Assessment and Treatment of Latent Tuberculosis Infection

Reference for Health Care Providers

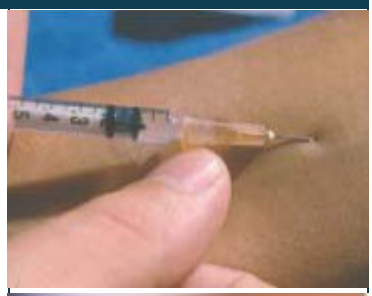
Southwestern Public Health
Oxford • Elgin • St.Thomas

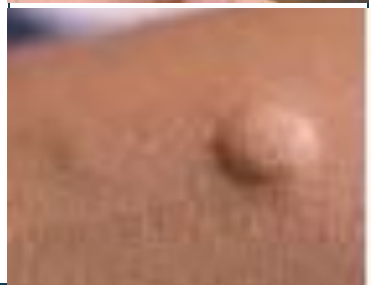
Indications for tuberculin skin testing (TST)

Who should be tested?

- Contacts of persons recently diagnosed with active disease
- Individuals who are at increased risk of exposure (HCW's) and who are at risk of poor outcomes should they develop TB disease.
- Immigrants from TB-endemic countries, especially those <20 years old and those who have arrived in the last 2 years
- Persons with medical conditions (e.g. immunosuppressive conditions) that increase the risk for progression to active disease

TB Skin Tests Are Not Recommended: For those with a low risk of infection and a low risk of progressing to TB disease if infected, to support a TB diagnosis in adults and adolescents >12 years of age, for routine mass screening (outside of occupational screening programs), for monitoring TB disease treatment response, for those with a history of documented TB disease or TB infection with adequate treatment, those with current major viral infections, or for those who have received a live vaccine in the past 4 weeks (unless the opportunity to perform the TST might be missed)





Interpretation: Deciding that the TB Test is Positive

There are multiple dimensions to consider when interpreting a positive TST or IGRA to help decide whether someone is at risk of developing TB and would benefit from tuberculosis preventive treatment

a) Pretest probability of TB infection, predictive value, and size of induration. (refer to table 1)

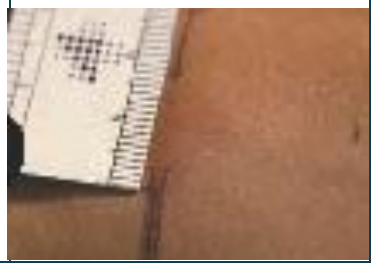
b) The likelihood of true exposure, false-negative and/or false-positive reactions (refer to table 2)

c) Risk of progression to active disease (refer to table 3)

The Canadian TB Standards 8th edition (Chapter 4) outline situations where IGRA testing is preferred over tuberculin skin testing.

Online tools can be used to assist with TST/IGRA interpretations.

- **The Online TST/IGRA Interpreter**
- **Periskope.org**



Evaluation: Clinical Picture

This should include:

a) Assessment for symptoms of active disease, including cough, fever, night sweats (refer to page 3)

b) Chest radiography (refer to page 3)

c) In the presence of symptoms or an abnormal chest x-ray, collect sputum for acid-fast bacilli (AFB) smear and culture (refer to page 3)

d) In people with no evidence of active TB, a recommendation should be made regarding therapy for LTBI (refer to page 4)

TABLE 1: Interpretation of TST Results in Various Risk Groups

Test Result	Situation in which reaction is considered positive
0-4 mm	• In general this is considered negative and no treatment is indicated
≥ 5 mm	• HIV infection • Contact with infectious TB case within the past 2 years • Presence of fibronodular disease on chest x-ray (healed TB and not previously treated) • Prior to organ transplantation (related to immune suppressant therapy) • Prior to receipt of biologic drugs, such as TNF alpha inhibitors, or antirheumatic drugs • Prior to other immunosuppressive drugs, e.g. corticosteroids • End-stage renal disease
≥ 10 mm	• TST conversion (within 2 years) • Diabetes, malnutrition (<90% of ideal body weight), cigarette smoking, daily alcohol consumption (>3 drinks/day) • Silicosis • Hematologic malignancies (leukemia, lymphoma) and certain carcinomas (e.g. head and neck) • Any population considered at low risk of disease

