

## CLINICAL REVIEW

## Advances in Diagnosis and Treatment of Latent Tuberculosis Infection

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In the United States, latent tuberculosis infection (LTBI) affects between 10 and 15 million people, of whom 10% may develop active tuberculosis disease. People at increased risk for tuberculosis reactivation include recent immigrants from countries with a high incidence of tuberculosis, children younger than age 5, people who have been infected with *Mycobacterium tuberculosis* within the past 2 years, or people with immunosuppression for a variety of reasons. Appropriate diagnosis and treatment of LTBI are critical for controlling and eventually eliminating tuberculosis as a public health problem. Although the tuberculin skin test is the traditional diagnostic measure for LTBI, reduced specificity has promoted the development and utilization of the interferon- $\gamma$  release assays as an in vitro blood test with specific antigens to *M. tuberculosis* (QuantiFERON-TB Gold In-Tube test and the T.SPOT-TB test are commercially available). Despite the rise of the new diagnostic tests, however, there is still no gold standard for diagnosing LTBI, and epidemiologic risks and comorbidities need to be taken into account before initiating therapy. Current diagnostic tests combined with recommended treatment regimens are valuable tools that, when used correctly, promise to hurry the elimination of tuberculosis. (J Am Board Fam Med 2014;27:704–712.)

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Historically known as a leading cause of global mortality, there has been a dramatic 41% reduction in the rates of mortality from tuberculosis (TB) and a 36% in prevalence over the past 2 decades.<sup>1</sup> In 2012, with an estimated 8.6 million new TB cases and 1.3 million TB fatalities across the globe, the health and economic burden of active TB disease remains elevated in low- and middle-income countries.<sup>2,3</sup> In addition, because there are approximately 2 billion people with latent or asymptomatic *Mycobacterium tuberculosis* infection, the increased

risk of progression to TB disease is a major global health concern.<sup>4</sup>

*M. tuberculosis* is transmitted through aerosol droplets from a person with active pulmonary TB disease.<sup>5</sup> An estimated 10% of individuals who inhale the aerosol droplets develop active TB disease at some point during their lifetime; the greatest risk of this is during the first 2 years after initial exposure.<sup>6</sup> However, immunocompromised individuals have a larger risk of TB reactivation, including up to 10% increased annual risk for people positive for the human immunodeficiency virus (HIV).<sup>7</sup> Of the remaining 90% of individuals who become infected, the organism remains dormant in the body, producing an asymptomatic latent TB infection (LTBI).<sup>8</sup> Key differences between active infections and LTBI<sup>2,4,5,7,9–11</sup> are listed in Table 1.

In the United States, between 10 and 15 million people—or 3.2% of the population—are estimated to have an LTBI.<sup>7,12</sup> Over the past 2 decades, the incidence trend in active TB disease has decreased in the United States from 14,874 new cases in 2003<sup>13</sup> to 13,293 new cases in 2007<sup>14</sup> and then to 9,951 new cases in 2012.<sup>15</sup> Specific groups that

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**Table 1. Key Differences Between Active and Latent Tuberculosis Infections**

	Active	Latent
Estimated numbers, 2012		
Global <sup>2,4</sup>	8.6 million people per year; 1.3 million deaths per year	2 billion people
United States <sup>7,9,10</sup>	9,945 tuberculosis cases (rate of 3.2 cases per 100,000 people)	10 to 15 million people
Clinical presentation <sup>4,5</sup>	Usually symptomatic Depends on primary disease, but usually includes persistent cough (>2 weeks); fever; night sweats; unexplained weight loss; fatigue; dyspnea; hemoptysis; chest pain; pleuritic pain	Asymptomatic
Chest radiograph <sup>4,11</sup>	Usually abnormal radiographic imaging Depends on primary disease, but usually includes the following: • If primary (recent) infection: middle or lower lobe infiltrates, ipsilateral hilar adenopathy, or cavitation • If secondary (reactivation) infection: upper lobe infiltrates or cavitation • If healed (previous) infection: hilar or upper lobe dense pulmonary nodules, with or without visible calcification	Normal radiographic imaging

