Chapter 5

Diagnosis of Latent Tuberculosis Infection (LTBI)

CONTENTS

Introduction

Purpose

Use this section to understand and follow national and Nevada State guidelines to do the following:

- Classify patients with latent TB infection (LTBI).
- Diagnose LTBI.

In the 2005 guideline "Controlling Tuberculosis in the United States: Recommendations from the American Thoracic Society, Centers for Disease Control and Prevention, and the Infectious Diseases Society of America," one of the recommended strategies to achieve the goal of reduction of TB morbidity and mortality is the identification of persons with LTBI at risk for progression to TB disease, and treatment of those persons with an effective drug regimen.[1]

Contacts are mentioned within this chapter, but their evaluation and follow-up are covered in more depth in this TB Manual, Chapter 8, *Contact Investigation*. For information on treatment, refer to Chapter 6, *Treatment of Latent Tuberculosis Infection* in this TB Manual.

Policy

In Nevada:

- Targeted testing for LTBI should be conducted only among persons in groups with identified risk factors for LTBI and/or progression to TB disease.
- Contacts should be evaluated as described in *Contact Investigation,* Chapter 8.

For roles and responsibilities, refer to the "Roles, Responsibilities, and Contact Information" topic in the *Introduction*, Chapter 1, section "Roles, Responsibilities, and Contact Information," pages 1.14 – 1.20.

LTBI is not a reportable disease in Nevada, therefore there are no records or statistics available at the state or county health departments other than the ones retained by the facility or practitioner performing TB screening and/or diagnosing LTBI.

Tuberculosis Classification System

The system for classifying tuberculosis (TB) is based on how the infection and disease develop in the body. Use this classification system to help track the status of TB in your patients and to allow comparison with other reporting areas.

Table 1: TUBERCULOSIS CLASSIFICATION SYSTEM[2]

Class	Type	Description
0	▪ No tuberculosis (TB) exposure ▪ Not infected	▪ No history of exposure ▪ Negative reaction to the tuberculin skin test (TST) or interferon gamma release assay (IGRA)
1	▪ TB exposure ▪ No evidence of infection	▪ History of exposure ▪ Negative reaction to the TST or IGRA
2	▪ TB infection ▪ No disease	▪ Positive reaction to the TST or IGRA ▪ Negative bacteriologic studies (if done) ▪ No clinical, bacteriologic, or radiographic evidence of TB disease
3	▪ TB disease ▪ Clinically active	▪ *Mycobacterium tuberculosis* complex cultured (if this has been done) ▪ Clinical, bacteriologic, or radiographic evidence of current disease
4	▪ TB disease ▪ Not clinically active	▪ History of episode(s) of TB **Or** ▪ Abnormal but stable radiographic findings ▪ Positive reaction to the TST or IGRA ▪ Negative bacteriologic studies (if done) **And** ▪ No clinical or radiographic evidence of current disease
5	▪ TB suspected	▪ Diagnosis pending

Adapted from: CDC. Classification system. In: Chapter 2: transmission and pathogenesis. *Core Curriculum on Tuberculosis (2013)* [Division of Tuberculosis Elimination Web site]. Updated May 2016. Available at: https://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf

High-Risk Groups

Certain factors identify persons at high risk for tuberculosis (TB) infection and/or for progression to TB disease. Persons in the high-risk groups listed in Table 2: **Persons at High Risk for Tuberculosis Infection and Progression to Tuberculosis Disease** are candidates for Tuberculosis screening in Nevada. Persons with risk factors from both columns may be at much higher risk than those with risk factors in only one column. For example, an individual born in a high-TB-prevalence country who is also infected with HIV is at much higher risk of having or developing active TB than a US-born individual with HIV infection.

TABLE 2: PERSONS AT HIGH RISK FOR TB INFECTION AND PROGRESSION TO TB DISEASE[3]

