who received a BCG vaccine at birth.[15] The American Academy of Pediatrics now recommends IGRAs for children ≥ 2 years old regardless of BCG immunization status, whereas TSTs are preferred for children < 2 years old due to lack of data regarding IGRA performance characteristics for children < 2 years old.[12] One advantage of a TST over an IGRA is the relative cost of the test. TSTs are less expensive, although this cost advantage may be negated by the full cost of 2 office visits.

There are 2 options for IGRA tests: T.SPOT-TB (Oxford Immunotec) and QuantiFERON-TB Gold Plus (Qiagen). TSTs and IGRAs both measure the immune response to *M tuberculosis* antigens. This reactivity can take a few weeks to a few months to develop. Therefore, a person exposed to another person with contagious TB should be tested immediately and again 8 to 10 weeks after the last exposure if the initial test result was negative. In general, health care providers should consider any positive result to be evidence of TB infection in children who are contacts to active TB cases and those with social or medical risk factors for TB disease.

Ruling out TB Disease

It is crucial to exclude TB disease before starting therapy for LTBI (Table 5).[9,16] Because TSTs and IGRAs both evaluate a person's immune response to *M tuberculosis* antigens as a result of an exposure (ie, has become infected), neither test can differentiate between LTBI and TB disease, and a negative TST or IGRA test result does not rule out TB disease in a symptomatic child. Rather, if the child has symptoms, an attempt at bacteriologic confirmation should be pursued. Young children often cannot expectorate sputum; therefore clinicians should attempt to obtain alternative specimens for microbiologic confirmation (ie, gastric aspirates or sputum induction). Although there are differing methods for inducing sputum, most methods include inhalation of salbutamol (albuterol) by metered dose inhaler, 5% hypertonic saline administered via a nebulizer, or sputum collection by a mucus extractor or expectoration.[17]

For symptomatic children identified as contacts to an adult with contagious TB in whom culture results are available, seeking microbiologic confirmation is often not needed, particularly for children with minimal radiographic findings in whom culture yield will be low (eg, intrathoracic lymphadenopathy). Children with a known source and symptoms should be treated for TB disease regardless of microbiologic findings.

TB is relatively rare in the US compared with most other countries; therefore, many providers may not have experience or feel comfortable with fundamental aspects of TB diagnosis and treatment. There should be a low threshold for consulting an expert in pediatric TB. Situations that may require expert help include ruling out active TB disease (eg, help in interpreting whether radiologic findings are consistent with TB), interpreting test results in immunocompromised patients, and identifying the appropriate regimen for children with immunologic suppression.

Treatment Regimens

Once TB disease is excluded, LTBI treatment is recommended for all children who have not previously received therapy.[18] Children are more likely to progress to TB disease, have more years of vulnerability to develop disease, and are more likely to tolerate LTBI treatment than adults. The LTBI treatment plan must always consider the drug-susceptibility pattern of the source (or presumed) case(s). There are 3 strongly recommended treatment regimens for presumed drug-susceptible LTBI in the US and 2 alternative regimens that are recommended for certain populations (Table 6).[19–24]

Strongly Recommended: 12 Weeks of Isoniazid and Rifapentine

The newest regimen for treating LTBI is dual therapy of high-dose isoniazid and rifapentine taken once weekly for 12 total doses (3HP). Rifapentine is a long-acting rifampin derivative with a longer half-life that allows for once-weekly dosing. A clinical trial conducted among children aged 2 to 17 years demonstrated that 3HP was safe, well-tolerated, and had higher treatment completion rates than 9 months of daily isoniazid (9H), the primary treatment regimen for many years.[25] Although studies have shown higher treatment completion rates when administered by directly observed therapy,[26] the burden and expense on the health care system is higher than that for self-administered or parent-administered therapy. The Centers for Disease Control and Prevention has expanded the option of parent-administered 3HP to children ≥ 2 years old and recommends that health care providers and parents make a joint decision about the best approach to therapy for each child.[27] The regimen consists of multiple pills, which need to be crushed and mixed with food; there are currently no child-friendly formulations of 3HP. Children and parents should be advised that rifapentine will cause urine, stool, tears, and other secretions to turn an orange color; however, the orange coloration is harmless and will disappear when the medication is stopped. 3HP can be used among individuals infected with HIV who are taking efavirenz- or raltegravir-based antiretroviral regimens.[27]