have increased risk of reactivation of LTBI to active TB disease include foreign-born people with previous TB infection (within 2 years) that was not treated or treated ineffectively; immunosuppressed people (e.g., HIV, head or neck cancer, chronic renal disease, diabetes mellitus); people with previous gastrointestinal surgical procedures (e.g., gastrectomy, jejunioileal bypass); people taking immunosuppressive treatment (e.g., tumor necrosis factor- $\alpha$  antagonists, chronic corticosteroid use, therapy after organ transplantation); people with poor nutrition status; or children <5 years old.<sup>12,16,17</sup> Groups at high risk for LTBI should be identified to diagnosis and treat these infections.<sup>18</sup>

**Diagnostic Tools in LTBI**

***Tuberculin Skin Test***

For over a century, the tuberculin skin test (TST), or Mantoux test, was the only screening tool for LTBI.<sup>19</sup> A 0.1 mL purified protein derivative of *M. tuberculosis*–secreted proteins is intradermally injected into the volar surface of the forearm, and a positive or negative delayed-type hypersensitivity reaction is evaluated (as millimeters of induration) after 48 to 72 hours.<sup>20</sup> If a baseline assessment is required for TST, especially for those people who receive annual TST testing (e.g., health care workers), and a possible immunologic “boost” to the injection, then the sequential 2-step testing, or a second TST, would occur following an initial negative TST.<sup>21</sup> Because annual TST testing may introduce the *Mycobacterium* antigens for recognition by the immune system, this immunologic “boost”

may produce a reaction upon TST administration, which is indicative of previous positivity and not necessarily recent conversion.<sup>9,21</sup>

Although the TST is an inexpensive diagnostic tool without laboratory analysis with clear definitions for interpretation, the intradermal administration and interpretation must be completed by experienced clinicians.<sup>22</sup> Patients must return to the clinic within 48 to 72 hours to receive the final interpretation of the test.<sup>23</sup> The test has low specificity, causing false positives in patients who had a previous history of the bacilli Calmette-Guérin (BCG) vaccination or exposure to nontuberculous mycobacteria (NTM).<sup>24,25</sup> It has low sensitivity in some populations, causing false negatives in immunocompromised patients with HIV infection, systemic infections, and chronic renal disease; people with prior gastrointestinal surgical procedures; people who had a live vaccination within the previous 2 months; people who are malnourished; or people taking systematic immunosuppressive medications.<sup>11,12</sup>

***Interferon- $\gamma$  Release Assays***

Interferon- $\gamma$  release assays (IGRAs) were developed to address the shortcomings of the TST. These in vitro blood tests assess the immunologic reaction of cytokines (interferon- $\gamma$ ) to specific antigens to *M. tuberculosis*.<sup>26</sup> The QuantiFERON-TB test (QFT) and the QFT Gold test (QFT-G) (Cellestis Ltd, Carnegie, Victoria, Australia) became available and approved by the US Food and Drug Administration in 2001 and 2005, respectively.<sup>27,28</sup>

After the Centers for Disease Control and Prevention (CDC) revised the 2005 guidelines on IGRAs, QFT-G In-Tube test (Qiagen, Valencia, CA) was approved in 2007 to evaluate the response to *M. tuberculosis*-specific antigens (CFP-10, ESAT-6, TB7.7) when compared with control media.<sup>29,30</sup> In 2008, the T.SPOT TB test (Oxford Immunotec, Abingdon, UK) was developed, requiring 5 mL of peripheral mononuclear cells for the enzyme-linked immunospot to evaluate the response to *M. tuberculosis*-specific antigens (CFP-10, ESAT-6) when compared with control media.<sup>31</sup> Results for the QFT-G In-Tube and T-SPOT.TB tests are recorded with qualitative (positive, negative, or indeterminate) and quantitative values within a period of 24 hours.<sup>28,30</sup> Key differences between the TST and IGRA as diagnostic measures for LTBI<sup>21,23,30,32,33</sup> are listed in Table 2.

