HHS Public Access

Author manuscript

Curr Opin Pediatr. Author manuscript; available in PMC 2016 June 07.

Published in final edited form as:

Curr Opin Pediatr. 2014 February ; 26(1): 106–113. doi:10.1097/MOP.0000000000000049.

Old and new approaches to diagnosing and treating latent tuberculosis in children in low-incidence countries

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Abstract

Purpose of review—The primary purpose is to review guidance on the testing and treatment of latent tuberculosis infection (LTBI) in children. Most children and adults with LTBI have positive tuberculin skin test (TST) or interferon gamma release assay (IGRA) results, normal examinations, and normal chest radiographs. Diagnosis of and treatment completion for LTBI are critical to diminish future cases of tuberculosis (TB) disease.

Recent findings—Children should be screened for TB risk factors, and only children with risk factors should be tested with either a TST or an IGRA. IGRAs measure interferon gamma production by lymphocytes after they are stimulated *ex vivo* by antigens that are primarily *Mycobacterium tuberculosis*-specific. The foundation of LTBI therapy in the United States has been 9 months of daily isoniazid, but shorter treatment regimens now exist, including a 12-dose regimen of weekly isoniazid and rifapentine. These shorter regimens are associated with higher completion rates.

Summary—There are two distinct modalities for LTBI diagnosis and several treatment regimens that can prevent TB disease in infected children. The selection of treatment regimen should take several factors into consideration, including adherence, drug susceptibility results of the presumed source case (if known), safety, cost, and patient preference.

Keywords

interferon gamma release assay; latent tuberculosis infection; targeted testing; tuberculosis prevention

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Conflicts of interest

There are no conflicts of interest.

The opinions and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

INTRODUCTION

Children comprise a minority of tuberculosis (TB) patients [1]. The risk of progression from latent tuberculosis infection (LTBI) to TB disease is greatest in infants, decreases when children are 5–10 years of age, and increases during adolescence [2,3]. The probability of TB disease developing can be reduced substantially with treatment. In the United States, the majority of pediatric TB cases are attributable to healthcare providers missing opportunities for prevention [4▪▪,5]. Missed opportunities include not testing children with TB risk factors for LTBI and not initiating or completing treatment in children who are diagnosed with LTBI. Diagnosis of and treatment completion for LTBI are essential components of the strategy to eliminate TB [6].

This review is intended to update general practitioners, including primary care pediatricians, on the fundamentals of preventing TB by diagnosing and treating LTBI. It will consider risk factors for LTBI; new options for LTBI diagnosis; new treatment regimens for preventing TB disease; frequency of, and monitoring for, adverse events; barriers to treatment initiation and completion; and strategies to increase adherence with LTBI therapy. Treatment of HIV-infected children with LTBI and of children infected after contact with persons with multidrug-resistant (MDR)-TB will not be discussed in detail because it is recommended that their management be done in consultation with an expert in pediatric TB.

PREDICTIVE FACTORS FOR *MYCOBACTERIUM TUBERCULOSIS* INFECTION

Associations with infection by *Mycobacterium tuberculosis* are well established [2]. Testing children who are unlikely to be infected gives poor predictive value of positive results. Thus, the American Academy of Pediatrics (AAP) does not recommend universal testing for LTBI. The dominant factors associated with LTBI among children in the United States are birth in or travel to a high-incidence country and being a contact of a household member with a history of LTBI or TB disease [7]. A simple screening tool incorporating these questions has been validated for LTBI screening in diverse community settings [8,9]. As the number of risks present increases, the tool becomes more specific and the positive predictive value of test results increases. Children with at least one factor associated with LTBI should be tested. However, one study indicated that a minority of pediatric providers use a standardized questionnaire among school-aged children [10]. More recently, association with parental birth abroad was reported for US-born children with TB [4▪▪]. This characteristic has yet to be prospectively validated, and is not usually included in screening questionnaires.

It is important to distinguish which children with LTBI have a high risk of progressing to TB disease. In contrast to the epidemiologic risk factors for acquisition of infection, the factors related to progression to disease are primarily associated with immunologic status: age younger than 5 years, *M. tuberculosis* infection within the past 2 years, and those factors also affecting adults, for example, HIV infection or other immunocompromising conditions or receipt of immunosuppressive medications [7].