Strongly Recommended: 4 Months of Daily Rifampin

Daily rifampin for 4 months (4R) is another safe regimen for treating LTBI with equivalent efficacy and better treatment completion rates than 9H.[21,28–31] A recent study found that rifampin was not inferior to 9H and that those taking it had better treatment completion.[28,31] The rifampin group was also associated with lower rates of adverse events, especially hepatotoxicity. Rifampin will also cause discoloration of secretions and can cause drug-drug interactions.[20]

Strongly recommended: 3 Months of Daily Isoniazid and Rifampin

A third short-course treatment regimen that has been found to be as effective and safe as 9H with better compliance is 3 months of daily isoniazid and rifampin (3HR).[22,32] Serious adverse events were rare in an 11-year randomized controlled trial,[32] with elevation in hepatic enzymes, rash, and gastrointestinal disturbances occurring in <2% of children.[22] Considerations for secretion discoloration and drug-drug interactions applies to this regimen as well.[20]

Alternative regimens: 6 or 9 Months of Daily or Twice-Weekly Isoniazid

The most well-known LTBI treatment historically has been 9H and, if taken as indicated, can prevent most progression to TB disease.[33] However, the effectiveness of this regimen is limited by poor treatment completion rates (approximately 50%) when families administer medication to children.[21,34] Therefore, whenever possible, clinicians should first consider whether regimens of 3HP, 4R, or 3HR are feasible before prescribing 9H. If a short-course regimen is not an available option, 6 months of isoniazid is now preferred over 9 months of therapy to lower the risk of hepatotoxicity from prolonged treatment duration.[20]

Isoniazid treatment continues to be important for certain patients, particularly in children who are intolerant of rifamycins or children who are receiving other medications that preclude use of rifampin (ie, cyclosporine, systemic corticosteroids, phenytoin, azole antifungal agents, and certain retrovirals, such as protease inhibitors).[20,35] Vitamin B_6 (pyridoxine) supplementation during therapy is recommended for people who are pregnant or breast-feeding, for breastfed infants, and those with HIV or nutritional deficiencies to prevent the development of peripheral neuropathy.[9]

Safety of Treatment for Latent TB Infection

Treatment regimens for LTBI are not only effective for children but are also very safe. The risk of adverse events is lower in children than in adults.[23,25,28] Serious adverse events related to treatment in children are rare,[21,23,28] and minor adverse events, including unfavorable adverse effects, such as gastrointestinal disturbances, while more common, can be mitigated by giving the medication with food. Children treated with 9H experience more adverse effects than those treated with 3HP or 4R.[22,27] Because all medications used to treat LTBI are metabolized by the liver, hepatotoxicity is a risk; adolescents should be counseled to not drink alcohol when undergoing treatment.

The incidence of hepatotoxicity among children is rarely detected among those taking 3HP, 4R, and 3HR[21–23] and occurs infrequently (approximately 1%) in children taking 9H,[21,23,24,36] with most experiencing reversal of signs and symptoms after treatment is discontinued. There are 2 reports from an adverse event reporting system in the US of severe liver injury in children taking isoniazid therapy, and 1 of those children underwent liver transplantation.[37]

Baseline and serial aminotransferase monitoring is not necessary for most children; however, it should be considered in those with a medical comorbidity, family history of hepatic disease, children with HIV infection, those taking medications that interact with isoniazid

or rifamycins, pregnant adolescents, and patients with underlying hepatic or biliary disease, including known or suspected fatty liver. Asymptomatic elevation in transaminases 2 to 3 times the upper limit of normal will occur in 8% of children who receive TB medications. This usually resolves with treatment completion; modification of therapy is not necessary.[38]

All children undergoing treatment for LTBI who develop significant abdominal pain or unexplained vomiting should stop the medication immediately and undergo a physical examination and a laboratory evaluation of liver function. If a child's transaminases levels are found to be 2 to 3 times the upper limit of normal and abdominal pain persists or > 5 times the upper limit of normal irrespective of symptoms, therapy should be discontinued and attempts to complete therapy resumed once liver function test results and transaminases levels improve.[23]

