

Chapter Two: Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection

A. Introduction

Targeted tuberculin skin testing (TST) is performed to identify persons at high-risk for tuberculosis (TB) who would benefit from treatment of latent TB infection (LTBI). Many factors influence the utility of this test, including the technical preparation and administration of the TST, the prevalence of LTBI in the population being tested, the medical conditions of the individual, previous Bacille Calmette-Guérin (BCG) vaccination, and presence of non-tuberculous mycobacteria. Thus, the interpretation and diagnostic accuracy of TST, while very useful in many situations, must be cautiously interpreted depending upon the clinical situation.

Recommendations outlined in this chapter are based on guidelines issued by the Centers for Disease Control and Prevention (CDC) and joint guidelines from the California Department of Health Services (CDHS) / California Tuberculosis Controllers Association (CTCA). However, certain standards for TST and LTBI treatment in Los Angeles County (LAC) differ from State and Federal recommendations due to differences in demographics and TB epidemiology between LAC and the United States as a whole (see Appendix F, *LAC TBC Program Standards, Targeted Skin Testing and Treatment of Latent TB Infection in Adults and Children*).

B. Performing and Interpreting the Tuberculin Skin Test

The Mantoux method is the standard test used to detect infection with *M. tuberculosis*. In general, it takes two to ten weeks after infection for a person to develop a delayed-type immune response to tuberculin. A properly performed TST consists of an intradermal injection of a measured amount (5 TU) of purified protein derivative (PPD). Multiple puncture tests such as the Tine test are not recommended.

The Mantoux test can be administered in conjunction with all vaccines. However, if a vaccine containing live virus (e.g., measles) has already been given, the TST should be deferred for at least one month after the administration of the vaccine, as a false-negative result may occur when reading the TST.

Administration of the Mantoux test can be done in all persons, including individuals infected with human immunodeficiency virus (HIV), pregnant women, and persons who have previously been vaccinated with BCG. Two-step testing, which takes into account the “booster” effect, is described later in this chapter. Appropriate infection control procedures should be followed for all Mantoux applications.

1. Procedure for Administration and Reading of the TST

Equipment

- Single dose disposable, needle-safe tuberculin syringe with ½ inch 26 or 27 gauge intradermal needle with a short bevel
- Five tuberculin units (TU) Tween stabilized PPD antigen
- Alcohol swabs
- Sharps disposal container for syringe and needle disposal
- Standard millimeter ruler

Administration

1. Wash hands with soap and water.
2. Use an individual disposable, needle-safe syringe and needle for each person.
3. Expose patient's left arm and rest it comfortably on a firm and well-lighted surface.
4. Draw slightly more than 0.1 ml of PPD antigen into the syringe.
5. Exclude air bubbles, making sure there is exactly 0.1 ml (5 TU) of PPD antigen in the syringe.
6. Select an injection site on the flexor (volar) surface of the forearm about 4 inches below the elbow in an adult or at the junction of the upper and middle third of the forearm. The area should be flat and not directly over a vein.
7. The skin should be cleaned using 70% alcohol and allowed to dry completely before the injection.
8. Stretch the patient's skin at the selected site tight between the thumb and index finger.
9. Face the bevel of the needle upward and hold the syringe almost parallel to the skin.
10. Use the tip of the needle to elevate the skin to maintain as flat an angle as possible while advancing the needle, bevel side up. The tip of the needle, when properly located, can be seen just below the skin surface.
11. Inject the PPD antigen intradermally. A tense white wheal six (6) to ten (10) millimeters in diameter should appear over the point of the needle.

12. Discard the syringe and needle immediately after use in a sharps disposal container. Do not recap, bend, or break needles and use current needle-safe equipment.
13. No dressing or special skin precautions are needed.
14. Instruct the patient to return in 48 to 72 hours for reading.

Reading

1. The TST should be read 48 to 72 hours after administration. It is acceptable to read and record a negative Mantoux up to 96 hours after application. If a test is read later than 96 hours and is negative, the test must be repeated. A positive reaction will still be measurable up to one week after testing, and may still be readable.
2. Use a millimeter ruler to measure the largest diameter of induration perpendicular to the long axis of the arm at the site of the injection. Induration is characterized by an elevated firm thickening of the skin. Erythema is of no diagnostic value and should not be measured.
3. Determine the edges of the induration by side lighting or palpating with your fingertip and marking the edges with a water-soluble ink pen.
4. Measure and record all results in millimeters of induration. If no reaction is found, "0 mm" should be recorded.

2. Interpretation of the TST

1. A reaction of five (5) millimeters or more of induration should be considered positive in the following persons:
 - Persons known or suspected to have HIV infection
 - Recent contacts to an infectious case of TB
 - Persons with an abnormal chest radiograph consistent with TB disease
 - Immunosuppressed individuals
2. A reaction of ten (10) millimeters or more should be considered positive for all other persons. (In certain jurisdictions, a fifteen (15) millimeter cut point is recommended for low-risk reactors, but this is not recognized in California.)