OPTIONS FOR LATENT TUBERCULOSIS INFECTION TESTING

Two options exist for the diagnosis of LTBI: the tuberculin skin test (TST) and IGRAs (Table 1) [11▪,12]. No reference standard currently exists for LTBI diagnosis, and, therefore, the pretest probability of infection and studies in children who have TB disease are used for estimating the sensitivity of these tests for LTBI and their predictive values [13▪▪]. TSTs are interpreted according to the individual's risk profile. The amount of induration in millimeters considered positive optimizes sensitivity for children at highest risk of progression to TB disease and improves specificity for children who are less likely to have been infected (Table 1) [13▪▪]. In a low-risk population, the vast majority of positive TSTs in children without a risk factor will be false-positive results, emphasizing the need to focus LTBI screening on those with an associated factor for LTBI in order to lessen unnecessary tests and treatment. For these reasons, policies that promote universal testing of persons (e.g., all children entering school) without a factor associated with infection should be discouraged.

IGRAs are blood tests that detect interferon gamma released by lymphocytes *ex vivo* after stimulation with overlapping peptide sequences that simulate *M. tuberculosis*-specific antigens. These peptide sequences have antigenic homology with three nontuberculous pathogenic mycobacterial species – *M. kansasii, M. marinum*, and *M. szulgai* – but the clinical significance of the potential cross-reaction has not been determined. IGRAs offer several advantages over the TST, including superior specificity for patients who are sensitized to purified protein derivative tuberculin antigens because of bacille Calmette–Guérin (BCG) vaccination or infection with a nontuberculous mycobacterium, for example, *M. avium*; a single definition for test positivity, and the need for only one healthcare encounter. Situations in which IGRAs are the preferred test for diagnosing LTBI in children are summarized in Table 2 [13▪▪,14]. One group in whom IGRAs may be of particular use is BCG-vaccinated children. The current generation of IGRAs was designed to take advantage of antigens that are present in *M. tuberculosis* complex, including wild-type *M. bovis*, but absent in BCG, which is prepared from attenuated strains of *M. bovis*. BCG vaccination diminishes TST specificity because of cross-reactive antigens, with complex interactions between the age at vaccination, the interval between vaccination and TST, the number of BCG doses, and the timing between TSTs (i.e., the skin test 'boosting' phenomenon) [15,16]. In studies to date, BCG vaccination has not been found to influence IGRA results.

Two commercial IGRA testing systems, Quanti-FERON-TB Gold (Qiagen) and T-SPOT.*TB* (Oxford Immunotec) are licensed by the US Food and Drug Administration for sale. Neither Centers for Disease Control and Prevention (CDC) nor the AAP recommends one IGRA over another [13▪▪,14]. IGRA incorporation into existing screening protocols in pediatric offices has been limited by insufficient data available in preschool-aged children, by the need for venipuncture and training on specimen handling, and by the incomplete market penetration of IGRAs. Another limiting factor is that indeterminate results for IGRA of up to 24% have been reported in children less than 5 years of age [17,18], reducing its utility as a diagnostic test in this population.

Focused testing of individuals with a risk for infection with *M. tuberculosis* is a more cost-effective strategy than universal screening; however, there is no consensus on which test to use, TST or IGRA [19]. One group for which testing is mandated is adults applying for resident immigrant status and their children at least 2 years of age. Both adults and children are required to have a TST or an IGRA done at the overseas health screening site, and those with positive test results are further required to have a chest radiograph (CXR) done.

TREATMENT REGIMENS

Children with positive TST or IGRA results must be evaluated for TB disease prior to initiation of treatment for LTBI. The evaluation should include a CXR and a thorough physical examination, with particular attention to peripheral lymphadenopathy, and possibly collection of specimens for acid-fast bacillus staining, mycobacterial culture, and drug susceptibility testing. If TB disease is suspected or the primary care physician cannot manage LTBI diagnosis and treatment, the child should be referred to the health department or a pediatrician familiar with TB, for evaluation and treatment.