For Tuberculosis Infection	For Progression to Tuberculosis Disease[4]
▪ High-priority contacts such as housemates or coworkers or contacts of persons who have smear-positive pulmonary or laryngeal tuberculosis (TB) ▪ Infants, children, and adolescents exposed to adults in high-risk categories ▪ Recent immigrants (primarily <5 years) from countries with high incidence of TB (Asian, African, Latin American, and Eastern European countries have TB rates 5–30 times higher than US rates, and an increasing percentage of TB cases in the United States are occurring among immigrants from those countries.) ▪ Some high-risk racial or ethnic minority populations, defined locally as having an- increased prevalence of TB (in Nevada this group includes persons coming from Mexico and the Philippines) ▪ Residents and employees of high-risk congregate setting (e.g. correctional institutions, nursing homes and other long-term care facilities providing care to high-risk residents and clients and homeless shelters.) ▪ Some healthcare workers who serve high-risk clients, especially emergency departments, staff involved in aerosol producing procedures and laboratorians who manipulate TB cultures and specimens ▪ Some medically underserved, low-income populations as defined locally (e.g. homeless, transient and undocumented populations) ▪ Persons who have recently spent over 3 months in high-incidence countries (such as missionaries from the Church of Jesus Christ of Latter-Day Saints) ▪ Persons associated with illicit drug use or any other locally identified high-risk substance abuse user	▪ Persons with HIV infection ▪ Infants and children aged <5 years ▪ Persons infected with *Mycobacterium tuberculosis* within the previous 2 years ▪ Persons with a history of untreated or inadequately treated TB disease ▪ Persons with radiographic findings consistent with previous TB disease ▪ Persons who use alcohol or illegal drugs (such as injection drugs or crack cocaine) ▪ Persons with any of the following clinical conditions or other immunocompromising conditions: • Silicosis • Diabetes mellitus • End-state renal disease (ESRD)/chronic renal failure, hemodialysis • Some hematologic disorders (e.g., leukemias and lymphomas) • Other malignancies (e.g., carcinoma of head, neck, or lung) • Body weight ≥10% below ideal body weight • Prolonged corticosteroid use • Use of other immunosuppressive treatments (e.g., prednisone or tumor necrosis factor-alpha [TNF- α] antagonists) • Organ transplantation • Gastrectomy • Chronic malabsorption syndromes • Jejunoileal bypass

Source: Adapted from: CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005;54(No. RR-17):4–5; CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):7–9. Also, Tuberculosis Infection Control: A Practical Manual for Preventing TB

Diagnosis of Latent Tuberculosis Infection

The diagnosis of latent tuberculosis infection (LTBI) has traditionally been based upon results of tuberculin skin testing (TST). However, the QuantiFERON®-TB Gold in-tube (QFT-GIT™) test, and the T-SPOT®TB test which are whole-blood interferon gamma release assays (IGRAs), are now other options available for detecting LTBI.

Use the Mantoux tuberculin skin test (TST) or an IGRA to test for *Mycobacterium tuberculosis* infection. IGRAs can be used in all circumstances in which the TST is used, and can usually be used in place of (and not in addition to) the TST.[5]

The CDC recently published Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection (MMWR June 25, 2010 / 59(RR05); 1-25.

CDC has also developed the Interferon-Gamma Release Assays Factsheet that will assist you in learning more about IGRAs. http://www.cdc.gov/tb/publications/factsheets/testing/IGRA.htm

For a summary of the TB classification numbers, refer to table 1 “Tuberculosis Classification System.”

Interferon Gamma Release Assays (IGRA)

Blood assay for *Mycobacterium tuberculosis* (BAMT) is a general term referring to recently developed in vitro diagnostic tests that assess for the presence of infection with *M. tuberculosis*. This term includes, but is not limited to, interferon gamma release assays (IGRAs). The latest IGRAs currently approved by the Food and Drug Administration (FDA) and available on the market are the QuantiFERON®-TB Gold in-tube (QFT-GIT™) test, QuantiFERON®-TB Gold Plus in-tube (QFT-GPIT™) test, and the T-SPOT®TB test.

IGRAs are attractive diagnostic aids for detecting *M. tuberculosis* infection, because unlike TSTs, IGRA results can be available within 24 hours and a single patient visit (no need for a second visit). As a laboratory-based blood assay, IGRAs are performed in qualified laboratories and are not subject to the biases and errors associated with TST placement and reading. However, errors in collecting, labeling, or transporting blood specimens, or while performing and interpreting these assays can decrease IGRA accuracy. However, availability of IGRAs is limited by the need for a fresh blood sample

collected and processed per manufacturer's recommendations and the potential for delays as a result of the long distances to a qualified laboratory offering these tests.