Follow-up

When possible, a child's follow-up appointment should be scheduled for 1 month after therapy initiation to address questions and assess for adverse effects; afterward, we recommend follow-up appointments every 4 weeks. Parents should receive education about potential adverse events and should be advised to stop treatment immediately and seek care if the child experiences a rash, abdominal pain, anorexia, nausea, or unexplained vomiting.[23] Consultation with a pediatric TB expert is recommended for any adverse effects or events that warrant discontinuing treatment, as well as treatment for infected children in contact with an adult with drug-resistant TB.

Resources for Health Care Providers

NPs who work in primary care should be identifying children at high risk for LTBI and obtaining the proper testing and treatment. As such, they play a key role in moving the US closer to TB elimination. Local health departments are ultimately responsible for TB prevention and control within their jurisdiction and are a great resource for any provider managing a patient with suspected or confirmed TB infection or disease. Four National Tuberculosis Centers of Excellence in the US also give providers a direct connection to TB experts who can assist them in providing high-quality and evidence-based care: https://www.cdc.gov/tb/education/tb_coe/default.htm

References

1. World Health Organization. Global tuberculosis report 2018. World Health Organization; 2018.
2. Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. Lancet Glob Health. 2014;2:e453–e459. [PubMed: 25103518]
3. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2017. https://www.cdc.gov/tb/statistics/reports/2017/default.htm. Accessed April 5, 2020.
4. Haddad MB, Raz KM, Lash TL, et al. Simple estimates for local prevalence of latent tuberculosis infection, United States, 2011–2015. Emerg Infect Dis. 2018;24:1930–1933. [PubMed: 30226174]
5. Miramontes R, Hill AN, Yelk Woodruff RS, et al. Tuberculosis infection in the United States: prevalence estimates from the National Health and Nutrition Examination Survey, 2011–2012. PLos One. 2015;10:e0140881. [PubMed: 26536035]

6. Golub JE, Cronin WA, Obasanjo OO, et al. Transmission of *Mycobacterium tuberculosis* through casual contact with an infectious case. Arch Intern Med. 2001;161:2254–2258. [PubMed: 11575983]
7. Murphy ME, Wilmore S, Satta G, et al. Occupational tuberculosis despite minimal nosocomial contact in a health care worker undergoing treatment with a tumor necrosis factor inhibitor. Ann Am Thorac Soc. 2016;13:2275–2277. [PubMed: 27925777]
8. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intrathoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. 2004;8:392–402. [PubMed: 15141729]
9. American Academy of Pediatrics. Report of the Committee on Infectious Diseases. Red Book: Tuberculosis. Online: American Academy of Pediatrics, 2018. https://redbook.solutions.aap.org/. Accessed April 15, 2020.
10. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for latent tuberculosis infection in adults: US Preventive Services Task Force recommendation statement. JAMA. 2016;316:962–969. [PubMed: 27599331]
11. American Academy of Pediatrics. Tuberculosis. Bright Futures, 2015. https://brightfutures.aap.org/Bright%20Futures%20Documents/Screening.pdf. Accessed April 15, 2020.
12. Kimberlin DWBM, Jackson MA, Long SS, eds. Tuberculosis. 31st ed. American Academy of Pediatrics; 2018.
13. Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations From the National Tuberculosis Controllers Association and CDC. Morb Mortal Wkly Rep. 2005;54:1–47.
14. Centers for Disease Control and Prevention. Fact Sheets. Tuberculin Skin Testing; Last reviewed May 4, 2016, https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm. Accessed April 5, 2020.
15. Machingaidze S, Wiysonge CS, Gonzalez-Angulo Y, et al. The utility of an interferon gamma release assay for diagnosis of latent tuberculosis infection and disease in children: a systematic review and meta-analysis. Pediatr Infect Dis J. 2011;30:694–700. [PubMed: 21427627]
16. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis. 2017;64:111–115. [PubMed: 28052967]
17. Grant LR, Hammitt LL, Murdoch DR, O'Brien KL, Scott JA. Procedures for collection of induced sputum specimens from children. Clin Infect Dis. 2012;54(Suppl 2):S140–S145. [PubMed: 22403228]
18. World Health Organization. Roadmap towards ending TB in children and adolescents. World Health Organization; 2018.
19. Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of latent tuberculosis infection: an updated network meta-analysis. Ann Intern Med. 2017;167:248–255. [PubMed: 28761946]
20. Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep. 2020;69:1–11.
21. Cruz AT, Starke JR. Completion rate and safety of tuberculosis infection treatment with shorter regimens. Pediatrics. 2018;141(2):e20172838. [PubMed: 29363561]
22. Spyridis NP, Spyridis PG, Gelesme A, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3-and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clin Infect Dis. 2007;45:715–722. [PubMed: 17712755]
23. Cruz AT, Ahmed A, Mandalakas AM, Starke JR. Treatment of latent tuberculosis infection in children. J Pediatric Infect Dis Soc. 2013;2:248–258. [PubMed: 26619479]
24. Chang SH, Nahid P, Eitzman SR. Hepatotoxicity in children receiving isoniazid therapy for latent tuberculosis infection. J Pediatric Infect Dis Soc. 2014;3: 221–227. [PubMed: 26625385]