### Current Diagnostic Recommendations

Although the prevalence of TB in the United States has decreased approximately 63% in the past 2 decades (3.2 TB cases per 100,000 people in 2012<sup>34</sup>), current diagnostic recommendations conclude that IGRAs permit several advantages over the TST in clinical practice.<sup>7,12,23,35–39</sup> Because IGRAs have specific antigens that target *M. tuberculosis*, they do not react with common NTM<sup>23,39</sup> or BCG vaccine strains<sup>12,36</sup> and do not produce an

immunologic “boost.”<sup>40,41</sup> Although there are additional costs, the administrative and laboratory analytical techniques for IGRAs follow a standard, objective protocol and provide results within 24 hours, enabling the identification and management of patients with LTBI from hard-to-reach groups.<sup>42</sup>

IGRAs have been recommended as tests in the diagnosis of *M. tuberculosis* infection in several different clinical scenarios.<sup>37,38,43</sup> IGRAs should be administered in adults, including BCG-vaccinated individuals<sup>37,38</sup> or people with immunocompromising conditions.<sup>23,44</sup> They should also be administered in situations where the TST has a positive result or in hard-to-reach population groups.<sup>42,45</sup> In addition, IGRAs may be considered in children >5 years old who have a suspected LTBI, whether from a high-incidence country or with confirmed household contacts.<sup>42,46</sup> However, another physician with expertise in the diagnostics and management of TB should review any clinical case where a child with an immunocompromising condition presents with a suspected LTBI.<sup>42</sup>

However, there may arise clinical scenarios in which IGRA diagnostic measures conclude a qualitative result as indeterminate or a quantitative value in the borderline zone after testing patients with a suspected diagnosis of LTBI. When IGRA results are near the cutoff points, which is consid-

**Table 2. Key Differences Between Tuberculin Skin Test (TST) and Interferon- $\gamma$  Release Assay (IGRA) as Diagnostic Measures for Latent Tuberculosis Infection**

Characteristics	TST	IGRA
Protocol <sup>23,30</sup>	After the 0.1-mL intradermal injection of PPD of <i>Mycobacterium</i> antigens into the patient, the area is measured between 48 to 72 hours for size of induration	After taking a 3- to 5-mL sample of peripheral blood mononuclear cells from the patient, the response of IFN- $\gamma$ production by T-lymphocytes upon stimulation with specific <i>Mycobacterium tuberculosis</i> antigens (CFP-10, ESAT-6, TB7.7) is measured within 24 hours
Estimated sensitivity <sup>21,32</sup>	75% to 90% (reduced in immunocompromised patients)	78% to 92%
Estimated specificity <sup>21,32</sup>	70% to 95% (reduced in BCG-vaccinated and NTM infections)	93% to 98%
Advantages <sup>23,33</sup>	No laboratory procedures or costs	May be more cost-effective Requires one visit Objectivity in test interpretation
Disadvantages <sup>32</sup>	Requires follow-up visit (48 to 72 hours later) High subjectivity in test interpretation	Requires laboratory procedures Should not be used in children <2 years of age because of limited data in children between 2 and 4 years of age

BCG, Bacillus Calmette-Guérin; IFN, interferon; NTM, nontuberculous mycobacteria; PPD, purified protein derivative.

ered the borderline zone, the test results should be cautiously considered in combination with the clinical evaluation.<sup>47,48</sup> However, if IGRAs produce an indeterminate or invalid result, whether low mitogen or high Nil (negative control), the tests should be repeated and reviewed by a TB specialist.<sup>30</sup>