3. TST conversion is defined as an increase of at least (10) millimeters of induration from less than ten (10) millimeters to ten (10) millimeters or more within two years, from a documented negative to positive TST. If the exact size of a previous negative TST is unknown, a skin test conversion is defined as a change from a documented negative to positive TST within a two-year period.
4. Patients who have a positive TST must receive a chest radiograph and undergo clinical evaluation for TB disease prior to starting treatment for LTBI, as described later in this chapter.
5. As the TST is neither 100% sensitive nor specific, interpretation of the TST must take many factors into account, such as current immune status, age, mechanical factors, and other risk factors for having LTBI. Thus, health care providers must interpret the TST in light of possible false-negative and false-positive results that may occur (see Table 2-1 below).

Table 2-1. Factors that may cause false-positive and false-negative reactions to the tuberculin skin test

Type of reaction	Possible cause
False-positive	Non-tuberculous mycobacteria BCG vaccination
False-negative	Anergy (see Table 2-9, page 2-16) Recent TB infection Very young age (<6 months old) Live-virus vaccination Overwhelming TB disease

3. Adverse Reaction to PPD

Adverse reactions to PPD are very uncommon and usually represent a high degree of sensitivity to tuberculin. A few sensitive persons may respond to skin testing with vesicular or ulcerating local reactions, lymphangitis, regional adenopathy, or fever. Allergic reactions to the phosphate-buffered saline diluent, the phenol preservative, and Tween 80, if they occur, are extremely uncommon. Immediate skin reactions to PPD have no clinical or epidemiological importance and do not indicate tuberculous infection. The PPD in doses used for tuberculin testing does not induce delayed hypersensitivity in non-infected individuals.

C. Candidates for Tuberculin Skin Testing and LTBI Treatment

TST screening should be focused on persons either at higher risk for TB exposure or infection, or at higher risk of TB disease once infected (see Tables 2-2 and 2-3 below). Groups at low risk for TB should not be routinely tested because testing in such groups will result in unnecessary testing, divert resources from those who are higher priorities, and result in a higher percentage of false-positive results. Repeat TST testing is generally not necessary for individuals with a documented previously positive TST.

Table 2-2. High-risk groups who are candidates for targeted testing

- Contacts of persons with infectious TB (pulmonary or laryngeal)
- Persons known or suspected of being HIV-infected
- Injection drug users
- Persons with certain medical conditions (see Table 2-3 below)
- Persons with radiographic evidence of old, healed TB
- Employees or residents of congregate settings, such as hospitals, correctional facilities, homeless shelters, nursing homes, or drug treatment centers
- Persons from an area of the world where the incidence of TB is high (See Table 2-4, page 2-6)
- Children and adolescents <18 yrs. old exposed to adults with high-risk conditions

In general, all individuals in high-risk groups are candidates for targeted testing and, if TST-positive, eligible for LTBI treatment. However, the unique TB epidemiological profile in our region, the increased risk of isoniazid (INH) hepatitis in persons who are pregnant or over 35 years of age, and resource limitations have necessitated the LAC TB Control Program (TBC) to make recommendations that focus treatment on the following high-risk groups (see Table 2-4, page 2-6). Thus, based on these standards, it is not recommended to test individuals for LTBI if it is known beforehand that the person will not be a candidate for treatment.

Table 2-3. Medical conditions that are associated with an increased risk of TB in an infected person

- Human immunodeficiency virus (HIV)
- Diabetes mellitus (especially insulin-dependent)
- Silicosis
- End-stage renal disease
- Chronic immunosuppression (including transplant recipients, persons on prolonged corticosteroid (equivalent to prednisone 15 mg daily for \geq one month) or other immunosuppressive therapy)
- Hematological and reticuloendothelial diseases (e.g., leukemia and Hodgkin's Disease)
- Malnutrition and clinical situations associated with rapid weight loss (including cancer of the head and neck, intestinal bypass, gastrectomy, chronic malabsorption, or body weight under 10% of ideal)

Table 2-4. Risk groups defined for targeted testing and treatment for LTBI (if TST positive) in Los Angeles County

Higher-risk groups	Comments
Persons with known or suspected HIV infection	All persons in these categories should be tested and are candidates for LTBI treatment, regardless of age. Testing and initiation of treatment should not be delayed in pregnancy
Persons with abnormal chest radiograph suggestive of TB and classified as TB Class 4	
Recent close contacts to infectious TB*	
TST converters	
Persons with medical conditions associated with an increased risk of TB (Table 2-3, page 2-5)	
Residents and employees of high risk congregate settings [†]	
Persons who abuse alcohol, cocaine, and intravenously-injected drugs	
Persons from countries with high TB rates who arrived in the US within the past three (3) years	All persons in these categories should be tested and are candidates for LTBI treatment, regardless of age.
Children and adolescents under 18 years of age exposed to adults with an increased risk of TB (Tables 2-2 and 2-3, page 2-5)	Initiation of treatment for pregnant women should be delayed until 3 to 6 months postpartum.
Lower-risk groups	Persons over 35 years of age should be excluded from testing. Initiation of treatment for pregnant women should be delayed until 3 to 6 months postpartum.
Persons from countries with high TB rates who have been in the US greater than three (3) years	
Persons with a positive TST who are not in the above categories	