25. Villarino ME, Scott NA, Weis SE, et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr. 2015;169:247–255. [PubMed: 25580725]
26. Njie GJ, Morris SB, Woodruff RY, Moro RN, Vernon AA, Borisov AS. Isoniazid-rifapentine for latent tuberculosis infection: a systematic review and meta-analysis. Am J Prev Med. 2018;55(2):244–252. [PubMed: 29910114]
27. Borisov AS, Bamrah Morris S, Njie GJ, et al. Update of recommendations for use of once-weekly isoniazid-rifapentine regimen to treat latent Mycobacterium tuberculosis infection. MMWR Morb Mortal Wkly Rep. 2018;67:723–726. [PubMed: 29953429]
28. Diallo T, Adjobimey M, Ruslami R, et al. Safety and side effects of rifampin versus isoniazid in children. N Engl J Med. 2018;379:454–463. [PubMed: 30067928]
29. Gaensbauer J, Aiona K, Haas M, Reves R, Young J, Belknap R. Better completion of pediatric latent tuberculosis treatment using 4 months of rifampin in a US-based tuberculosis clinic. Pediatr Infect Dis J. 2018;37(3):224–228. [PubMed: 28777204]
30. Ziakas PD, Mylonakis E. 4 months of rifampin compared with 9 months of isoniazid for the management of latent tuberculosis infection: a meta-analysis and cost-effectiveness study that focuses on compliance and liver toxicity. Clin Infect Dis. 2009;49:1883–1889. [PubMed: 19911936]
31. Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. N Engl J Med. 2018;379: 440–453. [PubMed: 30067931]
32. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. Clin Infect Dis. 2005;40:670–676. [PubMed: 15714411]
33. Comstock GW, Baum C, Snider DE Jr. Isoniazid prophylaxis among Alaskan Eskimos: a final report of the bethel isoniazid studies. Am Rev Respir Dis. 1979;119:827–830. [PubMed: 453704]
34. Hirsch-Moverman Y, Shrestha-Kuwahara R, Bethel J, et al. Latent tuberculous infection in the United States and Canada: who completes treatment and why? Int J Tuberc Lung Dis. 2015;19:31–38. [PubMed: 25519787]
35. Finch CK, Chrisman CR, Baciewicz AM, Self TH. Rifampin and rifabutin drug interactions: an update. Arch Intern Med. 2002;162:985–992. [PubMed: 11996607]
36. van Toorn R, Schaaf HS, Laubscher JA, van Elsland SL, Donald PR, Schoeman JF. Short intensified treatment in children with drug-susceptible tuberculous meningitis. Pediatr Infect Dis J. 2014;33:248–252. [PubMed: 24168978]
37. Centers for Disease Control and Prevention. Severe isoniazid-associated liver injuries among persons being treated for latent tuberculosis infection-United States, 2004–2008. MMWR Morb Mortal Wkly Rep. 2010;59:224–229. [PubMed: 20203555]
38. Donald PR. Antituberculosis drug-induced hepatotoxicity in children. Pediatr Rep. 2011;3:e16. [PubMed: 21772953]