TABLE 3: SELECTING A TUBERCULOSIS SCREENING TEST

Situations in Which an IGRA Is Preferred But a TST Is Acceptable	Situations in Which a TST Is Preferred But an IGRA Is Acceptable
▪ An IGRA is preferred for testing persons from groups that historically have low rates of returning to have TSTs read, as reported with: • Homeless • Drug-users • Undocumented individuals The use of IGRAs for such persons can increase test completion rates, so TB control efforts can be focused on only those individuals most likely to benefit from further evaluation and treatment. ▪ An IGRA is preferred for testing persons who have received BCG (as a vaccine or for cancer therapy). Use of IGRAs in this population is expected to: • Increase diagnostic specificity and improve acceptance of LTBI treatment regimens. • Eliminate the unnecessary follow-up tests associated with BCG-related false-positive results.	▪ A TST is preferred for testing children <5 years of age. • Use of an IGRA in conjunction with TST has been advocated by some experts to increase diagnostic sensitivity in this age group. • Recommendations regarding use of IGRAs in children have been published by the American Academy of Pediatrics.[6]
Situations in Which Either a TST or an IGRA May Be Used Without Preference	**Situations in Which Both an IGRA and a TST May Be Considered**
▪ An IGRA or a TST may be used to test recent contacts of persons known or suspected to have active TB • Use the same repeat testing schedule (8-10 weeks post exposure) for both test methods • Neither test can differentiate latent infection from active disease or predict subsequent likely hood of progression to active TB disease ▪ An IGRA or a TST may be used without preference for periodic screening of persons who might have occupational exposure to *M. tuberculosis*	▪ Although routine testing with both a TST and an IGRA is not generally recommended, results from both tests might be useful when the initial test is negative in the following situations: • When the risk of infection, progression to disease or poor outcome are increased (e.g. for persons with HIV infection, other immunosuppressive condition or children < 5 years). If one test is positive, consider this evidence for infection with *M.tb.* • When clinical suspicion exists for active TB (such as in persons with symptoms, signs, and/or radiographic evidence suggestive of active TB). Repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate, borderline, or invalid (A new

	blood sample should be used). • When testing is required in persons **unlikely** to be infected. If one test is positive perform another type to confirm (ex: if the TST is positive, draw an IGRA) if **BOTH** tests are positive, the person is considered to be infected.

Source: created from information in: CDC. Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* infection ---United States, 2010. *MMWR June 25,* 2010 / 59(RR05):1-25 http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm ; and Clinical Infectious Diseases "Official American Thoracic Society/infectious diseases Society of America/Centers for Disease Control and Prevention Clinic Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children" 2016 DOI:10.1093/cid/ciw694; pg 13.

Assessments of accuracy of tests for *M. tuberculosis* infection are hampered by the lack of confirmatory tests to diagnose LTBI and culture-negative active tuberculosis. Accuracy is a measure of the proportion of test results that are correct and encompasses assessment of specificity (the proportion of true negatives that have negative test results) and sensitivity (the proportion of true positives that have positive test results). Assessments of accuracy of tests for M. tuberculosis infection are difficult because there is no "gold standard" to confirm a diagnosis of LTBI or culture-negative active tuberculosis.

In the future, additional FDA-licensed products, in combination with Centers for Disease Control and Prevention (CDC)-issued recommendations, may become available and provide additional diagnostic alternatives.

Mantoux Tuberculin Skin Testing

The Mantoux method of tuberculin skin testing is also used to detect infection with *Mycobacterium tuberculosis.*

In general, it takes two to ten weeks after infection for a person to develop a delayed-type immune response to tuberculin measurable with the Mantoux tuberculin skin test (TST).[7] During the test, tuberculin is injected into the skin. The immune system of most persons with tuberculosis (TB) infection will recognize the tuberculin, causing a reaction in the skin. Repeated TSTs do not produce hypersensitivity. Guidelines for interpretation of the TST are found in the CDC Mantoux Tuberculin Skin Test Training Materials Kit at http://www.cdc.gov/tb/education/mantoux/default.htm

The size of the measured induration (a hard, dense, raised formation) and the patient's individual risk factors should determine whether TB infection is diagnosed.[8] Based on the sensitivity and specificity of the purified protein derivative (PPD) TST and the prevalence of TB in different groups, three cut-points have been recommended for defining a positive tuberculin reaction:

- Greater than or equal to 5 mm of induration

- Greater than or equal to 10 mm of induration
- Greater than or equal to 15 mm of induration[9]

For more information on cut-points for the TST, see the "Interpretation of the Tuberculin Skin Test" topic in this section, page 5.13.

Candidates for Mantoux Tuberculin Skin Testing

The Mantoux TST can be administered to all persons, including pregnant women,[10] persons who have previously been vaccinated with Bacille Calmette-Guérin (BCG),[11] and Human Immunodeficiency Virus (HIV)-infected persons. However, persons with a documented prior positive TST do not need another TST, and the Mantoux TST should not be administered until at least four weeks after vaccination with live-virus vaccines.