*A patient who has a TST <5 millimeters and has TB disease excluded should be started on treatment if there is a high probability of infection or the contact is under five years of age or immunocompromised (see Chapter Six)

[†]Defined as residents of prisons, jails, nursing homes, other long-term care facilities, AIDS residential facilities, and homeless shelters (see Chapter Seven)

D. Initial Clinical Evaluation for LTBI

In order to rule out TB disease, *all* persons who have a positive TST should undergo a medical history, physical examination, and chest radiograph, whether or not an individual is a candidate for LTBI. Once TB disease is ruled out, the patient should then be evaluated for treatment of LTBI.

1. Medical History and Assessment

The purpose of the history is to evaluate for possible active or prior TB disease in the patient and evaluate medical conditions and medications that may interfere with treatment of LTBI.

A complete medical assessment should include:

- Review of current symptoms

- History of skin test results, TB exposures, previous treatment for LTBI, TB disease, or BCG vaccination
- Review of high-risk status situations, such as country of origin or current living situation (e.g., homelessness or congregate living)
- Review of high-risk behaviors, such as drug and alcohol use and sexual activity
- Review of current medications and allergies
- Evaluation for HIV and review of HIV-related risk factors (see Table 3-3, page 3-2). All patients with any HIV risk factors should be counseled and offered HIV testing
- Review of medical conditions, including liver disease, diabetes, seizure disorder, malignancy, or other medical condition which may affect the progression of LTBI to active disease or which may contraindicate treatment of LTBI

2. Chest Radiograph

A chest radiograph should be performed preferably the same day but no longer than ten working days after the positive TST reading unless the patient has had documentation of a chest radiograph within the past three months. If the chest radiograph is read as normal, the patient may then be further evaluated for treatment of LTBI. If the radiograph is abnormal, the clinician should evaluate for possible TB disease or other pathology. If the chest radiograph is consistent with TB, bacteriologic studies should be initiated. LTBI treatment should not be started unless active TB has been ruled out.

3. Laboratory Evaluation

Baseline laboratory testing is not routinely indicated for all persons at the start of treatment for LTBI. Such testing may, however, be considered on an individual basis. Persons with the following characteristics are required to have baseline laboratory testing:

- HIV infection
- History of, or risk of, chronic liver disease (e.g., viral hepatitis)
- Alcoholism
- Intravenous drug use
- Taking other hepatotoxic medications
- All persons over 35 years of age
- Pregnant women and those in the immediate post-partum period (three to six months)

Baseline laboratory tests depend on which drug regimen is being used (see Table 2-5 below). If the aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory values exceed three times the upper limit of normal, INH should not be initiated except at the discretion of the physician (see Figure 2-2, page 2-18).

Table 2-5. Frequency and type of tests in persons receiving treatment of LTBI for whom laboratory monitoring is indicated*

LTBI regimen	Laboratory monitoring	Frequency
INH only	AST, ALT, total bilirubin	Baseline, then monthly for first 3 months, then every 3 months and as needed if symptomatic
RIF alone or INH plus RIF	Same as above plus CBC	Same as above
RIF plus PZA [†]	Same as RIF. Include uric to evaluate symptoms of joint pain or if patient has a history of gout	Baseline, at 2, 4, and 6 weeks, and as needed if symptomatic

NOTE: In HIV-positive individuals on PI or NNRTI, rifabutin should be substituted for rifampin

*See Appendix A-2 for definitions of abbreviations used in this manual

[†] Restricted to certain patients (see page 2-9)

E. LTBI Treatment Regimens

1. Isoniazid

The standard in LAC is to use isoniazid (INH) as a single drug for treating LTBI (see Table 2-6, page 2-11 for dosages and duration of treatment). A minimum of six months of INH should be given to treat LTBI within a nine month period of time in adults, with nine months of therapy given to children and adolescents up to age 18 years, and HIV-infected persons within a 12-month period of time. If an intermittent (twice-weekly) regimen is to be given, treatment must be given under directly observed therapy (DOT) and the length of therapy should be nine months.

Contraindications to INH must be evaluated before initiating treatment.

2. Alternative LTBI Treatment Regimens

Alternative LTBI regimens are available for those who are unable to tolerate the preferred INH regimen or satisfy the situations described below. Dosages and duration of therapy are described in Table 2-7, page 2-11. Contraindications to these drugs must be evaluated before initiating treatment. Special considerations for HIV-infected persons are detailed later in this chapter.

LTBI regimens for contacts to patients with multidrug-resistant TB (MDR-TB) are highly individualized and require consultation with TBC. Management of MDR-TB contacts is described in Chapter Six.

Rifampin Only

This six-month daily regimen is preferred to treat LTBI in adults and children exposed to cases with mono-resistance to INH or who cannot tolerate to INH.

