Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease

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Division of Tuberculosis Elimination

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Diagnosis of LTBI

Currently, the available methods of testing for 
*M. tuberculosis* infection are the *Mantoux tuberculin skin test* (TST) and the *interferon-gamma release assays* (IGRA) such as the *QuantiFERON*®-TB Gold test (QFT-G).

**The Mantoux Tuberculin Skin Test (TST)**

The TST is used to determine if a person is infected with 
*M. tuberculosis*. In this test, a substance called *tuberculin* is injected into the skin. Tuberculin contains *antigens* used for diagnosing TB infection; it is *not a vaccine*. An antigen is a protein substance that can produce an immune response. Tuberculin is made from proteins derived from tubercle bacilli that have been killed by heating. In most people who have TB infection, the immune system will recognize the tuberculin because it is similar to the tubercle bacilli that caused infection. This will cause a reaction to the tuberculin at the site of the injection. Tuberculin used for the skin test is also known as *purified protein derivative*, or PPD. For this reason, the TST is sometimes called a PPD skin test.

**Administering the TST**

The TST is given by using a single dose disposable tuberculin syringe to inject 0.1 ml of 5 *tuberculin units* of liquid tuberculin between the layers of the skin (intradermally), on the forearm (Figure 3.1). A tuberculin unit is a standard strength of tuberculin. When giving the TST, institutional guidelines for infection control should be followed.
Most people with TB infection have a positive reaction to the tuberculin.

The reaction is an area of induration, or swelling, around the site of the injection.

The Mantoux TST is the preferred type of TB skin test.

A patient’s forearm should be examined by a trained health care worker 48 to 72 hours after the tuberculin is injected. Health care workers should not ask patients to read their own skin test results. Most people with TB infection will have a positive reaction to the tuberculin. The reaction is an area of induration (swelling that can be felt) around the site of the injection. The diameter of the indurated area is measured in millimeters across the forearm (Figure 3.2); erythema (redness) around the indurated area is not measured, because the presence of erythema does not indicate that a person has TB infection (Figure 3.3).

In the past, multiple-puncture tests (for example, the Tine test) were a popular skin testing method for TB; however, the multiple-puncture test is no longer recommended. The multiple-puncture tests are done by puncturing the skin of the forearm with a device having a set of short prongs or tines coated with tuberculin. However, since the amount of tuberculin that actually enters the skin cannot be measured, multiple-puncture tests are not reliable and should not be used. Because the amount of tuberculin can always be measured during a Mantoux TST, this type of test is more accurate, and is the preferred skin testing method.
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Figure 3.1 Giving the Mantoux TST.

Figure 3.2 Only the induration is being measured. This is CORRECT.

Figure 3.3 The erythema is being measured. This is INCORRECT.
Interpreting the Reaction

Interpreting a TST reaction depends on the size of the induration and the person’s risk factors for TB (Table 3.2).

An induration of **5 or more millimeters** is considered a positive reaction for the following people:

- People living with HIV
- Recent close contacts of people with infectious TB
- People with chest x-ray findings suggestive of previous TB disease
- People with organ transplants
- Other immunosuppressed patients (for example, patients on prolonged therapy with corticosteroids, equivalent to 15mg per day or more of prednisone for at least 1 month, or those taking TNF-α antagonists)

An induration of **10 or more millimeters** is considered a positive reaction for the following people:

- People who have recently come to the United States (within the last 5 years) from areas of the world where TB is common (for example, Asia, Africa, Russia, Eastern Europe, or Latin America)
- People who inject illegal drugs
- People who live or work in high-risk congregate settings (for example, nursing homes, homeless shelters, or correctional facilities)
- Mycobacteriology laboratory workers
- People with medical conditions, other than HIV, that increase the risk for developing TB disease (see Table 3.1)
- Children younger than 4 years
- Infants, children, or adolescents exposed to adults in high-risk categories
An induration of 15 or more millimeters is considered a positive reaction for people with no known risk factors for TB. However, targeted testing should be done only in high-risk groups since a positive test result in low-risk groups can be inaccurate.