If the person being tested is a contact, follow the procedures outlined in *Contact Investigation,* Chapter 8, of this TB Manual. Additionally, reference Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis at: http://www.cdc.gov/mmwr/pdf/rr/rr5415.pdf

Pregnancy

Tuberculin skin testing is entirely safe and reliable for pregnant women, and pregnant women at high risk for TB infection or disease should be tested. Screen pregnant women for TB infection if they have any of the following conditions:

- Symptoms suggestive of TB disease
- HIV infection
- Behavioral risk factors for HIV
- Medical conditions other than HIV infection that increase the risk for TB disease
- Close contact with a person who has pulmonary or laryngeal TB disease
- Immigration from an area of the world where incidence of TB is high

Bacille Calmette-Guérin Vaccine

BCG vaccines are live attenuated vaccines derived from a strain of *Mycobacterium bovis.* Because their effectiveness in preventing infectious forms of TB has never been demonstrated, they are not recommended as a TB control strategy in the United States, except under rare circumstances. BCG is used commonly in other countries as an effective means to prevent severe forms of tuberculosis in children, such as TB meningitis and miliary TB. A history of BCG vaccination is not a contraindication for tuberculin skin testing, nor does it influence the indications for a TST. Administer and measure TSTs in BCG-vaccinated persons in the same manner as in those with no previous BCG vaccination.

Diagnosis and treatment of LTBI should be considered for BCG-vaccinated persons with a TST reaction of equal to or greater than 10 mm induration, especially any of the following:

- Persons continually exposed to populations with a high prevalence of TB (e.g., some healthcare workers, employees and volunteers at homeless shelters, and workers at drug treatment centers).
- Persons born or have lived in a country with a high prevalence of TB
- Persons exposed to someone with infectious TB, particularly if that person has transmitted TB to others[12]

Evaluate these patients for symptoms of TB. If a patient has symptoms of TB disease, obtain chest radiography and (if the patient has a cough) collect sputum specimens.

Bacille Calmette-Guérin Talking Points

1. Tuberculin reactivity caused by BCG vaccination wanes with time but can be boosted with a TST.[13]
2. There is no method to distinguish tuberculin skin test reactions caused by vaccination with BCG from those caused by mycobacterial infections. [14]
3. A diagnosis of *M. tuberculosis* infection should be considered for any BCG-vaccinated person who has TST reaction ≥10 mm of induration.[15]
4. Treatment for LTBI should be considered for a person who is TST positive and has previous BCG vaccination if the person is:
    - A contact to a person with infectious TB or
    - Born in (or resided in) a country of high prevalence of TB or
    - Exposed to persons at risk for TB.[16] (see table 2)
5. BCG vaccination should be considered for infants and children who reside in high morbidity countries to prevent meningeal TB.[17]
6. There is no scientific evidence of protective ability of BCG for preventing pulmonary TB in adolescents or adults.[18]

Anergy Testing

Anergy testing is not routinely recommended in conjunction with TST for HIV-infected persons in the United States.[19]

Anergy testing is a diagnostic procedure used to obtain information about the competence of the cellular immune system. Conditions that cause an impaired cellular immune system include HIV infection, severe or febrile illness, measles or other viral infections, Hodgkin's disease, sarcoidosis, live-virus vaccination, and corticosteroid or immunosuppressive therapy. Persons with conditions such as these may have suppressed reactions to a TST even if infected with TB. However, there are no simple skin testing protocols that can reliably identify persons as either anergic or nonanergic

and that have been proven to be feasible for application in public health TB screening programs. Factors limiting the usefulness of anergy skin testing include the following:

- Problems with standardization and reproducibility
- Low risk for TB associated with a diagnosis of anergy
- Lack of apparent benefit of treatment for LTBI in groups of anergic HIV-infected persons

For more information on Anergy testing, see page 49 of http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5417a1.htm?s_cid=rr5417a1_e

Also, see JAMA article "The Case Against Anergy Testing as a Routine Adjunct to Tuberculin Skin Testing

Documented Prior Positive Tuberculin Skin Test

Persons who have tested positive in the past and can provide documentation of their status do not need to have another TST. Instead, perform a TB symptom assessment questionnaire to identify any symptoms of TB disease.[20] Persons who are symptomatic should receive a chest radiograph to determine the presence of active disease.

Live-Virus Vaccines

The Mantoux TST can be administered in conjunction with all non-live vaccines. However, the measles, mumps, rubella (MMR) vaccine, varicella, and live attenuated influenza vaccines—may transiently suppress the response to PPD.[21] Therefore, if a vaccine containing live virus has already been given, the TST should be deferred until (or repeated) at least four weeks after the vaccine was administered.