Isoniazid plus Rifampin

This four-month daily regimen is an alternative to nine months of INH for adults with TB Class 4. It is also recommended for suspects (TB class 5) who have been started on four-drug treatment for TB but are later determined to be TB Class 4. The time for treatment as a suspect case should be included in the total four months recommended for treating LTBI. RIF alone for four months may also be an alternative to INH and RIF in treating persons with TB Class 4.

Rifampin plus Pyrazinamide

Approval from the TB Control Program is required before using this regimen. This regimen is not to be used except in HIV-infected adults who are at very high risk for tuberculosis and unlikely to take six months of INH. Particular caution is necessary in patients taking other medications associated with liver injury, and those with a history of alcoholism even if alcohol use is discontinued during treatment. Rifampin/pyrazinamide is contraindicated for persons with underlying liver disease or for those who have had isoniazid-associated liver injury. Rifampin/pyrazinamide must be given by directly observed therapy (DOT). This regimen requires more frequent monitoring for side effects because serious liver reactions have been reported, including death. Intermittent therapy is not recommended.

F. Documentation, Monitoring, and Follow-up

1. Documentation Procedures and Practices

Initial documents to be completed for patients in LAC Health Centers include the *TB Screening History* (form H-2288) and the *TB Screening Form* (form H-304). Follow-up for LTBI is recorded on the *TB Preventive Treatment Record* (form H-261). As detailed in Chapter One, certain Class 2 TB patients may be followed by an Extended Role Nurse (ERN). See Appendix E for examples of forms.

2. Clinical Monitoring

Individuals taking treatment for LTBI must be evaluated monthly for the duration of therapy. At each visit, patients should be asked in the language they best understand about signs and symptoms of drug intolerance or toxicity (see Chapter Five for toxicity and side effect profiles of TB medications), signs and symptoms of TB disease, and adherence to the medication regimen. ***No more than a one-month supply of medication is to be dispensed at a time and no refills should be given.***

Regimens that contain rifampin and pyrazinamide require more frequent monitoring. Liver function studies including serum aminotransferase (AT) and bilirubin must be performed at baseline, weeks two, four, and six of therapy. Asymptomatic serum AT increases are expected but do not require that treatment be stopped unless the AT level is greater than three times the upper limit of normal range in which case the regimen should not be resumed. Treatment should also be stopped and not resumed if any of the following findings occur: AT greater than normal range accompanied by symptoms of hepatitis, or a serum bilirubin greater than normal whether symptoms are present or not. Rifampin/pyrazinamide must be given by DOT.

3. Laboratory Monitoring

Routine laboratory follow-up intervals are listed in Table 2-5, page 2-8, for persons for whom routine laboratory monitoring is indicated. Patients for whom signs or symptoms of drug toxicity are apparent should also receive appropriate laboratory tests.

LTBI treatment should be discontinued if AST or ALT values are higher than three times the normal value or if there is clinical evidence of hepatitis (see Figure 2-2, page 2-18).

4. Management of Adverse Reactions

See Chapter Five for managing adverse reactions due to TB medications.

5. Interrupted or Incomplete Treatment

Completion of therapy should be based on the total number of doses administered—not on duration of therapy. If treatment is interrupted, the recommended number of doses of the regimen should be provided within a certain maximum time period (see Tables 2-6 and 2-7, page 2-11). Patients who have had lapses in therapy but are still able to complete the recommended number of doses in the allotted time period should be encouraged to complete therapy and do not require restarting treatment.

Patients who have had lapses in therapy that are frequent or too prolonged, thus precluding completion of doses in the time frames specified, should be assessed by the physician to determine whether or not to restart treatment. If it is decided to re-treat the patient, the entire regimen should be restarted. Specific factors to be considered in determining whether to restart treatment include:

- The individual's risk for developing TB disease
- Total number of doses of LTBI treatment administered
- Time elapsed since the last dose of treatment for LTBI
- Patient adherence issues (previous attempts at completion, willingness to continue, etc.)

When therapy is restarted after an interruption of more than three months, a medical examination, including chest radiograph, is indicated to exclude active disease.

An effort should be made to encourage patients to adhere to the LTBI treatment regimen. However, if a patient has failed three attempts to complete treatment, no further effort may be merited. Patients who interrupt therapy and are at high risk of developing TB disease (for example, contacts of patients with infectious TB, HIV-infected patients, or TB class 4 patients) should be contacted by the PHN for re-evaluation. Non-adherent patients at very high risk of developing TB disease should be given every opportunity to complete LTBI therapy and should be considered for intermittent therapy with DOT as well as incentives and enablers (see Chapter Four, page 4-14).