### Current Gaps in Diagnostic Measures

The definitive diagnosis of LTBI is complicated and requires a case-by-case review. There is no current gold standard diagnostic measure<sup>32,49</sup> or ability to directly diagnose LTBI with radiographic imaging<sup>11</sup> or serum biomarkers.<sup>50</sup> The current diagnostic tools of TST and IGRAs cannot distinguish between evidence of prior TB disease or present active TB disease.<sup>51</sup>

Future studies should target the accuracy of LTBI diagnostic testing in high-risk populations. First, because the host immunologic response is key to the IGRA response, people with immunocompromising conditions, such as autoimmune diseases, end-stage renal disease, or after transplantation, require a more cautious evaluation of diagnostic tests.<sup>23,35,52</sup> Second, the TST is preferred over IGRA as the diagnostic tool in children under <5 years old.<sup>45</sup> Because young children may have variable immune responses to TB infection, however, both tests should continue to be evaluated for diagnostic sensitivity.<sup>43,45</sup> Finally, the borderline zone as well as the “wobble” phenomenon at the cutoff value should be further evaluated for clinical decision making. This may reduce the number of patients, especially health care workers, who are managed with preventive LTBI therapy.<sup>53–55</sup>

### Treatment of Latent Tuberculosis Infection (LTBI)

After active TB disease has been excluded by clinical and laboratory evaluation, any patient diagnosed with LTBI should be considered for LTBI treatment, which reduces the risk of TB reactivation. Patients may encounter challenges in adhering to LTBI treatment, including limited access to health services, disease-related stigma, or minimal family or social support.<sup>10</sup> LTBI treatment is completed when the patient has taken the appropriate quantity of pharmacologic doses.<sup>56</sup> Two of the 3 medications of choice—isoniazid (INH) and rifampin (RIF)—have opposing mechanisms of action on cytochrome P450 enzymes (the former inhibits and the latter induces these enzymes), so patients

with multipharmacologic regimens should be closely monitored.<sup>57</sup> Dosages for pharmaceutical management recommended by the CDC<sup>58</sup> are presented in Table 3.

As the medication of choice, INH should be prescribed daily for a total of 9 months in HIV-negative and HIV-positive children and adults, whether daily as self-administered therapy or biweekly as directly observed therapy (DOT).<sup>58–60</sup> However, INH prescribed for a total of 6 months, whether a daily or biweekly regimen, is an appropriate alternative in HIV-negative children and adults.<sup>58–60</sup> The American Academy of Pediatrics recommends 9 months of INH for children.<sup>58</sup> Although delaying the INH treatment regimen is preferred after delivery in pregnant women, it may be administered if there is high risk for disease progression, such as documented recent close contact with an active case or immunosuppression.<sup>61</sup> Adverse effects may include hepatic toxicity; therefore, physicians should discuss avoiding alcohol and promote adherence to the treatment regimen.<sup>62</sup> Baseline hepatic enzyme levels should be evaluated for individuals with HIV or underlying liver disease or pregnant or postpartum women; INH therapy should be routinely clinically monitored in patients with abnormal baseline results, including symptomatology related to liver inflammation, and liver function tests.<sup>58,63</sup> Children should be monitored for symptomatology of hepatotoxicity rather than by routine laboratory evaluation. An additional adverse effect is peripheral neuropathy, which may be prevented by recommended pyridoxine (vitamin B<sub>6</sub>) supplementation.<sup>64</sup> Other adverse reactions include dermatitis or lupus-like syndrome.<sup>57</sup>

As an alternative medication, RIF should be prescribed daily for a total of 4 months for HIV-negative patients who are intolerant to INH, have suspected hepatic toxicity, or have resistance to INH.<sup>58–60</sup> Adverse effects include orange discoloration of body fluids, gastrointestinal disturbances, hypersensitivity reactions, and elevated hepatic enzymes.<sup>65</sup> Recent research studies demonstrated that patients taking RIF for 4 months had reduced adverse side effects and increased compliance to completion of recommended treatment compared with those on 9 months of INH.<sup>66,67</sup>