Most people who have a positive TST reaction will usually have a positive reaction every time they are tested, regardless of whether they receive treatment. This is because the TST detects the immune response to tuberculin, not the presence of tubercle bacilli in the body.

Thus the TST should not be performed on a person who has a documented history of either a positive TST result or treatment for TB disease.

**Interpreting the TST Reaction for Occupational Exposure**

For **people who may be exposed to TB on the job** (such as health care workers and staff of nursing homes or correctional facilities), the interpretation of the TST reaction as positive or negative depends on

- ④ The employee’s individual risk factors for TB
- ④ The risk of exposure to TB in the person’s job

Therefore, in facilities where the risk of exposure to TB is very low, 15 or more millimeters of induration may be considered a positive reaction for employees with no other risk factors for TB. In facilities where TB patients receive care, 10 or more millimeters of induration may be considered a positive reaction for employees with no other risk factors for TB.
### Table 3.2
Interpreting the TST Reaction

<table>
<thead>
<tr>
<th>5 or more millimeters</th>
<th>10 or more millimeters</th>
<th>15 or more millimeters</th>
</tr>
</thead>
<tbody>
<tr>
<td>An induration of <strong>5 or more millimeters</strong> is considered <strong>positive</strong> for</td>
<td>An induration of <strong>10 or more millimeters</strong> is considered <strong>positive</strong> for</td>
<td>An induration of <strong>15 or more millimeters</strong> is considered <strong>positive</strong> for</td>
</tr>
<tr>
<td>③ People living with HIV</td>
<td>③ People who have come to the U.S. within the last 5 years from areas of the world where TB is common (for example, Asia, Africa, Eastern Europe, Russia, or Latin America)</td>
<td>③ People with no known risk factors for TB</td>
</tr>
<tr>
<td>③ Recent contacts of persons with infectious TB</td>
<td>③ People who inject illegal drugs</td>
<td></td>
</tr>
<tr>
<td>③ People who have previously had TB disease</td>
<td>③ Mycobacteriology lab workers</td>
<td></td>
</tr>
<tr>
<td>③ Patients with organ transplants and other immunosuppressed patients (including patients taking a prolonged course of oral or intravenous corticosteroids or TNF-(antagonists)</td>
<td>③ People who live or work in high-risk congregate settings</td>
<td></td>
</tr>
<tr>
<td></td>
<td>③ People with certain medical conditions that place them at high risk for TB (silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, and certain intestinal conditions)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>③ Children younger than 4 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>③ Infants, children, and adolescents exposed to adults in high-risk categories</td>
<td></td>
</tr>
</tbody>
</table>
False-Positive Reactions

The TST is a valuable tool, but it is not perfect. Several factors can cause people to have a positive reaction even if they do not have TB infection. This is called a false-positive reaction.

The causes of false positive reactions may include, but are not limited to, the following:

1. Infection with nontuberculous mycobacteria (NTM) (mycobacteria other than \textit{M. tuberculosis})
2. BCG vaccination
3. Administration of incorrect antigen
4. Incorrect measuring or interpretation of the TST reaction

Infection with NTM can sometimes cause a false positive reaction to the TST. Another cause of a false positive reaction is BCG (bacille Calmette-Guérin), a vaccine for TB disease that is used in many countries. BCG, however, is rarely used in the United States because studies have shown that it is not completely effective. People who have been vaccinated with BCG may have a positive reaction to the TST even if they do not have TB infection.

However, there is no reliable way to distinguish a positive TST reaction caused by vaccination with BCG from a reaction caused by true TB infection. When using the TST, people who have been vaccinated with BCG should always be further evaluated for LTBI or TB disease as if they were not vaccinated with BCG.

A false-positive reaction may also occur if an incorrect antigen is used or when the results are not measured or interpreted properly.
Anergy is the inability to react to skin tests because of a weakened immune system.

People who do not react to any of the substances used for anergy testing (including tuberculin) are considered anergic.