Table 2-6. Recommended isoniazid LTBI treatment regimens*

Isoniazid Regimen	Age	Dose mg/kg	Daily max, mg	Minimum Duration of Therapy
Daily	Adult	5	300	6 months (180 doses within 9 months) 9 months (270 doses within 12 months) for HIV-positive and TB Class 4
	Child [†]	10-15	300	9 months (270 doses within 12 months)
Twice-weekly**	Adult	15	900	9 months (76 doses within 12 months)
	Child [†]	20-40	900	9 months (76 doses within 12 months)

*See Appendix B for definitions of abbreviations used in this manual

**Twice-weekly regimens must be given by DOT

[†]Under 18 years of age

Table 2-7. Alternative LTBI treatment regimens (see text for specific indications for therapy)*

LTBI Regimen	Age	Daily dose, mg/kg	Max daily dose, mg	Minimum Duration of therapy
RIF alone [†]	Adult	10	600	6 months (180 doses within 9 months)
	Child	10-20	600	6 months (180 doses within 9 months)
INH plus RIF [†]	Adult**	INH 5	300	4 months (120 doses within 6 months)
		RIF 10	600	
RIF plus PZA [†]	Adult**	RIF 10	600	2 months (60 doses within 3 months)
		PZA 15-20	2000	

*See page A-2 for definitions of abbreviations used in this manual

** Not recommended in children

[†] Intermittent therapy is not recommended (see page 2-9)

NOTE: In HIV-positive individuals on PI or NNRTI, rifabutin should be substituted for rifampin. See page 2-13

6. Management of Broken Appointments

Priorities for management of broken appointments (BA) for patients on LTBI are determined according to the risks of developing active TB if LTBI treatment is stopped prematurely (see Table 2-8, page 2-12). Thus, the highest priority should be given to contacting persons who are at the greatest risk of developing TB disease.

Table 2-8. Guidelines for broken appointments by priority

Priority	High-risk group	Action	
		1 st BA	2 nd BA
I (Highest)	Persons with known or suspected HIV infection	Personal contact by PHN or ERN within 1 week. Reschedule within 2 weeks*	To physician for disposition
	Persons with abnormal chest radiograph suggestive of TB and classified as TB Class 4		
	Recent close contacts to active pulmonary or laryngeal TB		
	TST converters—including children		
	Persons with medical conditions associated with an increased risk of TB (Table 2-3, page 2-5)		
II	Residents and employees of high-risk congregate settings	Reschedule clinic appointment with <i>Educational Appointment Letter</i> (H-1833) via mail or personal contact	Close with <i>Educational Closure Letter</i> (H-1834)
	Children and adolescents <18 years of age, exposed to adults with high-risk conditions		
	Persons who abuse alcohol, cocaine, or intravenously-injected drugs		
	Persons born in countries with high TB rates who immigrated to the USA within ≤ 3 years		
III (lowest)	All other reactors	Close with H-1834	

* It is acceptable to mail the appointment notification to patients who have completed several months of LTBI therapy and who have an adequate supply of medications

7. Closure Procedures

An individual who has completed therapy as defined by total number of doses administered may be discharged from the clinic as having completed treatment when the patient returns for the final month of medication. Closure should be documented on the *TB Screening Form* (form H-304) whether or not the person has completed LTBI treatment. Patients who have completed LTBI treatment are to be given a *Preventive Therapy Completion Card*. The *Educational Closure Letter* (form H-1834) is to be sent to patients who have BAs and thus are presumed not to have completed LTBI treatment. See Appendix E for examples of forms.

8. Follow-up For Patients After Closure

No routine visits are necessary for patients after completion of LTBI treatment. Patients should be reminded about symptoms of TB disease. In some cases, individuals may require another complete course of LTBI therapy if they have been re-exposed as a close contact to an infectious case of TB and have HIV/AIDS or are otherwise immunosuppressed.

G. LTBI Considerations in Special Populations

1. Pregnancy

Pregnancy alone does not increase the risk for TB disease and routine TB screening is not recommended in pregnancy. However, pregnant women who are at high risk for TB infection or progression to TB disease should be tested for LTBI.

Standards for screening, diagnosis, and treatment of LTBI in this population are generally identical to the general population with the following considerations:

- Treatment for LTBI should generally be delayed until the mother is three to six months post-partum due to an increased risk of developing INH-related hepatitis unless the patient is in a high-risk category as defined in Table 2-4, page 2-6. In these high-risk groups, treatment should be initiated during pregnancy. INH has no known teratogenic effect on the fetus.
- Chest radiograph should be performed with appropriate lead shielding.
- Baseline and monthly LFTs must be obtained during treatment (see Figure 2-2, page 2-18).
- If a woman already receiving LTBI treatment becomes pregnant, treatment is to be continued until completion of therapy.

2. HIV-Infected Individuals

The following considerations apply to LTBI treatment in HIV-infected individuals:

- Given the high risk of progression, initiation of LTBI treatment should be started regardless of age as soon as TB disease has been ruled out, assuming no contraindications to INH treatment exist.
- INH is the preferred treatment in LAC.
- As an alternative, two months of daily PZA and RIF is effective in treatment of LTBI in the HIV-infected population (see Table 2-7, page 2-11), and may be appropriate for those who are unable or unwilling to take nine months of INH therapy. However, it should be used with caution. Approval from the TB Control Program is required before using this regimen because of the potential for liver damage and death.
- Rifabutin should be substituted in situations where RIF should not be given such as in HIV-infected persons taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. Dosage adjustment may be necessary (see Table 4-6, page 4-9), and TBC should be consulted before making this substitution.

