Diagnosing Latent TB Infection (LTBI)
Video Transcript

This program is presented by the Global Tuberculosis Institute and is based on recommendations from the Centers for Disease Control and Prevention. This is the second in a series of videos for primary care providers. In this video, you'll learn about diagnosing latent tuberculosis infection, also called LTBI. Other videos discuss screening for and treating LTBI and monitoring those on treatment.

Tuberculosis, also called TB, is caused by *Mycobacterium tuberculosis* and is spread from person to person through the air. People who are ill with pulmonary or laryngeal TB disease can spread infectious particles into the air when they cough, sneeze, shout, laugh or sing. Infection occurs when another person inhales these particles, and they reach the alveoli of the lungs, where an immune response is initiated.

In most cases, the immune response successfully maintains this containment in a dynamic process to suppress further multiplication of the bacteria. This is latent TB infection. In about 10% of otherwise healthy people, the bacteria are not contained by the immune system after they are inhaled. The bacteria in the lungs multiply and the person progresses to TB disease, also known as active TB.

Individuals with LTBI are *not* ill with TB disease; however, they can progress to TB disease later, if immune containment is overcome by the bacteria. This is sometimes called reactivation TB. People with LTBI have an estimated 5-10% lifetime risk of progressing to active TB. In the majority of people, reactivation TB occurs in the lungs, resulting in pulmonary TB. However, about 20% of cases are extrapulmonary, with disease occurring in other sites. A person can have both pulmonary and extrapulmonary TB. It is important to diagnose and treat people with LTBI to *prevent* them from becoming ill with TB disease and becoming infectious to others, thus helping to prevent transmission of the disease.

Latent TB infection is a clinical diagnosis based a patient's medical history, prior exposure to TB disease, test results for TB infection, chest radiograph, physical exam, and in some circumstances, negative results from a sputum sample. If a person tests positive for TB infection, you *must* rule out TB disease before beginning treatment for latent TB infection. Treating someone for LTBI when they really have TB disease can lead to poor outcomes, including drug resistance.

<u>Latent TB Infection vs. TB Disease</u>

Someone with latent TB infection has no symptoms and cannot spread bacteria to others. People with LTBI have fewer bacteria in their body than people with TB disease. Although they test positive for TB infection, their chest radiographs are normal, and sputum specimens, if done, are smear and culture negative.

Someone with TB disease usually *does* have some or all of the common TB symptoms, which may include cough, chest pain, fever, weight loss, night sweats, hemoptysis, fatigue, and loss of appetite. The test for TB infection may be positive in a person with TB disease and the chest radiograph is usually abnormal in someone with pulmonary TB disease. Sputum specimens are usually smear and culture positive in people with pulmonary TB disease, but they may be negative.

Testing for TB Infection

Before testing for TB infection, ask patients about risk factors and symptoms of TB disease. Remember, people with signs and symptoms of TB disease should be evaluated for the disease, rather than evaluated for LTBI.

See the resource list for a sample tool to assess a person's risk for TB infection and progression to disease if infected. Test those with an increased risk. Testing is *not* recommended for individuals without risk factors. For more information on who to test, view the video on screening for LTBI. You don't need to test people who have written documentation of a previously positive test result or documentation of treatment for TB infection or disease.

Educating Patients

Provide education before testing for TB infection, since the concept of latent TB infection may not be widely understood. There may be ethnic and cultural factors and health beliefs that influence a person's understanding of TB, or their willingness to be tested and treated. For example, some people may believe that you should not take medicine unless you are ill.

Explain the difference between LTBI and TB disease and that people with LTBI have inactive TB bacteria in their body. Discuss the risk factors for acquiring infection or developing disease. Focus on the patient's own risk factors and why these indicate the need for testing and treatment, if infected. Clearly explain the test results and what they mean.

Providing careful education and addressing barriers or misconceptions up front can help ensure that patients understand the need to begin and *complete* treatment for LTBI. Use educational messages and materials that are culturally appropriate and provide information in a language the patient understands.

