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EDITORIAL

Latent Tuberculosis: A Concealed Global Burden

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Introduction

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by

Mycobacterium tuberculosis antigens with no evidence of clinically manifest active TB[1]. As there is no "gold standard" test for LTBI, the global burden is not known with certainty; however, up to one third of the world's population is estimated to be infected with *M. tuberculosis*[2–4], and the vast majority have no signs or symptoms of TB disease and are not infectious, although they are at risk for active TB disease and for becoming infectious. Several studies have shown that, on average, 5–10% of those infected will develop active TB disease over the course of their lives, usually within the first 5 years after initial infection[5]. The risk for active TB disease after infection depends on several factors, the most important being immunological status[1].

Prevention of active TB disease by treatment of LTBI is a critical component of the WHO End TB Strategy *(6)*. The efficacy of currently available treatments ranges from 60% to 90% *(1)*. The potential benefit of treatment should, however, be carefully balanced against the risk for drug-related adverse events. Management of LTBI involves a comprehensive package of interventions: identifying and testing those individuals who should be tested, delivering effective, safe treatment in such a way that the majority of those starting a treatment regimen will complete it with no or minimal risk of adverse events, and monitoring and evaluation of the process.

Identification of populations for testing and treatment of latent tuberculosis infection

Generally, persons at risk for developing TB disease fall into 2 broad categories:

- Those who have an increased likelihood of exposure to persons with TB disease
- Those with clinical conditions or other factors associated with an increased risk of progression from LTBI to TB disease

Also at risk are those with certain conditions and other factors associated with progression from LTBI to TB disease. These conditions and factors include the following:

- HIV infection
- Injection drug use
- Radiographic evidence of prior healed TB
- Low body weight (10% below ideal)
- Other medical conditions, such as: silicosis, diabetes mellitus, chronic renal failure or on hemodialysis, gastrectomy, jejunoileal bypass, solid organ transplant, head and neck cancer, conditions that require prolonged use of corticosteroids or other immunosuppressive agents such as TNFá antagonists
- Recent TST converters (that is, persons with baseline testing results who have an increase of 10 mm or more in the size of the TST reaction within a 2-year period).
- Infants and children under the age of 5 years who have a positive TB test result

Of note, the risk of progression is greatest in the first 1 or 2 years after infection.

Diagnosis of Latent TB Infection

The diagnosis of LTBI is based on information gathered from the medical history, TST or IGRA result, chest radiograph, physical examination, and in certain circumstances, sputum examinations. The presence of TB disease must be excluded before treatment for LTBI is initiated because failure to

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do so may result in inadequate treatment and development of drug resistance (see Table 1).

No symptoms or physical findings suggestive of TB disease. TST or IGRA result usually positive. Chest radiograph is typically normal. If done, respiratory specimens are smear and culture negative. Cannot spread TB bacteria to others. Should consider treatment for LTBI to prevent TB disease. Symptoms may include one or more of the following: fever, cough, chest pain, weight loss, night sweats, hemoptysis, fatigue, and decreased appetite. TST or IGRA result usually positive. Chest radiograph is usually abnormal. However, may be normal in persons with advanced immunosuppression or extrapulmonary disease. Respiratory specimens are usually smear or culture positive. However, may be negative in persons with extrapulmonary disease or minimal or early pulmonary disease. May spread TB bacteria to others. Needs treatment for TB disease.

Tests for TB Infection

A. Tuberculin Skin Test (TST)

The TST is used to determine if a person is infected with *M. tuberculosis*. If a person is infected, a delayed-type hypersensitivity reaction is detectable 2 to 8 weeks after infection. The skin test is administered intradermally using the Mantoux technique by injecting 0.1ml of 5 TU purified protein derivative (PPD) solution. The reading and interpretation of TST reactions should be conducted within 48 to 72 hours of administration.

B. Interferon–Gamma Release Assays (IGRAs)

IGRAs are used to determine if a person is infected with *M. tuberculosis* by measuring the immune response to TB proteins in whole blood. Specimens are mixed with peptides that simulate antigens derived from *M. tuberculosis* and controls. In a person infected with *M. tuberculosis*, the white blood cells recognize the simulated antigens and release interferon-gamma (IFN-γ); results are based on the amount of IFN- ã released.

As noted earlier, there are 2 U.S. Food and Drug Administration (FDA) approved IGRAs commercially available:

- QuantiFERON® -TB Gold-in-Tube test (QFT-GIT)
- T-SPOT® *TB* test

Table-I

Differentiating Between Latent TB Infection and TB Disease

LTBI	TB Disease
No symptoms or physical findings suggestive of TB disease.	Symptoms may include one or more of the following: fever, cough, chest pain, weight loss, night sweats, hemoptysis, fatigue, and decreased appetite.
TST or IGRA result usually positive.	TST or IGRA result usually positive.
Chest radiograph is typically normal.	Chest radiograph is usually abnormal. However, may be normal in persons with advanced immunosuppression or extrapulmonary disease.
If done, respiratory specimens are smear and culture negative.	Respiratory specimens are usually smear or culture positive. However, may be negative in persons with extrapulmonary disease or minimal or early pulmonary disease.
Cannot spread TB bacteria to others.	May spread TB bacteria to others.
Should consider treatment for LTBI to prevent TB disease.	Needs treatment for TB disease.

Advantages of IGRAs include the following: Requires a single patient visit to conduct the test.

- Does not cause booster phenomenon.
- Laboratory test not affected by health care worker perception or bias.
- Results can be available within 24 hours.
- Unaffected by BCG and most environmental mycobacteria.