Once TB disease has been excluded, the provider can discuss LTBI treatment options with the family. Historically, the approach to LTBI therapy in the United States has been monolithic, relying upon isoniazid (isonicotinylhydrazine, INH) in all but a few select clinical situations. Data supporting non-isoniazid-based regimens have largely been derived from studies in adults. The decision as to which regimen to use should take adherence, drug susceptibility results of the presumed source case (if known), safety, cost, and patient preference into consideration [2]. Children at high risk of TB disease may be candidates for directly observed therapy (DOT), in which a healthcare worker or other trained person watches a patient swallow each dose of medication. DOT is one of the few interventions to be associated with improved treatment adherence [20]. In Houston, twice weekly LTBI therapy via DOT was shown to be effective in a cohort of over 400 children [21]. Other effective strategies include calendars for parental monitoring, treatment with incentives in the form of small toys or books provided to the child [22], school-based DOT [23], and adherence coaching for adolescents [24].

The current standard of practice in the United States for treating LTBI is 9 months of daily INH, unless documented resistance to INH is shown in the source case. INH is bactericidal and it is highly efficacious if taken as indicated. The chief problem with this regimen is that adherence with a 9-month regimen is poorer than with shorter regimens, limiting effectiveness.

A 4-month course of rifampin has been shown to be less costly, better tolerated, and more likely to be completed in adults than 9 months of INH [25]; the current AAP recommendation is a 6-month course [14], but no study has ever used this regimen. A course of treatment using rifampin is recommended when the child is known to be exposed to an infectious person with an INH-resistant strain or is intolerant to INH [14]. Rifampin is well tolerated by children [26], and the 4-month course probably will result in improved adherence but needs further study.

A shorter course regimen, a 3-month combination of daily INH and rifampin, has been shown to be successful in children and associated with good adherence in the United Kingdom [27], although this regimen has not been included in guidelines for the United States. Rifapentine, a longer-acting rifamycin, can be administered once weekly in combination with INH. A recent landmark study indicated that 12 weekly doses of INH and rifapentine was noninferior to 9 months of INH in persons at least 12 years of age and had higher completion rates [28▪▪]. This is now a CDC-recommended regimen [29]. As with all intermittent dosing of TB medication (intermittent dosing can be once, twice or thrice weekly), this combination therapy is recommended only via DOT, as even one missed dose results in an almost 10% dose reduction. Follow-up of a cohort of younger children (2–11 years old) is ongoing. To date, this regimen also appears to be well tolerated and safe in this age group [30].

For children less than 12 years of age, the preferred regimen remains 9 months of INH until further data and experience are available. However, certain scenarios may warrant the use of 4 months of daily rifampin or 3 months of weekly INH/rifa pentine. These situations are discussed in Table 3 [14,31]. For adolescents, 3 months of weekly INH/rifapentine given by DOT may be considered, especially when adherence is questionable. For families who can afford the cost of rifampin (or for regions where LTBI therapy is provided free to children), 4 months of rifampin may be the next best alternative to 9 months of INH for school-aged children and adolescents for whom INH/rifapentine is not available.

One important scenario relates to children with LTBI for whom immunosuppressive therapy [e.g., tumor necrosis factor-α (TNF-α) antagonists] has been or will be initiated by the child's specialist. Although it is optimal to complete as much of the LTBI course as possible prior to the child becoming immunosuppressed, this is not always possible. At a minimum, expert opinion for the treatment of adults is that 4 weeks of LTBI therapy should be taken prior to initiating immunosuppression. This is a circumstance under which shorter course regimens would be preferable, so that a larger percentage of therapy can be completed prior to initiation of immunosuppression. However, clinicians must first be sure that the rifampin or rifapentine does not interact with any other medications, because rifamycins are potent inducers of cytochrome P450 enzymes that catalyze the oxidation of other drugs.

