Outpatient Practice Management Tips

Testing for Latent Tuberculosis

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Tuberculosis (TB) is a common cause of morbidity and mortality worldwide. The number of new cases continues to increase despite intense efforts to eradicate the disease. According to the World Health Organization, the global incidence rate of TB increased to 8.8 million cases in 2002 with a growth rate of 2.4% per year.¹ In the United States, about half of the new cases occur in persons immigrating to this country.²

Treatment of persons with active TB is the number one priority targeted to prevent the spread of infection. A secondary priority, particularly in developed countries where there is a lower incidence of the disease, is the identification and treatment of persons with latent TB infection (LTBI).³ The majority of new cases of TB are derived from a pool of patients with LTBI. Thus, identifying and treating persons with latent infections is an important public health measure, since it not only prevents active TB from occurring in individuals with latent infection, but also prevents the interpersonal spread of the disease. Understanding the available tests and how to correctly interpret and apply the results is the first step in recognizing patients at risk and in providing appropriate treatment.

Studies available to diagnose LTBI

The goal of testing for LTBI is to identify persons who are at increased risk for developing TB and who would benefit from treatment of the infection.⁴ This includes healthcare workers and persons who have had recent contact with someone who has active TB as well as those with underlying medical conditions such as diabetes mellitus and lymphomas (tables 1 and 2). Since only persons who would benefit from treatment should be tested, a decision to test presupposes a decision to treat if the test result is positive. There are two tests available to confirm a diagnosis of LTBI: the tuberculin skin test, and the measurement of interferon- γ in whole blood.

The tuberculin skin test has been available since the 1900s and is based on the observation by Robert Koch that infection with *Mycobacterium tuberculosis* caused cutaneous reactivity to tuberculin, the heat-killed, purified protein derivative (PPD) from cultures of *M. tuberculosis*. The standard tuberculin test consists of an intracutaneous injection of 0.1 ml (5 tuberculin units) of PPD into the volar forearm

Table 1. Increased risk and who should be tested for latent tuberculosis infection.

Risk	Persons at risk
Increased risk due to exposure of infectious cases	Persons with recent close contact with person known to have active TB Children <4 years of age Tuberculin converters* Health care workers employed at facilities where persons receive treatment for TB
Increased risk due to individual characteristics	Foreign-born persons from countries with high prevalence of TB (Asia, Africa and Latin America) Homeless persons Persons living or working in a long-term care facility (e.g., nursing home, prison, health care facility, etc.)
Increased risk of active TB once infection has occurred	Persons infected with HIV Intravenous drug abusers Persons with the following medical risk factors End stage renal disease Silicosis Diabetes mellitus Immunosuppressive therapy Hematological malignancy Malnourished or who lost more than 10% of their ideal body weight Gastrectomy or jejunioileal bypass

*An increase in induration of at least 10 mm on tuberculin skin tests within a 2-year period.

TB, tuberculosis

Table 2. Characteristics or clinical features of persons who should receive treatment for LTBI corresponding to degree of induration on skin testing.

Diameter of induration	Characteristics or clinical features
5 mm	HIV infection Recent close contact with a person with active TB* Fibrotic changes on chest radiograph consistent with prior TB Organ transplant recipients and other immunocompromising conditions requiring the equivalent of 15 mg/day of prednisone for 1 month
10 mm	Foreign-born from high prevalence regions such as Asia, Africa and Latin America and immigrating to this country within the last 5 years Intravenous drug and alcohol abuse Residing or working in a high risk congregate setting (e.g., correctional facility, nursing home, homeless shelter, hospital, etc.) Employed in a mycobacteriology lab Medical conditions that places persons at high risk Less than 4 years of age or <18 years of age and exposed to adults in high risk categories
15 mm	No known risk factors for TB

*Recent close contact is defined as at least 12 hours of contact with a person with infectious TB. Persons who have had an initial negative skin test reaction after contact with a person with active TB should receive treatment for LTBI and should be retested 10 to 12 weeks after exposure.

If the skin test is again negative (≤ 5 mm) and the person has been removed from the source of exposure, treatment can be discontinued. Persons with HIV or other immunocompromising conditions should be given treatment regardless of skin test results if they have come in contact with persons with active TB.

LTBI, latent tuberculosis infection; TB, tuberculosis

(figure 1). The reaction is read 48 to 72 hours after injection. Reactivity to this antigen may persist up to 1 week facilitating accurate delayed interpretation.⁵

The size of the reaction is determined by measuring the diameter of induration in millimeters (mm). The indurated area refers to the raised region, not the surrounding erythema. The “pen technique” is a useful method for distinguishing the indurated area from the surrounding erythema (figure 2). To employ this technique, a line is lightly drawn with a pen in the horizontal and vertical planes until the edge of the induration is reached. To determine the size of the reaction, the induration is measured transversely to the long axis of the forearm from the most medial point.