When giving the TST and the MMR, one of the following three sequences may be used:

- Apply the TST at same visit as the MMR.
- Delay the TST at least four weeks if the MMR is given first.
- Apply the TST first and then give the MMR when the TST is measured.[22]

American Academy of Pediatrics. Pickering LK ed. Red Book: 2003 Report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village, IL; American Academy of Pediatrics 2003: http://aapredbook.aappublications.org/content/dtl/2003/1/

Multiple Puncture Tests

Multiple puncture tests (MPTs), such as the Tine test, should not be used. The MPTs are not reliable because the amount of tuberculin injected intradermally cannot be precisely controlled and there is no standard for interpretation.

Administration of the Tuberculin Skin Test

The TST should be placed by a healthcare worker who has received appropriate training and is following written protocols.

Table 3: BEFORE YOU BEGIN TO ADMINISTER A TUBERCULIN SKIN TEST

Before You Begin to Administer a Tuberculin Skin Test	
Review Information	CDC. *Mantoux Tuberculin Skin Test Facilitator Guide*: http://www.cdc.gov/tb/education/mantoux/default.htm Follow all infection control procedures and standard precautions (including hand washing before and after the procedure and the use of gloves and a sharps container)
Gather Equipment	▪ Gloves ▪ Alcohol pads or alternative skin cleanser ▪ Safety needle ▪ Tuberculin syringe (Do not pre-draw tuberculin into syringes prior to test. The solution interacts with the plastic syringe and loses its efficacy.) ▪ Purified protein derivative (PPD) (Tubersol® or Aplisol®: Sharps container **Note:** Date PPD tuberculin vials when opened and discard them after 30 days. See the package insert for appropriate storage information.

Read the PPD labels carefully before administering a TST. The packaging of tetanus toxoid-containing vaccines (TTCVs) is similar to Tubersol® and Aplisol®, and all are refrigerated. See the CDC's "Errors Involving Mix-up of Tuberculin Purified Protein Derivative and Vaccine Products" (*TB Notes Newsletter*. 2005;No. 1): http://www.heartlandntbc.org/assets/training/mini-fellowship/PediatricToolBox/CDC/newsletters/notes/TBN_1_05/Errors_mix_up.htm

How to Administer a Tuberculin Skin Test

1. Obtain the patient's written consent, if required by the provider, agency, institution or health department performing the test.
2. Inject air into the vial air space (not into the solution). Injection of air into the air space in the vial prevents creation of negative pressure within the vial, allowing the antigen to be withdrawn easily. Injecting air into the solution creates bubbles and may interfere with withdrawing the correct amount of antigen.[23] **Note:** This step is done for the first test drawn from the vial, it is not necessary for subsequent tests.
3. The injection should be placed on the palm-side-up surface of the forearm, about two to four inches below the elbow. Your local institutional policy may specify the preference for the right or left forearm for the skin test. The area selected should be free of any barriers to placing and reading the skin test, such as muscle margins, heavy hair, veins, sores, tattoos, or scars.
4. After choosing the injection site, clean the area with an alcohol swab by circling from the center of the site outward. Allow the site to dry completely before the injection.
5. Using a disposable tuberculin safety needle and syringe, inject 0.1 ml of PPD tuberculin containing 5 tuberculin units (TU) intradermally with the needle bevel facing upward. Because some of the tuberculin solution can adhere to the inside of the plastic syringe, the skin test should be given as soon as possible after the syringe is filled.
6. The injection should produce a discrete, pale elevation of the skin (a wheal) 6 to 10 mm in diameter. **Note:** If a 6- to10-mm wheal is not produced, repeat the test on the opposite arm or the same arm, 2 inches from the original site.
7. Record the date and time of TST administration, location of injection site, dose, name of the person who administered the test, the name and manufacturer of the tuberculin product used, its lot number, its expiration date, and, the reason for the testing.[24]

Measurement of the Tuberculin Skin Test

A trained healthcare worker should read the TST 48 to 72 hours after the intradermal injection. Patients should never be allowed to read their own TSTs.[25]

- A positive reaction can be measured any time after 48 hours, up to 7 days after placement. If the results appear negative and more than 72 hours have passed, the test should be repeated. It can be repeated immediately, or seven to ten days later, if two-step testing is required for employment.

See the topic titled "Two-Step Tuberculin Skin Testing" in the Infection Control section of this manual and Guidelines for Preventing Transmission of Mycobacterium Tuberculosis in Health-Care Setting 2005 at: http://www.cdc.gov/mmwr/pdf/rr/rr5417.pdf

Before you measure a TST, review information in the CDC's *Mantoux Tuberculin Skin Test Facilitator Guide* at this hyperlink: http://www.cdc.gov/tb/education/mantoux/default.htm.