Testing Methods

There are 2 approved testing methods available to detect TB infection in the US, Interferon-Gamma-Release Assays, also called IGRAs, and the Mantoux tuberculin skin test, also called the TST. These tests help identify people who are infected with *M. tuberculosis* but *cannot* distinguish between latent TB infection and TB disease. These tests are not 100% sensitive or specific, and a negative reaction to either test doesn't exclude the diagnosis of LTBI or TB disease. When evaluating someone for LTBI, consider the complete clinical and epidemiologic information, particularly for high-risk populations, such as young children or people living with HIV. Keep in mind that both TST and IGRA results can be affected by immunosuppression.

Testing Methods: IGRA

IGRAs, which are blood-based tests, have several advantages over the TST. They require only 1 office visit and results may be ready in 24 hours after they are received by the laboratory. IGRA test results are easier to interpret since the interpretation is included in the report, and they are not affected by the BCG vaccine, which we'll talk about shortly.

Two types of IGRAs are available in the United States: QuantiFERON-TB Gold-Plus or QFT, and the T-Spot.*TB* test. Both measure the immune response to TB proteins in blood. If someone is infected with TB bacteria, the white blood cells release interferon-gamma. Tests results are based on measurements of the amount of interferon-gamma released. Unlike the TST, IGRA results are not interpreted according to risk; they are reported as negative or positive, based on a defined cut point.

For QuantiFERON, the results are reported as negative, positive, or indeterminate. An indeterminate test result represents a test failure. Lab reports should include the quantitative values that form the basis for the results.

Results for the T-Spot.*TB* test are reported as negative, borderline, positive, or invalid. Borderline results are considered equivocal, neither negative or positive, and represent a zone of uncertainty. An invalid T-Spot.*TB* test result represents a test failure. Reports of T-Spot.TB results should also include quantitative values.

A repeat IGRA or a TST can be useful if the initial IGRA is indeterminate, invalid, or borderline. Consider the risk of infection and progression when assessing quantitative and qualitative IGRA results, particularly borderline results from TB-Spot.TB or results around the cut point with QFT. Consult a TB expert for repeat borderline, invalid, or indeterminate results. Your laboratory can also provide additional information on interpreting IGRA results.

Testing Methods: TST

The TST is a delayed type hypersensitivity test. Some people refer to this as the PPD, for the small amount of purified protein derivative, also known as tuberculin, which is injected intradermally in the person lower arm, creating a small wheal. The patient must return within 48 to 72 hours for an examination of any reaction.

When the individual returns, look for a raised, hard area, called an induration, and measure its size with a millimeter ruler across the width of the arm, *not* lengthwise. Repeat a TST that wasn't properly placed or measured and recorded in millimeters.

TSTs are interpreted based on the size of the induration, the person's risk for TB infection, and their risk of progression.

People with a high risk of progressing to TB disease are considered positive if the induration is 5 or more millimeters. This includes people in recent contact with someone with infectious TB disease; people with immunosuppression, including those living with HIV, organ transplant patients, those

with prolonged use of corticosteroids, and people taking or about to start TNF-alpha inhibitors; and people *without* a history of appropriate treatment whose radiographs show abnormalities that look like fibrotic scarring, which could be old healed TB.

Others are considered positive if the induration is 10 or more millimeters. This includes those who were born, lived in or had significant travel to countries other than the US, Canada, Australia, New Zealand, or the countries of northern or western Europe; injection drug users; people who work in mycobacteriology labs and people with certain other medical conditions that increase their risk of progression to TB disease.

Other groups considered positive at 10 or more millimeters are residents or employees of high-risk settings, such as correctional facilities and homeless shelters.

Children who are frequently exposed to adults at high risk for TB infection are considered positive at 10 mm or more, as are children younger than 4 years of age *without* any other risk factors, though testing is *not* recommended for individuals without risk factors. However, testing for TB infection is sometimes required by law or for credentialing for certain professions. Individuals 4 years of age or older with no known risk factors are considered positive if the induration is 15 or more millimeters.

Test Selection

Though either test is acceptable in most situations, IGRAs are preferred in people who are BCG-vaccinated or who are unlikely to return to have their TST read.

TSTs are preferred for children younger than 2 years of age, since there is limited data on IGRA use in this population, though some experts will use IGRAs in children as young as 1 year of age.