H. Special Issues in Tuberculin Skin Testing

1. BCG Vaccination

BCG vaccination is generally not recommended for use within the United States because of questionable and variable efficacy in protecting individuals from TB disease. It may also interfere with the ability to determine TST reactivity, causing a false-positive reaction. In BCG-vaccinated individuals who immigrate to the United States from countries where TB is endemic, it may not be possible to distinguish a positive TST due to true LTBI versus BCG vaccination. However, TST reactivity due to BCG vaccination in such individuals is highly variable and will tend to wane over time.

The standards in LAC regarding the use of and evaluation of persons with previous BCG vaccination are:

- BCG vaccination is not generally recommended. Rare exceptions may apply, but are utilized only in special circumstances under consultation with TBC.
- A history of previous vaccination with BCG (with or without a BCG vaccination scar) is not a contraindication to TST, nor does it influence the indications for a TST. Administration and reading of the TST in these individuals are performed in the same manner as in those who had no previous BCG vaccination. As with other individuals, those with a positive TST must have active TB ruled out, and if applicable, the patient should be offered treatment for LTBI.
- It is the standard of TBC that a positive TST *beyond one year* of documented BCG vaccination should be interpreted and managed as true LTBI. In the case of a young child under two years of age, or in an individual who has had documented BCG vaccination within the past year, it may be reasonable to attribute a positive TST to the BCG vaccine, depending on clinical circumstances. However, persons with a positive TST who are contacts to an infectious case of TB or are continuously exposed to populations at high-risk for TB should be considered TB-infected, no matter when vaccination was given. Patients with a history but no documentation of BCG vaccination within one year prior to skin testing should be managed as if they had no previous vaccination.

Management of Individuals With Positive TSTs Within One Year of BCG Vaccination

Routine TB screening of individuals within one year of BCG vaccination, including infants less than one year of age who had BCG vaccination at birth, may result in false-positive results. Thus, routine screening of such individuals is not recommended. However, should such screenings occur, the following are recommended for patients with a positive TST and documented BCG vaccination within one year of TST:

- If no other TB risk factors are identified, treatment for LTBI is generally not necessary. The reaction should be recorded in terms of millimeters of induration and it should be documented that the positive TST is due to BCG vaccination.

- Routine follow-up for TB screening is not necessary. The patient and/or parent should be educated about symptoms of TB and told to return to clinic should symptoms occur (see Table 3-1, page 3-1). The patient should be retested if he/she requires skin testing as a contact to someone with infectious TB or as an entrance requirement for the LAC School Mandate Program (see page 7-10).

2. Two-step Testing

In some persons infected with TB, especially older persons, the ability to mount a positive TST reaction may wane over time. An initial TST placed in these individuals may not fully react, and be interpreted as negative. However, a repeat TST within a year or more may react and show a positive reaction. This effect is known as the booster phenomenon, and a positive “boosted” response should be considered the valid baseline for that individual. In a person who has never been infected with TB (assuming no BCG vaccination or non-TB mycobacterial infection), repeated TST testing itself will not elicit a positive reaction.

Two-step testing is a screening method that takes into account a possible booster phenomenon in an individual and should be considered for any person when serial testing is to occur. While boosting is most common in persons aged 55 or older, some employers who require TB screening utilize a two-step test for all new employees regardless of age while others select an age cut-off point of usually 45 to 55 years to reduce the likelihood that a boosted reaction is not misinterpreted as a recent conversion.

Candidates for two-step TST include employees of health care facilities, employees who undergo periodic TB screening, and residents of congregate living settings (details for screening those populations are described in Chapter Seven, page 7-7). Two-step testing should be performed only for initial TB screening. Subsequent periodic testing requires only one TST. Therefore, an individual who can provide documentation of a negative TST by the Mantoux technique within the preceding year has no need for two-step testing, as it is very unlikely the TST result is the result of waning immunity.

Procedure and interpretation for two-step skin testing (see Figure 2-1, page 2-17):

1. Administer the Mantoux TST.
2. Examine the TST in 48 to 72 hours. If initial TST is negative, repeat TST within one to three weeks using the same dose and strength of tuberculin and have patient return in 48 to 72 hours for the second reading. A positive TST means the individual is considered infected, and should be evaluated for treatment of LTBI.

OR

As an alternative, the initial TST can be examined in seven days, since a truly positive TST persists for many days beyond 72 hours. If the initial TST is negative, a repeat TST can be administered at the same visit and the individual should be instructed to return in 48 to 72 hours for the second reading. A positive TST means the individual is considered infected, and should be evaluated for treatment of LTBI.

3. If the second test is negative, the individual is classified as uninfected. If the second test is positive, the individual is considered infected with TB.
4. Subsequent evaluations for TB in health care workers and those in congregate living setting should be done according to facility or CalOSHA TB employee health policies.

All persons who have a positive TST must receive a chest radiograph and undergo clinical evaluation for TB disease prior to starting treatment for LTBI. These procedures are described earlier in this chapter.