How to Measure a Tuberculin Skin Test

1. Measure the TST site crosswise to the long axis of the forearm (from the thumb side of the arm to the little finger side of the arm or vice versa).
2. Induration is a hard, dense, raised formation. Measure only induration hardness. Do **not** measure erythema (redness). A TST with erythema, but no induration, is nonreactive.
3. Record the test result in mm, not as "positive" or "negative." An exact reading in mm may be necessary to interpret whether conversions occur on a subsequent test. Record a TST with no induration as "0 mm." Where there is induration, do not round off the reading, but record it exactly as read.
4. Report adverse reactions to a TST (e.g., blistering, ulcerations, necrosis) to the FDA's MedWatch Program at 1-800-FDA-1088, or via the Internet at this hyperlink: http://www.fda.gov/medwatch/ .

Interpretation of the Tuberculin Skin Test

TSTs should be interpreted by a trained healthcare worker. Use Table 4 below to interpret TSTs.

Call the local health authority in your area regarding TST reactions when interpretation and medical follow-up are unclear.

Before you interpret a TST, review information in the CDC's *Mantoux Tuberculin Skin Test Facilitator Guide* at this hyperlink: http://www.cdc.gov/tb/education/mantoux/default.htm.

How to Interpret a Tuberculin Skin Test

Use the table below to determine when a reaction is positive.

Table 4: POSITIVE TUBERCULIN SKIN TEST REACTIONS

Induration Size	Considered Positive For:
5 mm or more	▪ Persons with human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) ▪ Recent contacts to an infectious case of tuberculosis (TB) disease ▪ Persons with fibrotic lesions on chest radiograph consistent with healed TB ▪ Persons with organ transplants or other immunosuppressed persons (such as those receiving the equivalent of >15 mg/day of prednisone for >1 month) ▪ Persons receiving treatment with tumor necrosis factor-alpha (TNF-α) antagonists
10 mm or more	▪ Foreign-born persons recently arrived (within 5 years) from countries with a high TB incidence or prevalence (e.g., most countries in Africa, Asia, Latin America, Eastern Europe, the former USSR, or from refugee camps) ▪ Persons who inject drugs or use other high-risk substances, such as crack cocaine ▪ Alcoholics ▪ Residents and employees in high-risk, congregate settings (e.g., correctional institutions; long-term residential care facilities, such as nursing homes, mental institutions, etc.; hospitals and other healthcare facilities; homeless shelters; and refugee camps) ▪ Mycobacteriology laboratory personnel ▪ Persons with other medical conditions that increase the risk of TB disease ▪ Children younger than 5 years of age, or children and adolescents exposed to adults in high-risk categories
15 mm or more	▪ Persons with no known risk factors for TB

When interpreting TST results, be aware of the following.

Skin test conversions: For persons previously skin tested, an increase in induration of 10 mm or more within a two-year period is classified as a conversion to positive.

False-negative reactions may be due to the following:

- Anergy

See “Anergy Testing” under “Candidates for Mantoux Tuberculin Skin Testing” in this section, pages 5.9 – 5.10.

- Recent TB infection (within the past 8-10 weeks)
- Very young age (less than six months of age, because the immune system is not fully developed)
- Overwhelming TB disease
- Vaccination with live viruses (e.g., measles, mumps, rubella, varicella, oral polio, or yellow fever)

TB skin testing should be done either on the same day as vaccination with live virus or at least four weeks after vaccination.

See “Live-Virus Vaccines” under “Candidates for Mantoux Tuberculin Skin Testing” in this section, pages 5.9 – 5.10.

- Some viral infections (measles, mumps, chickenpox, influenza, or HIV)
- Corticosteroids or other immunosuppressive agents given for two or more weeks

False-positive reactions may be due to the following:[26]

- Nontuberculous mycobacteria (NTM) or mycobacterium other than tuberculosis (MOTT)
- BCG vaccination

See “Bacille Calmette-Guérin Vaccine” under “Candidates for Mantoux Tuberculin Skin Testing” in this section.

Human Immunodeficiency Virus Screening

The Centers for Disease Control and Prevention (CDC) recommends the following:

- Routine HIV screening for all patients ages 13–64 seeking health care for any reason, without regard to patient's known risks for HIV infection
- Annual HIV screening of patients known to be at high risk[27]

Follow-Up Activities

After testing, complete the following tasks:

If the person has signs or symptoms of TB, evaluate for TB disease as described in the "Diagnosis of Tuberculosis Disease" section in *Diagnosis of Tuberculosis Disease*, Chapter 3. Refer to Table 1: **When to Suspect Pulmonary Tuberculosis in Adults**, page 3.10.