There is a high level of interobserver variability in interpreting the skin test. This variability can be significant, since interpreting the induration as 9 mm versus 10 mm or 13 to 14 mm versus 15 mm may shift patients from a negative category into a positive category and vice versa.

Figure 1. Method for injecting 0.1 ml of PPD (5 tuberculin units) intradermally. Use a tuberculin syringe (3/8 inch 26-27 gauge needle) with the needle bevel upward to create a white wheal 6-10 mm in diameter in the volar or flexor surface of the forearm.¹¹

Figure 2. The raised or indurated area (center) is measured and not the area of erythema (indicated by the perpendicular lines). The indurated area is measured transversely to the long axis of the forearm.¹¹

The criteria for interpreting the reaction as positive, indicating the presence of TB infection, vary depending upon the characteristics of the person being tested. The general principle used in TB testing is that for patients with high-risk characteristics, the sensitivity of the tuberculin skin test is increased if a lower cut-off is used to define a positive test.

The whole blood interferon- γ test is a quantitative *in vitro* assay that evaluates the cell mediated immune response to *M. tuberculosis*. The test is based upon the principle that previously sensitized T lymphocytes release interferon- γ in response to stimulation by PPD. This assay has been shown to have excellent agreement with tuberculin skin testing.⁶ It should be noted that neither PPD nor the whole blood interferon- γ assay can distinguish between TB infection and bacilli Calmette-Guerin (BCG) induced reactivity. A novel assay that is not widely available measures the amount of interferon- γ released by T lymphocytes following exposure to the antigen ESAT-6 (normally absent in BCG) and may be useful for diagnosing LTBI in patients previously vaccinated with BCG.⁷

Testing for LTBI

The current recommendations from the American Thoracic Society and the Centers for Disease Control and Prevention are designed to focus tuberculin skin testing towards persons at high risk for developing active TB and who will receive treatment for LTBI if results are positive (table 1).⁴ Unlike previous recommendations, age alone should not influence the decision to treat. In past recommendations age was used in the treatment decision because of the concerns related to the heightened awareness for increased risk of hepatotoxicity with isoniazid that increases with advancing age. In one early series, rates of hepatotoxicity were reported to be 3 out of every 1000 persons 20 to 34 years of age and 23 out of every 100 in persons 50 to 64 years of age.⁸ It should be kept in mind that mortality for isoniazid induced hepatotoxicity is very low, and complete recovery from nonfatal hepatotoxicity is the rule. Current recommendations state that persons who are at increased risk for developing active TB, because of certain medical conditions or because of exposure to infectious cases, and those for whom the risk of developing active TB exceeds the risk of developing isoniazid induced hepatotoxicity are candidates for LTBI testing. Persons should not undergo testing if they are not candidates for treatment. The risk of developing active TB is greatest immediately following exposure, therefore persons who have had a recent close contact with an individual with active TB represent a high priority group for LTBI testing.

Cut-off points for determining a positive tuberculin reaction

Regardless of a positive skin test result and prior to beginning treatment for patients with LTBI, a thorough assessment including chest radiographs and sputum analyses must be performed to exclude active TB infection. The threshold for determining a positive test is based upon

different likelihoods of the tests representing true positives in the different settings. For example, persons at greatest risk have a lower threshold (5 mm diameter of induration) compared to those with few risk factors (15 mm diameter of induration). A person is identified as a “tuberculin converter,” and thus recently infected, when the amount of induration found on tuberculin skin testing increases by ≥ 10 mm within a 2-year period. Tuberculin conversion should be distinguished from the booster phenomenon in which a reaction to skin testing is initially negative and is found to be positive upon retesting 2 weeks later, even though the person is not newly infected. The booster phenomenon represents a false negative result in a person with prior LTBI due to waning immunity. To avoid misinterpretation of a person being a new tuberculin converter, two-step testing should be performed in all persons who are likely to be retested at a later date.

Many foreign countries continue to use BCG vaccination as part of their TB control program, particularly in infants. As mentioned previously, sensitivity to tuberculin is highly variable in persons vaccinated with BCG, and depends upon the strain of BCG used and the person receiving the vaccine. BCG vaccination is not routinely used in the United States because of the variable protective efficacy ranging from 0-80%.⁹ Although non-infected persons vaccinated with BCG may develop a false-positive result upon tuberculin skin testing, the majority (92%) of these persons are skin test negative, especially if they were vaccinated during infancy or early childhood.¹⁰ Thus, it is recommended that a previous history of BCG vaccination should be ignored when interpreting skin test results.

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