3. Anergy Testing

Anergy is the inability to mount a delayed-type cutaneous, cellular immune response to an antigen to which one has been previously sensitized. Patients who are anergic may have a negative TST reaction even if they have TB infection. This condition may be caused by many factors (see Table 2-9 below).

Administering other delayed-type hypersensitivity antigens, such as mumps and candida, commonly comprises anergy testing. However, because anergy testing is not standardized, the effectiveness of such testing is limited, and it is no longer recommended for validating a negative TST and should not be used to determine a patient's status and need for treatment of LTBI.

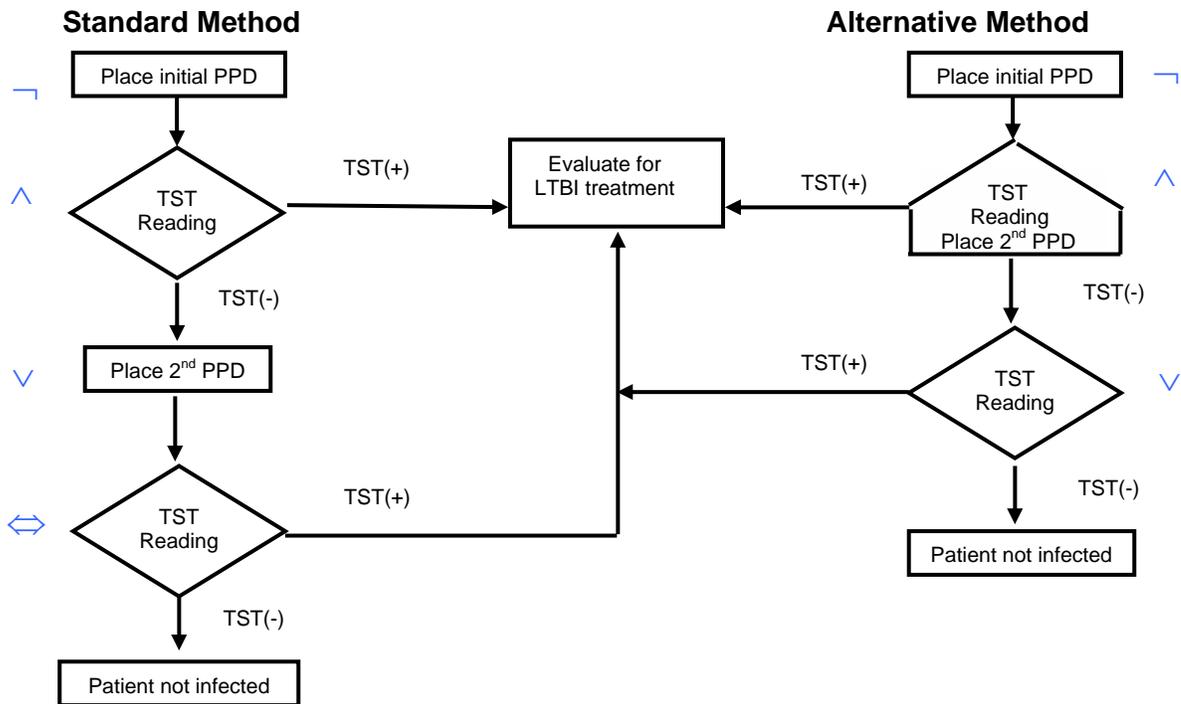
Table 2-9. *Causes of anergy*

- HIV infection or AIDS
- Chronic corticosteroid therapy or other immunosuppressive therapy
- Some hematologic and reticuloendothelial diseases, such as leukemia or lymphoma
- End-stage renal disease
- Overwhelming pulmonary or miliary TB disease
- Clinical situations associated with substantial rapid weight loss or chronic undernutrition
- Sarcoidosis
- Extremes of age (newborn or elderly)
- Live-virus vaccination
- Certain viral infections (measles, mumps, chicken pox), or bacterial infections (typhoid fever, pertussis, brucellosis, leprosy)

Figure 2-1. Two-step Testing

Standard Method: (Step 1) Administer TST: (Step 2) Read TST in 48 to 72 hours; if TST + evaluate for LTBI treatment, if negative; (Step 3) Administer second TST in one to three weeks; (Step 4) Read second TST in 48 to 72 hours; if TST + evaluate for LTBI treatment. If negative, TST is truly negative.

Alternative Method: (Step 1) Administer TST: (Step 2) Read TST in one week, if TST + evaluate for LTBI treatment, if negative administer second TST; (Step 3) Read TST in 48 to 72 hours; if TST + evaluate for LTBI treatment. If negative, TST is truly negative and there's no "booster" response.