ADVERSE DRUG EVENTS

Most children tolerate TB medications far better than adults, and serious adverse events are rare [2]. Consequently, baseline and serial laboratory evaluation are unnecessary for the otherwise healthy child who is not receiving other potentially hepatotoxic medications. Asymptomatic increases of serum transaminase concentrations (two to three times the upper limit of normal) are common in children and have no clinical significance; thus, routine measurement of transaminase concentrations may result in further unnecessary testing, unnecessary treatment interruptions, or cessation of therapy if mild increases are noted. Measuring baseline serum transaminase concentrations is reasonable for children and adolescents having HIV infection, receiving medications that may potentially interact with TB medication, having underlying or recent hepatic or biliary disease, or being pregnant or in the first 6 weeks postpartum.

Children should be followed up regularly by providers. Although monthly visits are strongly preferred and recommended, this may not be feasible for some families. At all visits, parents should be given written instructions and informed of possible adverse events so that they will know to stop administering medications if such events are observed. Lack of parental education about adverse events and failure to seek timely care might contribute to severe hepatotoxicity and other adverse drug effects [32]. In consideration of drug-induced liver injury, it is reasonable to interrupt the treatment regimen and promptly evaluate a child (by physical examination and laboratory evaluation) who has anorexia, nausea and vomiting, or abdominal pain. Signs and symptoms of hepatic toxicity should prompt immediate medication cessation with thorough relevant laboratory testing, including hepatic transaminases and bilirubin (conjugated and unconjugated). For children with a serum transaminase concentration, with or without symptoms, great enough to warrant stopping treatment or hyperbilirubinemia, additional testing should be done in consultation with an expert in pediatric TB. In addition, tests for agents causing viral hepatitis should be obtained because these pathogens remain a common cause of hepatic dysfunction.

Suspected drug-associated urticaria or more severe systemic reactions should prompt immediate cessation of the drug(s) and change to a different regimen after symptom improvement. A history of exposure to other medications, new foods, detergents, soaps, and skin lotions should be obtained. In children receiving other medications, clinicians should verify that the selected LTBI regimen will not result in major drug–drug interactions. Isoniazid is known to possibly affect anticoagulant agents, some anticonvulsants, benzodiazepines, and other classes of drugs. Rifampin interacts with multiple classes of drugs, including several antiepileptics, antifungals, antiretrovirals, hormonal contraceptives (e.g., birth control pills), and immunosuppressants.

BARRIERS TO COMPLETION OF THERAPY AND STRATEGIES FOR IMPROVING ADHERENCE

At least one-half of children who begin LTBI therapy with the 9-month INH regimen successfully complete treatment [20,33]. Most treatment default occurs in the first couple of months. There have been several studies attempting to outline characteristics of families of children who complete and those who fail to initiate or complete LTBI treatment. Adherence has been associated with greater TB knowledge, convenient appointment times [34], having a medical home [35], being of African or Latin American origin [33], self-selection of the treatment regimen, and promptly seeing a provider after having a positive TST result [23]. Nonadherence was associated with believing that taking medication would be challenging, and with having been previously recommended for LTBI treatment, and was more common in children of families from eastern Europe and Asia [33]. A recent study found that the only factor associated with successful completion of LTBI treatment was administration of medications by local health departments through DOT [20]. In this study, completion of therapy was approximately 50% when families administered medication, in contrast to greater than 95% when workers from the health department administered medication via DOT.

A less resource-intense alternative to DOT is enhanced self-administered therapy (ESAT). ESAT programs provide medication to families monthly, with periodic phone calls to remind families about adherence and to ask about adverse events. The rate of completion of LTBI therapy using INH was 86% using ESAT in one cohort [20].

To improve treatment completion, practitioners need to routinely use measures to enhance adherence. Some measures may be best carried out in partnership with local health departments. Children at high risk for progression to disease are candidates for DOT. However, DOT is a limited resource in many settings. Other strategies to increase familial adherence are listed in Table 4. Administration of LTBI therapy through school-based clinics [23] or through extended-hour community-based clinics [35] has been shown to improve completion of therapy. From a practical standpoint, if a child completes at least 6 months of isoniazid before defaulting, therapy may be considered completed, as it is unlikely the family will be interested in restarting a course of therapy, and a 6-month course of daily INH is known to have intermediate efficacy, at least for adults [36]. However, if INH is chosen, 9 months of therapy should be the goal.