Table 1

Risk of Progression From Tuberculosis Infection to Tuberculosis Disease in Children and Adolescents[8]

Risk Factors for Acquisition of TB Infection		
Close Contacts	Country of Origin	High-Risk Residential Setting
Children who are close contacts of a recently diagnosed person with contagious TB are at especially high risk for TB infection	Children born in or traveled to (travel >1 week) any country outside of the United States, Canada, Northern and Western Europe, New Zealand, and Australia	Children housed in congregate settings, including homeless shelters, juvenile detention centers, immigration and customs enforcement detention facilities, or other group-based housing are at higher risk for TB infection
Risk Factors for Progression From TB Infection to Disease		
Immunosuppression	Chronic Medical Conditions	Timing of Infection
HIV infection	Diabetes	Recent TB infection (ie, within the past 2 years)
Other immune deficiencies	Chronic renal disease	
Solid organ transplant recipients	Malnutrition	
On immunosuppressive therapy (eg, tumor necrosis factor antagonists, chemotherapy)		
Age < 2 years, 10–18 years		

TB = tuberculosis.

Table 2

Epidemiologic Risk Factors for Acquisition of Tuberculosis Infection and Progression From Infection to Disease[a]

Age at Infection, years	No Progression to TB Disease, %	Intrathoracic TB,[b] %	CNS TB, %
< 1	50	30–40	10–20
1 to < 2	75–80	10–20	2.5
2 to < 5	95	5	0.5
5 to10	98	2	< 0.5
➢10	80–90	10–20	< 0.5

CNS = central nervous system; TB = tuberculosis.

[a]Reprinted with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union. Marais, B. J., et al. (2004). "The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era." *Int J Tuberc Lung Dis* 8(4):392–402.[8]

[b]Includes pulmonary parenchymal disease, pleural effusions, and intrathoracic lymphadenopathy.

Table 3

American Academy of Pediatrics-Endorsed Tuberculosis Infection Risk Factor Questionnaire in Previously Healthy Children[a]

Bright Futures Visits	**1, 6, 12 months; annually beginning at 2 years through 17 years**
Risk assessment	• Is your child infected with HIV
	• Has a family member or contact had tuberculosis disease?
	• Has a family member had a positive IGRA or TST result?
	• Was your child born in a high-risk country (countries other than the United States, Canada, Australia, New Zealand, or Western and Northern European countries)?
	• Has your child traveled (had contact with resident populations) to a high-risk country for more than 1 week?

IGRA = interferon-γ release assay; TST = tuberculin skin test.

[a]Adapted from Bright Futures Medical Screening Reference Table (brightfutures.aap.org/Bright%20Futures%20Documents/MSRTable_MCVisits_BF4.pdf) and the Centers for Disease Control and Prevention: www.cdc.gov/tb/topic/testing/whobetested.htm

Table 4

Criteria for Positive Tuberculin Skin Test for Pediatric Patient, by Risk Group[a],14

Induration ≥ 5 mm	Induration ≥ 10 mm	Induration ≥ 15 mm
Children in close contact with a contagious person with TB disease	Children at increased risk for disseminated disease, including children < 5 years old and children with other medical conditions[b]	Children ≥ 5 years old without any risk factors
Children with possible TB disease due to clinical findings	Children born in or with recent travel to high-prevalence regions of the world[c]	
Children who are immunosuppressed, including HIV infection, or receiving immunosuppressive therapy	Children regularly exposed to adults who are living with HIV, homeless, users of illicit drugs, residents of nursing homes, incarcerated, or otherwise institutionalized.	

TB = tuberculosis.

[a]These criteria apply regardless of previous bacille Calmette-Guérin immunization. Erythema alone at a tuberculin skin test site does not indicate a positive test result, rather the induration should be measured in millimeters. Tests should be read at 48 to 72 hours after placement.

[b]Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition.

[c]Any country outside of the United States, Canada, Northern and Western Europe, New Zealand, and Australia.