I. Policies and Procedures for Targeted Skin Testing Evaluation of Latent TB Infection

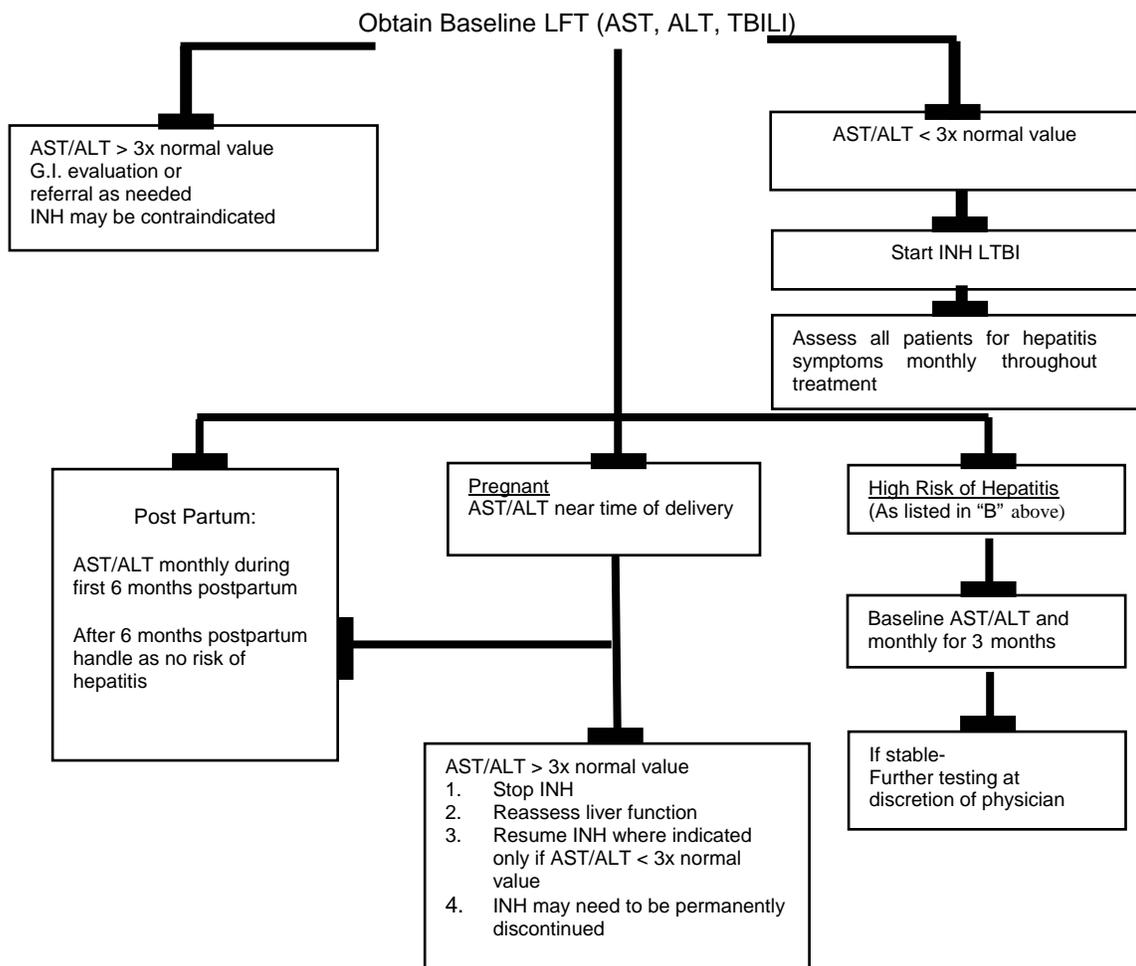
Based on the guidelines for “*Targeted Skin Testing and Treatment of Latent Tuberculosis Infection in Adults and Children*” (see Appendix N), TBC has established policies and procedures for targeted skin testing and evaluation of latent tuberculosis infection for implementation in the public health centers (see Appendix F). These policies and procedures are **not** applicable to any individual who is being tuberculin skin-tested as an intervention to interrupt or prevent the transmission of TB in the community (i.e., contact investigation, source case finding, etc.). These policies and procedures apply only to those individuals who are not a part of such routine public health interventions, and also to persons who are seeking a tuberculin skin test which is unsolicited by the public health center. The purpose of these policies and procedures is to ensure that skin testing is reserved for those individuals who will benefit the most from screening and treatment of latent TB infection (LTBI).

Figure 2-2. Liver Function Monitoring for INH Therapy of LTBI

- A. No Risk of Hepatitis
 - 1. No baseline LFT
 - 2. Symptomatic monitoring monthly
 - 3. Stop INH when symptomatic and draw LFT
 - 4. Resume INH where indicated only if AST is less than 3x normal value and M.D. reorders

- B. High Risk of Hepatitis
 - 1. History of hepatitis, liver disease, daily use of alcohol, current or past injection drug use
 - 2. Pregnant or 3-6 months postpartum (including post abortion)*
 - 3. ≥ 35 years old **

Monitor the Patient at High-Risk For Hepatitis as Follows:



* LTBI therapy is not recommended unless other risk factors present. Hold until 3-6 months postpartum.

** LTBI therapy is not recommended for persons ≥ 35 years old with normal chest x-ray and no other risk factor; the exception is those individuals born in countries with a high TB rate who have resided in the USA ≤ 3 years.