CONCLUSION

There are two modalities for diagnosing LTBI, as well as several effective treatment regimens, which can be used for infected children. The first step in screening children and adolescents is a risk factor assessment. Diagnostic tests should optimize sensitivity in children at risk for rapid progression to disease (e.g., infants, recently infected, immunocompromised) and optimize specificity for children with fewer risk factors or vaccination with BCG, thereby decreasing the number of uninfected children receiving therapy. If LTBI is diagnosed, the decision as to which AAP/CDC-recommended regimen to use should consider adherence factors and factors that may limit the choice of medications.

Acknowledgments

None.

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KEY POINTS

- Use of a standardized questionnaire to select children for testing based on assessment of established factors associated with TB focuses on children with the highest risk for having LTBI and possible progression to TB disease.
- Use of IGRAs, with their improved specificity particularly for children who have received the BCG vaccine, may decrease the number of uninfected children receiving therapy and enable limited resources to be focused on children who would benefit the most from therapy.
- Multiple LTBI treatment regimens have been studied to varying degrees: selection of regimen should take efficacy, adherence, family preference, possible side-effects, cost, and availability of DOT into consideration.
- Children at the highest risk for progression to TB disease should be considered candidates for DOT to optimize adherence. For children for whom DOT is unavailable, adherence may be increased by incentives and enablers.

Table 1

Immunogenic comparison of the tuberculin skin test and the interferon gamma release assay in children and interpretation of test results

Variable	TST	IGRA
Antigens included	Multiple	2–3
Cross-reaction with BCG vaccine	Yes	No
Cross-reaction with NTM species	Yes	Rare[a]
Sensitivity[b]	55–83%	52–94%
Specificity	70–92%	90–100%
Number of healthcare encounters	2	1
Cost	Low	Higher
Requires experience in clinical interpretation	Yes	Yes
Risk of having boosted reaction	Yes	No[c]
Distinguishes TB disease from LTBI	No	No
Single cut-off for positivity	No	Yes
TST cut-offs by risk factors	Yes	
≥5 mm	Immunocompromised, contact with TB case, suspected of having TB disease, children with fibrotic changes on CXR consistent with prior disease	Single cut-off for positivity regardless of age,[d] epidemiologic risk factors, comorbidities, or concern for TB disease
≥10 mm	Children <4 years of age, children exposed to high-risk adults,[e] recent (<5 years) immigrants from high-incidence countries,[f] and some chronic medical conditions (e.g., diabetes)	
≥15 mm	Positive regardless of risk factors	

BCG, bacille Calmette–Guérin; CXR, chest radiograph; IGRA, interferon gamma release assay; LTBI, latent tuberculosis infection; NTM, nontuberculous mycobacteria; TB, tuberculosis; TST, tuberculin skin test.

[a] Possible cross-reaction with *M. kansasii, M. marinum*, and *M. szulgai*.

[b] Sensitivity data are extracted from two pediatric meta-analyses of children with TB disease.

[c] Evidence exists suggesting that the TST, especially in IGRA-negative persons, can boost the IGRA result if the TST is administered more than 3 days prior to an IGRA.

[d] T-SPOT. TB has a borderline result between negative and positive.

[e] High-risk adults: recent immigrants from high- prevalence countries, occupants of congregate settings (jails, nursing homes, homeless shelters, healthcare workers exposed to TB), HIV-infected, injection drug users.

[f] High-incidence countries: countries outside the United States, Canada, Scandinavia, western Europe, Australia, and New Zealand. Adapted from [11▪, 12, 13▪▪].