Table 5

Evaluation for Active Tuberculosis Disease in Children With a Positive Test Result for Infection[9,16]

Evaluation	Components
History[a]	> 2 weeks of fever, cough, or lymphadenopathy Weight stasis or weight loss Decreased activity or playfulness *Symptoms such as hemoptysis and night sweats are less sensitive in children than in adolescents and adults*
Physical examination[a]	Intrathoracic: reduced breath sounds, focal rales, increased work of breathing Lymphadenopathy: most commonly anterior cervical chain or supraclavicular, nontender, often > 2 × 2 cm in size Meningitis: mental status examination, focal cranial nerve deficits
Chest radiograph[a]	Posterior-anterior and lateral radiographs should be obtained to evaluate for intrathoracic disease. The most common findings of TB disease in children are intrathoracic (hilar, mediastinal) lymphadenopathy, focal infiltrates, atelectasis, parenchymal calcifications, and pleural effusions; cavitary lesions are rare before adolescence. *The thymic silhouette can mask lymphadenopathy on the frontal radiograph, making obtaining a lateral radiograph especially critical in young children*
Microbiologic evaluation for children with suspected disease	Sputum or gastric aspirates for AFB stain and culture Sputum or gastric aspirates for *Mycobacterium tuberculosis* PCR, Xpert (Cepheid, Sunnyvale, CA) MTB/RIF, or other molecular tests for rapid identification of drug resistance Consider lumbar puncture for infants (< 12 months old) with suspected intrathoracic TB, infants and children with miliary TB, and children with altered mental status or focal cranial nerve findings

AFB = acid-fast bacilli; MTP = Mycobacterium tuberculosis; TB = tuberculosis; PCR = polymerase chain reaction; RIF = rifampicin.

[a]Should be performed for all children with a positive test of infection to adequately exclude TB disease.

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Table 6

Recommended Treatment Regimens for Latent Tuberculosis Infection in Children[20–24][a]

Regimen (mo)	Dose	Interval	Total Doses	Adverse Effects
3INH/RPT[b]	INH, age 2–11 years: 25 mg/kg INH, age ≥ 12 years: 15 mg/kg (max: 900 mg for both) RPT, 10–14 kg: 300 mg 14.1–25 kg: 450 mg 25.1–32 kg: 600 mg 32.1–50 kg: 750 mg > 50 kg: 900 mg	Weekly	12	Flu-like symptoms, nausea, GI upset, rash, muscle or bone pain, itching, red eyes, discoloration of secretions, decreased effectiveness of hormonal contraception, hepatic enzyme elevation, hepatitis
4RIF	15–20 mg/kg per day (max: 600 mg)	Daily	120	Anorexia, nausea, GI upset, rash, fatigue discoloration of secretions, decreased effectiveness of hormonal contraceptive
3INH/RIF	INH: 10–20 mg/kg (max: 300 mg) RIF: 15–20 mg/kg (max: 600 mg)	Daily	90	Rash, nausea, epigastric pain, photosensitivity reaction, hepatic enzyme elevation, discoloration of secretions, decreased effectiveness of hormonal contraceptive
6INH	10–20 mg/kg per day (max: 300 mg)[d] 20–40 mg/kg (max: 300 mg)[d]	Daily Twice weekly	180 52	GI upset, rash, peripheral neuropathy, hepatic enzyme elevation, hepatitis
9INH[c]	10–20 mg/kg per day (max: 300 mg)[d] 20–40 mg/kg (max: 300 mg)[d]	Daily Twice weekly	270 76	

GI = gastrointestinal; INH = isoniazid (isonicotinic acid hydrazide); RIF = rifampin; RPT = rifapentine.

[a]Adapted from Centers for Disease Control and Prevention: www.cdc.gov/tb/topic/treatment/ltbi.htm

[b]Only for children ≥ 2 years of age due to lack of safety and pharmacokinetic data for younger children. Not recommended for adolescents who are pregnant or might become pregnant within the 12-week regimen.

[c]Preferred treatment for children being treated for HIV with certain protease inhibitors or adolescents who are pregnant or who might become pregnant (supplement with pyridoxine/vitamin B_6 for these groups and others at risk of malnutrition to prevent peripheral neuropathy).

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