False-Negative Reactions

Some people have a negative reaction to the TST even though they have TB infection. This is called a false-negative reaction. The reasons for these false-negative reactions may include, but are not limited to the following:

- Anergy
- Recent TB infection (within the past 8-10 weeks)
- Very young age (younger than 6 months)
- Recent live-virus measles or smallpox vaccination
- Incorrect method of giving the TST
- Incorrect measuring or interpretation of TST reaction

A common cause of false-negative reactions is anergy. Anergy is the inability to react to skin tests because of a weakened immune system. Many conditions, such as HIV infection, cancer, measles or other viral infections, or severe TB disease itself, can weaken the immune system and cause anergy. HIV infection is an important cause of anergy.

Anergy testing in conjunction with skin testing is no longer routinely recommended as a part of TB testing; however, in some situations anergy testing may be used to guide decisions regarding therapy for patients. Anergy testing can be done by giving skin tests using substances other than tuberculin. The recommended substances for anergy testing include mumps, Candida (a type of fungus), or tetanus extracts. Most healthy people will have a skin test reaction to one or more of these substances.

People who do not react to any of the substances, including tuberculin, are considered anergic. People who have a reaction to any of the substances are NOT anergic.
Another cause of false-negative reactions is recent TB infection (infection within the past 8 to 10 weeks). It can take 2 to 8 weeks after TB infection for the body’s immune system to be able to react to tuberculin and for the infection to be detected by the TST. For this reason, it is recommended that close contacts of someone with infectious TB disease who have a negative reaction to the TST be retested 8 to 10 weeks after the last time they were in contact with the person who has TB disease.

A third cause of false-negative reactions is very young age. Because their immune systems are not yet fully developed, children younger than 6 months may have a false-negative reaction to the TST.

Vaccination with live viruses may also lead to a false-negative reaction. The Advisory Committee on Immunization Practices recommends that skin testing be done on either the same day as vaccination with live-virus measles vaccine or 4 to 6 weeks after vaccination to prevent possible false-negative reactions. Also, skin testing should not be done until at least 1 month after a smallpox vaccination.

A false-negative reaction may also occur when the TST is given incorrectly or the results are not measured or interpreted properly.

Both false-positive and false-negative reactions to the TST are summarized in Table 3.3.

Any patient with symptoms of TB should be evaluated for TB disease, regardless of his or her TST reaction. In fact, people with symptoms of TB should be evaluated for TB disease right away, at the same time that the TST is given. TB symptoms and the diagnosis of disease are discussed later in this module.
### Table 3.3

**False-Positive and False-Negative Reactions to the TST**

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Possible Cause</th>
<th>People at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>False-positive</strong></td>
<td>Nontuberculous mycobacteria (NTM)</td>
<td>People infected with NTM</td>
</tr>
<tr>
<td></td>
<td>BCG vaccination</td>
<td>People vaccinated with BCG</td>
</tr>
<tr>
<td></td>
<td>Administering of incorrect antigen</td>
<td>Any person being tested</td>
</tr>
<tr>
<td></td>
<td>Incorrect interpretation of TST result</td>
<td>Any person being tested</td>
</tr>
<tr>
<td><strong>False-negative</strong></td>
<td>Anergy</td>
<td>HIV-infected people, other people with weakened immune systems, severe TB disease, and some viral illness (e.g., measles and chicken pox)</td>
</tr>
<tr>
<td></td>
<td>Recent TB infection</td>
<td>People infected with <em>M. tuberculosis</em> within the past 8 to 10 weeks</td>
</tr>
<tr>
<td></td>
<td>Very young age</td>
<td>Children younger than 6 months</td>
</tr>
<tr>
<td></td>
<td>Recent live-virus measles or smallpox vaccination</td>
<td>Any person who will be or recently received a live-virus vaccination</td>
</tr>
<tr>
<td></td>
<td>Incorrect method of giving TST</td>
<td>Any person being tested</td>
</tr>
<tr>
<td></td>
<td>Incorrect interpretation of TST</td>
<td>Any person being tested</td>
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