However, a third therapeutic strategy has recently received greater attention when compared with the recommended 9 months of INH and the alternative 4 months of RIF. The 12-dose regimen of INH and rifapentine (RPT), or a once weekly



**Table 3. Pharmaceutical Management of Latent Tuberculosis Infection<sup>58</sup>**

Medication	Duration	Dose	Frequency	Total Doses (n)
Isoniazid	9 months	Adults: 5 mg/kg	Daily	270
		Children: 10–20 mg/kg*		
		Maximum dose: 300 mg		
	6 months	Adults: 15 mg/kg	Twice weekly by DOT	76
		Children: 20–40 mg/kg*		
		Maximum dose: 900 mg		
Isoniazid and rifapentine	3 months	Adult: 5 mg/kg	Daily	180
		Children: Not recommended		
		Maximum dose: 300 mg		
	3 months	Adults: 15 mg/kg	Twice weekly by DOT	52
		Children: Not recommended		
		Maximum dose: 900 mg		
Rifampin	4 months	Adults and children >12 years:	Once weekly by DOT	12
		INH <sup>†</sup> : 15 mg/kg rounded up to nearest 50 or 100 mg; 900 mg maximum		
		RPT <sup>‡</sup> :		
		•10.0–14.0 kg: 300 mg		
		•14.1–25.0 kg: 450 mg		
		•25.1–32.0 kg: 600 mg		
		•32.1–49.9 kg: 750 mg		
		•≥50 kg: 900 mg maximum		
		Adult: 10 mg/kg <sup>‡</sup>	Daily	120
		Maximum dose: 600 mg		

\*The American Academy of Pediatrics recommended INH dosage.

<sup>†</sup>INH is formulated as 100- and 300-mg tablets. RPT is formulated as 150-mg tablets in blister packs that should be kept sealed until use.

<sup>‡</sup>In the United States, the recommended latent tuberculosis infection treatment in children is a 9-month INH regimen. For latent tuberculosis infection treatment in infants, children, and adolescents when INH cannot be tolerated or the child has had contact with a patient infected with an INH-resistant but rifamycin-susceptible organism, the American Academy of Pediatrics recommends a 6-month daily rifampin dosage (180 dosages) of 10 to 20 mg/kg. DOT, directly observed therapy; INH, isoniazid; RPT, rifapentine.

dose for 3 months, can be prescribed for HIV-negative patients >12 years old.<sup>58,68</sup> Because RPT is a pharmacological derivative of RIF, clinical trials have demonstrated that although adverse effects are similar to monotherapy INH or RIF, there are fewer drug–drug interactions with RPT.<sup>63</sup> One multicenter randomized clinical trial concluded that participants who followed this 12-dose regimen by DOT demonstrated increased compliance to treatment and equivalent therapeutic outcomes when compared with those taking INH monotherapy.<sup>69,70</sup> Key diagnostic and treatment recommendations for practice according to the Strength of Recommendations Taxonomy are presented in Table 4.<sup>71</sup>

## Conclusions

Diagnostic measures that accurately identify LTBI in patients with increased risk for developing TB dis-

ease, followed by the recommended pharmacologic regimen, is the main priority to decrease the incidence, prevalence, and mortality of TB.<sup>4</sup> However, the prevalence of LTBI and risk of reactivation to TB disease present multiple challenges, including coinfection with HIV, immunosuppression, substance abuse, immigration, and multidrug resistance.<sup>6</sup> IGRAs can be an important diagnostic tool that focuses on those population groups who are at higher risk for progression to active TB disease, including people with prior BCG vaccination and hard-to-reach groups.<sup>16,45</sup> With targeted screening programs, the number of individuals who require treatment of LTBI should decrease. Take-home points for specific population groups to be tested for LTBI<sup>10,12,58</sup> are presented in Table 5.