If the person is a contact, follow the procedures for testing and evaluation in the Contact Investigation section.

If the person is a participant in two-step screening, see the topic titled "Two-Step Tuberculin Skin Testing" in the Infection Control section.

If the TST result is positive, an interview, symptom check and a chest radiograph should be obtained for the patient, and possible further testing may also be indicated.

Chest Radiography

All individuals who test positive on a tuberculosis screening test and persons being considered for LTBI treatment should have a chest radiograph to rule out pulmonary TB disease. If the chest radiograph is consistent with pulmonary TB disease, three sputa specimens for AFB smear and culture are collected. For information on how to classify TB, see the "Tuberculosis Classification System" section, page 5.3, in this chapter. Refer to Table 5 below to determine when to obtain a chest radiograph and what follow-up is required for chest radiograph results.

A posterior-anterior radiograph of the chest is the standard view used for the detection and description of chest abnormalities in adults. In some instances, other views (e.g., lateral, lordotic) or additional studies (e.g., computed tomography [CT] scans) may be necessary.

Children younger than five years of age should receive posterior-anterior and lateral radiographs.[28]

For more information on chest radiography, refer to the Francis J. Curry National Tuberculosis Center's *Radiographic Manifestations of Tuberculosis: A Primer for Clinicians* (Francis J. Curry National Tuberculosis Center Web site; 2006) at this hyperlink: http://www.nationaltbcenter.ucsf.edu/products/product_details.cfm?productID=EDP-04 .

For persons recently exposed to TB, follow the procedures for testing and evaluation in this TB Manual, Chapter 8, *Contact Investigation*.

Table 5: TARGETED TESTING FOR LATENT TUBERCULOSIS INFECTION: WHEN CHEST RADIOGRAPHS ARE REQUIRED AND HOW TO FOLLOW UP ON RADIOGRAPHY RESULTS

Signs or Symptoms of TB Disease?	TST or IGRA Result?	Recent Exposure to Infectious TB?	Chest Radiograph: Required and Results?	Follow-up Action
Yes	Positive or negative	Yes or no	CXR Required: Yes Results: normal or abnormal	▪ Classify as Class 5. ▪ Evaluate for TB disease. Refer to the Diagnosis of Tuberculosis Disease section.
No	Negative	No	CXR not recommended unless the patient has HIV infection or other forms of immunosuppression are present	▪ Classify as Class 0
No	Positive	No	CXR Required: Yes Results: normal	▪ Classify as Class 2. ▪ Consider treatment for LTBI. Refer to the Treatment of Latent Tuberculosis Infection section.
			CXR Required: Yes Results: abnormal non-calcified fibrotic lesions suggestive of old, healed TB; comparison film available and stable	▪ Classify as Class 4 or 5. ▪ Consider evaluating for TB disease. Refer to the Diagnosis of Tuberculosis Disease section.
			CXR Required: Yes Results: abnormal consistent with TB disease; no comparison film	▪ Classify as Class 3 or 5. ▪ Evaluate for TB disease. Refer to the Diagnosis of Tuberculosis Disease section.

Definitions of abbreviations: CXR = chest radiograph; HIV = human immunodeficiency virus; IGRA = interferon gamma release assay; LTBI = latent tuberculosis infection; TB = tuberculosis; TST = tuberculin skin test.

Resources and References

Resources

- ATS, CDC, IDSA. “Diagnostic Standards and Classification of Tuberculosis in Adults and Children” (*Am J Respir Crit Care Med* 2000;161[4 Pt 1]). Available at: https://www.atsjournals.org/doi/full/10.1164/ajrccm.161.4.16141
- CDC. *Core Curriculum on Tuberculosis (2013)* [Division of Tuberculosis Elimination Web site]. May 2016. Available at: https://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf
- CDC. *Self-Study Modules on Tuberculosis* (Division of Tuberculosis Elimination Web site; 1999). Available at: https://npin.cdc.gov/publication/self-study-modules-tuberculosis
- Clinical Infectious Diseases “Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children” 2016;00(0):1-33 Oxford University Press for the Infectious Diseases Society of America. DOI:10.1093/cid/ciw694. Available at: https://www.cdc.gov/tb/publications/guidelines/pdf/cid_ciw694_full.pdf

References

[1] ATS, CDC, IDSA. Controlling tuberculosis in the United States: recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR* 2005;54(No. RR-12):15.

[2] CDC. Classification system. In: Chapter 2: transmission and pathogenesis. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: http://www.cdc.gov/tb/pubs/corecurr/default.htm . Accessed July 3, 2006.

[3] CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005;54(No. RR-17):4–5; CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):7–9, 22.