Limitations of IGRAs include the following:

- Blood sample must be processed within 8-30 hours after collection.
- Limited data exist on use in groups such as children younger than 5 years of age, persons recently exposed to TB, immunocompromised persons, and those who will be tested repeatedly (serial testing).

Selecting a Test to Detect TB Infection

- IGRAs are the preferred method of testing for:
  - o Groups of people who have poor rates of return for TST reading and interpretation (e.g., homeless persons)
  - o Persons who have received BCG vaccination
- TST is the preferred method for testing for: Children under the age of 5 years
- Either TST or IGRA may be used without preference for other groups that are tested for LTBI.

Special Considerations in Testing for TB Infection

BCG Vaccine

In many parts of the world where TB is common like Bangladesh, BCG vaccine is used to protect infants and young children from serious, life-threatening disease, specifically miliary TB and TB meningitis. The World Health Organization (WHO) recommends that BCG vaccine be administered during infancy in TB endemic countries. BCG vaccination is not generally recommended in the United States. The effect of BCG vaccine on TST results often causes confusion. TST reactivity caused by BCG vaccine generally wanes with the passage of time, but periodic skin testing may prolong (boost) reactivity in vaccinated persons. A person with a history of BCG vaccination can be tested and treated for LTBI if they react to the TST. TST reactions should be interpreted based on risk stratification regardless of BCG vaccination history.

IGRAs use *M. tuberculosis* specific antigens that do not cross react with BCG, and therefore, do not cause false positive reactions in BCG recipients.

HIV Infection

The risk of progression from LTBI to TB disease is 7% to 10% each year for those with both LTBI and untreated HIV infection. Those with LTBI who are not HIV-infected have a 10% risk over their lifetime. Thus the risk of progression to TB disease is 10 times greater for those who are HIV infected. This risk is reduced with antiretroviral therapy for HIV, but is still higher than that in HIV-negative persons with LTBI.

HIV-infected persons should be tested for LTBI as soon as their HIV status becomes known. A negative TST or IGRA result does not exclude LTBI as they may have a compromised ability to react to tests for TB infection.

After the initiation of antiretroviral therapy (ART), repeat testing for LTBI is recommended for HIV-infected persons previously known to have negative TST or IGRA results. This is because the immune response may be restored by ART.

Other Diagnostic Considerations

Chest Radiograph

A chest radiograph should be ordered as part of a medical evaluation for a person who has a positive TST or IGRA result. A chest radiograph is also indicated in the absence of a positive test result for TB infection when a person is a close contact of an infectious TB patient and treatment for LTBI will be started (e.g., "window prophylaxis" in a young child or immunocompromised person).

Children less than 5 years of age should have both posterior-anterior and lateral views; all others should have at least posterior-anterior views.

Persons with nodular or fibrotic lesions consistent with old TB are high-priority candidates for treatment of LTBI after TB disease is excluded. Persons with fully calcified, discrete granulomas do not have an increased risk for progression to TB disease.

Sputum Examination for AFB Smear and Culture

Sputum examination is indicated for persons with positive test results for TB infection and either an abnormal chest radiograph or the presence of respiratory symptoms (even when the chest radiograph is normal).

Physical Examination and Medical History

Physical examination and medical history, which includes obtaining information about previous positive tests for TB infection, previous treatment for LTBI or TB disease, and a risk assessment for liver disease, are indicated for an individual with positive TB test results. Written documentation of a previously positive TST or IGRA result is required; a patient's verbal history is not sufficient.

Treatment options for LTBI

Isoniazid monotherapy for 6 months is recommended for treatment of LTBI in both adults and children in countries with high and low TB incidence. *(Strong recommendation, high-quality evidence. Existing* recommendation)

Rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for children and adolescents aged < 15 years in countries with a high TB incidence. *(Strong recommendation, low-quality evidence. New recommendation)*

Rifapentine and isoniazid weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children in countries with a high TB incidence.

(Conditional recommendation, moderate-quality evidence. New recommendation)

The following options are recommended for treatment of LTBI in countries with a low TB incidence as alternatives to 6 months of isoniazid monotherapy: 9 months of isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months of isoniazid plus rifampicin, or 3–4 months of rifampicin alone.

(Strong recommendation, moderate–high-quality evidence. Existing recommendation)

In settings with high TB incidence and transmission, adults and adolescents living with HIV who have an unknown or a positive TST and are unlikely to have active TB disease should receive at least 36 months of isoniazid preventive therapy (IPT), regardless of whether they are receiving ART. IPT should also be given irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy.

Table-II

Recommended dosages of drugs for the treatment of LTBI

Drug regimen	Dose per kg body weight	Maximum dose
Isoniazid alone, daily for 6 or 9 months	Adults, 5 mg Children, 10 mg (range, 7-15 mg)	300 mg
Daily rifamoicin alone for 3-4 months	Adults, 10mg Children, 15 mg (range, 10-20 mg)	600 mg
Daily isoniazid plus rifampicin for 3-4 months	Isoniazid: Adults, 5 mg Children, 10 mg (range, 7-15 mg) Rifampicin Adults, 10 mg Children, 15 mg (range, 10-20 mg)	Isoniazid, 300 mg Rifampicin, 600 mg
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Individuals aged ≥ 12 years; Isoniazid: 15 mg Individuals aged 2-11 years; isoniazid: 25 mg Rifapentine; 10.0-14,0 kg = 300 mg 14.1-25.0 kg = 450 mg 25.1-32.0 kg = 600 mg 32.1-50.0 kg =750 mg >50 kg = 900mg	Isoniazid, 900 mg Rifapentine, 900 mg

(Conditional recommendation, low quality evidence. Existing recommendation).

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