Consider availability, logistics, and resources when selecting a test for TB infection. For the majority, IGRAs are the most convenient test.

Testing with *both* TST and IGRA isn't recommended in general, but there are some situations where using both tests should be considered, particularly when the consequences of a missed LTBI diagnosis are significant. For example, a second test can be used to increase sensitivity when the initial test is negative in a person who is likely to be infected *and* has a high risk of progression to TB disease. In this case, the individual would be considered infected if either test is positive.

Special Considerations for Testing

The BCG vaccine is currently given in many parts of the world where TB is common to protect infants and young children from serious complications of TB disease; its effect wanes over time. The vaccine isn't given in the US. Unlike the TST, IGRA results are not affected by BCG and thus are the preferred test for those who received BCG, either as a vaccine or for cancer therapy. Explain this to your BCG-vaccinated patients, who may believe that BCG is effective as a prevention agent or might have heard that the vaccine will cause them to have a positive test for TB infection.

Test people before they start immunosuppressive therapy, such as TNF-alpha inhibitors. People living with HIV should be tested for TB infection at diagnosis. Test for each known exposure to TB. For people living with HIV who are at high risk of repeated or ongoing exposure to people with infectious TB disease, periodic testing for TB infection is recommended. Also consider periodic testing for others with immunosuppression who are at risk of ongoing exposure, based on medical history and local epidemiology.

Retest people with advanced HIV infection and a CD4 count of less than 200 who have a negative test for TB infection and do not have any indications for empiric LTBI treatment, such as recent exposure to a person with infectious TB disease, AFTER they initiate antiretroviral therapy and attain a CD4 count of 200 or greater. This can help ensure that the initial test was a true negative result.

Remember, diagnostic accuracy of the TST and IGRA is limited in immunosuppressed persons, including those living with HIV. A negative test does not exclude diagnosis of LTBI or TB disease, so you should consider epidemiological, historical, and other clinical information when using IGRA or TST results for medical and public health management.

For people who receive serial testing with a TST, a 2-step test is recommended due to the boosting phenomenon associated with the TST. Consult the resources for additional information on 2-step testing.

A second test may be needed for contacts, people who were recently exposed to someone with infectious TB. All contacts whose *first* test is negative should be re-tested 8 to 10 weeks after their last exposure, since it can take this amount of time for an immune response to develop. Use the same method for the initial and repeat test.

Medical Evaluation

Evaluate individuals with a positive test for TB infection to rule out TB disease. Conduct a physical exam and obtain a complete medical history. Ask about past TB exposure, other risk of infection, and prior TB test results or treatment. If the person was treated for TB previously, ask about the regimen used and length of treatment.

Obtain a chest radiograph for individuals with a positive test result for TB infection to help distinguish between LTBI and TB disease. Get a chest radiograph even for someone with a negative test, but who has symptoms consistent with TB disease, or for children under 5 and immunocompromised persons who were recently exposed to a person with TB disease.

Get posterior to anterior and lateral views for children, which is especially important for those less than 5 years of age. For other groups, a single posterior to anterior view is usually adequate. If the chest radiograph is normal, and there aren't any symptoms or findings consistent with TB disease, the individual can be considered to have latent TB infection. Remember, when discussing results, provide education about TB infection, answer questions, and counsel patients about the importance of initiating and completing LTBI treatment.

If a person has either an abnormal chest radiograph or respiratory symptoms, such as cough, and active TB disease is in the differential diagnosis, obtain at least 3 sputum samples for testing. Collect sputum samples at least 8 hours apart; one should be collected in the early morning. Send the sputum samples for AFB smear and culture, as well as nucleic acid amplification testing, if available. If you suspect or diagnose someone with TB disease, you *must* notify your local or state health department.

Consult a TB expert for complex clinical situations, such as individuals on or about to start TNF-alpha inhibitors or evaluation of children or people living with HIV. TB disease may present differently in these individuals.

Thank you for viewing this video on diagnosing latent TB infection, which is the second in a series. The other videos discuss screening, treatment, and monitoring those on treatment. For more information and the additional resources mentioned in this video, visit this website: globaltb.njms.rutgers.edu/