Table 2

Indications for preferred use of interferon gamma release assays or the tuberculin skin test for the diagnosis of latent tuberculosis infection in children

Preferred test	Scenario
TST preferred, IGRA acceptable	<5 years of age
IGRA preferred, TST acceptable	BCG vaccinated
	Unlikely to return for TST reading
Either TST or IGRA	Recent contacts (≥5 years of age) of persons with confirmed or suspected TB disease
	Periodic screening of persons with ongoing exposure (e.g., adolescents in correctional facilities)
Both IGRA and TST[a]	Initial TST or IGRA is negative in the following situations: the risk for infection, the risk for progression, or the risk for a poor outcome is increased (e.g., HIV infection, children <5 years old); additional evidence of infection is required to encourage adherence (e.g., persons who believe the positive TST result is attributable to BCG); in healthy persons who have a low risk for both infection and progression; or clinical suspicion exists for TB disease and confirmation of *M. tuberculosis* infection is desired
	IGRA is indeterminate; an alternative to TST placement for children with one indeterminate IGRA is to obtain another IGRA result with the same testing product or the alternative product
	Initial test is negative and the risk of progression to disease is high

IGRA, interferon gamma release assay; TB, tuberculosis; TST, tuberculin skin test.

[a]In most cases, the child presents with a positive TST; children with suspected TB disease or nontuberculous mycobacterial disease are not included in this table. Adapted from [13▪▪, 14].

Table 3

Selection of specific drug regimens given particular scenarios for the treatment of latent tuberculosis infection in children

Regimen	Scenario	Notes
INH	Standard of practice	Daily dosing
	Medication provided intermittently	Treatment must be given by DOT
	Intolerant of rifampin	Severe adverse drug effects much less common than in adults; hypersensitivity reactions occur in up to 4% of adults
	Child is receiving medications which may interact with rifampin or rifapentine	An FDA-generated list of medications potentially interacting with rifampin is available at: http://www.accessdata.fda.gov/drugsatfd a_docs/label/2013/050420s075,050627s014lbl.pdf
RIF	Intolerant of INH	Possible severe adverse reactions occur in <1% of children receiving INH. Fewer data exist for RIF
	INH-resistant TB in a person in contact with a child, RIF-susceptible *M. tuberculosis* isolate	There are no data for intermittent dosing of rifampin for LTBI therapy in children
	Short course is desirable, but INH+RPT is unavailable or not indicated (child <2 years of age)	Adherence is higher for short course regimens
INH+RPT[a]	Adherence concerns	No data are available for children <2 years of age
	Short course is desirable or need to complete therapy urgently (e.g., prior to initiation of immunosuppressive therapy or if child will be traveling)	Scant data on optimal duration of therapy before beginning immunosuppression; many experts recommend at least 4 weeks
INH+RIF	Short course is desirable, but INH+RPT is unavailable	Administer daily[b]

DOT, directly observed therapy; FDA, Federal Drug Administration; INH, isoniazid; RIF, rifampin; RPT, rifapentine; TB, tuberculosis.

[a] Should only be administered under DOT; use may be limited by availability of rifapentine and/or DOT services.

[b] This regimen has not been included in guidelines for the United States.

Table 4

Potential barriers to the diagnosis and treatment of latent tuberculosis infection in children and adolescents and possible solutions to address these barriers

Stage	Potential barrier	Possible solution
Diagnosis		
	Lack of medical home	Screen in nontraditional venues (e.g., schools)
	Failure to return for TST reading	Use an IGRA
	Concern for false-positive results	Use IGRAs; only test children with at least one TB risk factor
	Concern for false-negative results	Consider testing certain high-risk children by both the TST and the IGRA
Treatment		
	Failure to initiate therapy	
	Family refuses to initiate	Cannot mandate LTBI therapy; if families do not cite reason, document that risks/benefits explained to them
	Fail to understand importance of treatment	Educate families on the age-related risk of disease progression in their preferred language
	Confusion about the effect of BCG on the TST	Use an IGRA (Table 1)
	Cannot afford medication	Discuss cost of medications with families before prescribing; inform them of least expensive locations to purchase medications; consider DOT
	Concern for adverse events	Educate families on possible adverse events and frequency; preemptively address internet searching for medication information as most information will refer to adult data
	Concern for treatment duration	Consider shorter treatment courses; understand what time constraints the family may be under
	Default on therapy	
	Fail to understand the importance of treatment	Educate families; regular clinic visits to reinforce progress; consider DOT for children at risk for disease progression
	Cannot remember to take medication	Consider use of DOT (including by school nurses); set cell phone alarms

BCG, bacille Calmette–Guérin; DOT, directly observed therapy; IGRA, interferon gamma release assay; TST, tuberculin skin test.