[4] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):8-9.

[5] CDC. Guidelines for using the QuantiFERON®-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. *MMWR* 2005;54 (No. RR-15):52.

[6] American Academy of Pediatrics. Tuberculosis. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. Red book: 2009 report of the Committee on Infectious Disease. 28th ed. Elk Grove Villiage, IL: American Academy of Pediatrics, 2009:680--701..

[7] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):11; CDC, NTCA. Guidelines for the investigation of contacts of persons with infectious tuberculosis: recommendations from the National Tuberculosis Controllers Association and CDC. *MMWR* 2005;54(No. RR-15):13; County of Los Angeles Tuberculosis Control Program. *Tuberculosis Control Program Manual: 2003 Edition*:2-1. Available at: http://www.lapublichealth.org/tb/TBManual/TBmanual.pdf . Accessed February 6, 2007.

[8] Francis J. Curry National Tuberculosis Center. *Diagnosis and treatment* [Web page]. Available online at: http://www.nationaltbcenter.ucsf.edu/abouttb/diagnosis_and_treatment.cfm . Accessed November 30, 2006.

[9] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):1–2.

[10] CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005;54(No. RR-17):49.

[11] CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005;54(No. RR-17):50.

[12] CDC. Candidates for treatment of latent TB infection. In: Chapter 6: treatment of LTBI. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: http://www.cdc.gov/tb/pubs/corecurr/default.htm . Accessed July 3, 2006.

[13] Sepulveda RL, Ferrer X, Latrach C, Sorensen, RU. The influence of Calmette-Guérin Bacillus immunization on the booster effect of tuberculin testing in healthy young adults. *Am Rev Respir Dis* 1990;142:24–28.

[14] McKay, A, Kraut A, Murdzak C, Yassi A. Determinants of tuberculin reactivity among health care workers: interpretation of positivity following BCG vaccination. *Can J Infect Dis* 1999;10:134–139.

[15] CDC. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: http://www.cdc.gov/tb/pubs/corecurr/Chapter9/Tableofcontents.htm . Accessed January 20, 2007.

[16] CDC. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: http://www.cdc.gov/tb/pubs/corecurr/Chapter9/Tableofcontents.htm . Accessed January 20, 2007.

[17] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49[No. RR-6]:11.

[18] CDC. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: http://www.cdc.gov/nchstp/tb/pubs/corecurr/Chapter9/Chapter_9_Interpretation.htm . Accessed January 20, 2007; Smith PG. Case-control studies of the efficacy of BCG against tuberculosis. In: International Union Against Tuberculosis, ed. *Proceedings of the XXVIth IUATLD World Conference on Tuberculosis and Respiratory Diseases.* Singapore: Professional Postgraduate Services International 1987:73–9.

[19] CDC. Tuberculin skin testing. In: Chapter 4: testing for TB disease and infection. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: http://www.cdc.gov/tb/pubs/corecurr/default.htm . Accessed July 3, 2006.

[20] CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR* 2005;54(No. RR-17):53.

[21] CDC. *Epidemiology and Prevention of Vaccine-Preventable Diseases.* Atkinson W, Hamborsky J, McIntyre L, Wolfe S., eds. 9th ed. Washington, DC: Public Health Foundation; 2006:24–25, 143.

[22] CDC. *Epidemiology and Prevention of Vaccine-Preventable Diseases.* Atkinson W, Hamborsky J, McIntyre L, Wolfe S., eds. 9th ed. Washington, DC: Public Health Foundation; 2006:24–25, 143.

[23] CDC National Center for Health Statistics. Skin test preparation steps: filling syringes. In: Skin Test Preparation Steps: Filling Syringes. *National Health and Nutrition Examination Survey (NHANES) Manual.* Hyattsville, MD: National Center for Health Statistics.

[24] CDC. Part two: reading the Mantoux tuberculin skin test. *Mantoux Tuberculin Skin Test Facilitator Guide* [Division Tuberculosis Elimination Web site]. Available online at: http://www.cdc.gov/tb/pubs/Mantoux/part2.htm . Accessed November 30, 2006.*Manual* 2004:1.3.

[25] CDC. Tuberculin skin testing. In: Chapter 4: testing for TB disease and infection. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: http://www.cdc.gov/tb/pubs/corecurr/default.htm . Accessed February 6, 2007.

[26] CDC. Tuberculin skin testing. In: Chapter 4: testing for TB disease and infection. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: http://www.cdc.gov/tb/pubs/corecurr/default.htm . Accessed February 6, 2007.

[27] CDC. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR* 2006;55(No. RR-14):1–17.

[28] CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6):25.