With limited pharmacological discoveries in the past 4 decades, the advent of new strategies for active TB disease is encouraging for TB prevention

**Table 4. Key Diagnostic and Treatment Recommendations for Practice According to the Strength of Recommendations Taxonomy<sup>71</sup>**

Clinical Recommendation	Strength of Recommendation*	References
Sequential 2-step tuberculin skin tests should be performed in people who require baseline evaluations and have initial negative test results.	C	21
Tuberculin skin tests are preferred over interferon- $\gamma$ release assays as the diagnostic tool in children <5 years old.	B	45
Interferon- $\gamma$ release assays should be administered in adults, including BCG-vaccinated individuals or people with immunocompromising conditions.	A	37, 38, 44
Interferon- $\gamma$ release assays should be administered in hard-to-reach groups for prompt identification and management of LTBI.	A	42, 45
Baseline laboratory values of hepatic enzyme levels should be performed in patients with HIV or underlying liver disease or in pregnant or postpartum women, in whom abnormal results should be evaluated routinely during LTBI therapy.	B	58
Daily regimen of isoniazid for a duration of 9 months is the medication of choice for LTBI in adults and children.	A	58
Equivalent therapeutic outcomes of a 12-dose regimen of isoniazid and rifapentine for a duration of 3 months, when compared with the daily regimen of isoniazid for a duration of 9 months, have demonstrated increased compliance.	A	69, 70

\*Strength of recommendations: A = consistent and good quality patient-oriented evidence; B = inconsistent or limited quality patient-oriented evidence; C = consensus, usual practice, opinion, disease-oriented evidence, and case series for studies of diagnosis, treatment, prevention, or screening.

BCG, bacillus Calmette-Guérin; HIV, human immunodeficiency virus; LTBI, latent tuberculosis infection.

and control.<sup>72</sup> Current research trials are investigating the use of the 12-dose INH and RPT regimen by DOT in low-income countries with high TB prevalence, as well as the actual cost-effectiveness and safety of using new regimens in clinical practice.<sup>70</sup>

Along with the scientific advancements in diagnostic measures and multipharmaceutical regimens

based on the infectious etiology of LTBI, the influence of social determinants of health on LTBI transmission and prevention may be key to global control of LTBI.<sup>73–76</sup> By focusing on screening high-risk population groups for TB reactivation, individuals may be identified and educated about LTBI and recommended treatment.<sup>77</sup> Together with cost-effective diagnostic measures, educa-

**Table 5. Take-Home Points on Specific Population Groups to Test for Latent Tuberculosis Infections (LTBI)**

Categories	Population Groups	Description
High risk of exposure or infection with <i>Mycobacterium tuberculosis</i> <sup>10,12,58</sup>	Close contact	Children, adolescents, or adults with close contact with high-risk adults
	Congregated living conditions	Employees or residents of long-term care facilities, correctional facilities, homeless shelters
	Foreign born	People who moved from countries with a high burden of TB to the United States (<5 years)
High risk of LTBI progression to TB disease <sup>10,12,58</sup>	History of TB	People acquiring latent TB infection within the previous 2 years or people with previous untreated/ineffective treatment of active TB with no sign of active TB at the time of starting latent TB treatment
	Age	Children <4 years
	Substance use	People who inject illicit drugs
	Immunosuppression	People with poor nutrition status; previous surgical interventions (e.g., gastrointestinal surgical procedures); immunosuppressive medications (e.g., tumor necrosis factor- $\alpha$ antagonists, chronic corticosteroid use); immunocompromising conditions (e.g., HIV, chronic renal failure, diabetes mellitus, cancer)

HIV, human immunodeficiency virus; TB, tuberculosis.

tional programs may facilitate patient understanding about LTBI and the importance of compliance to pharmacological treatment, leading toward improved global control of LTBI.

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