TABLE 2: Likelihood of True Exposure, False Negative and/or False Positive Reactions

Causes of False Negative TST
✓Error in administration or reading
✓Age <6mos or advanced age
✓Immunization within the past 4 weeks with MMR, varicella or yellow fever vaccines
✓Immune suppression
✓Major viral illness in the past 4 weeks (e.g. measles, mumps, mononucleosis)
✓Severe malnutrition, chronic renal failure, severe physiological stress (surgery, burns)
✓Active tuberculosis or other severe illness
Causes of False Positive TST
✓ Infection with non-tuberculosis mycobacteria (i.e., environmental mycobacteria)
✓ Prior BCG vaccination. Can be ignored as a cause of a positive TST if: • It was given in infancy and the person tested is now over age 10 years • There is a high risk of progression from TB infection to disease (e.g. person with co-morbidities) • There is a high probability of TB infection: close contacts of an infectious TB case, Indigenous Canadians from a high-risk community, or immigrants from a country with high TB incidence • Immigrants from countries with a high burden of TB – BCG World Atlas available online at: www.bcgatlas.org
✓ BCG should be considered the likely cause of a positive TST if: • It was given after 12 months of age AND • There has been no known exposure to active TB disease or other risk factors AND the person is either Canadian-born non-Aboriginal OR an immigrant from a country with low TB incidence

TABLE 3: Risk of Developing Active Disease

Risk Factors for Progression to Active Disease	
Very High Risk	People living with HIV, those with TB close contact, silicosis
High Risk	Stage 4 or 5 chronic kidney disease with or without dialysis, transplant recipients (solid organ or hematopoietic), fibronodular disease, receiving immunosuppressing drugs (TNF inhibitor or steroids), cancer.
Moderate Risk	Granuloma on chest x-ray, diabetes, heavy alcohol use (at least 3 drinks/day), heavy tobacco cigarette smoker (at least 1 pack/day)
Low Risk	General (adult) population with no known risk factor, persons with a positive two-step TST booster and no known risk factor

Clinical Picture

Neither the TST or IGRA can distinguish between TB infection and TB disease as both tests measure immune response. Therefore, for those with a positive TST or IGRA, additional testing is required to rule out TB disease.

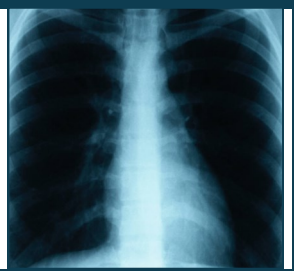
- Many people with pulmonary tuberculosis have a normal physical exam, even if symptomatic.
- The most common symptom of pulmonary TB disease is a new or worsening cough of at least 2–3 weeks duration.
- Cough is initially dry and may become productive after several weeks.
- Fever and night sweats may be absent in the very young and elderly.
- Hemoptysis, anorexia, weight loss and chest pain are generally seen in more advanced disease.

Note: TB can occur in any part of the body with site-specific symptoms. Lymph node TB is the most common extrapulmonary site. Few cases of extrapulmonary TB are considered communicable.

Radiograph

A person with latent TB has a normal chest x-ray, and those with active TB may have an abnormal x-ray.

- Chest x-rays should always be interpreted in the context of clinical and laboratory findings.
- Interpretation of chest x-rays is most accurate when it's done by experienced clinicians.
- 10% of persons with HIV infection and active TB disease will have a normal chest x-ray.



Sputum Collection

- Patients should be asked to produce 3 sputum specimens. The specimens can be collected on the same day, at least 1 hour apart (early morning collection not essential).
- Patients need to produce 5 to 10 cc of sputum per specimen. They should be advised to produce sputum from deep in their lungs.
- If immediate delivery (<1 hour) is not possible, patients can put specimens in a paper bag and refrigerate at 2-8ºC pending transport to the lab. Delivery to the lab should occur as soon as possible to avoid overgrowth of normal flora.

Note: Instructions for patient sputum collection can be obtained from Southwestern Public Health

Timelines for Test Results:

- Smear for AFB – results are available in 1 business day from arrival at the lab.
- Real time PCR for detection of mycobacterium tuberculosis complex (MTBC) and mycobacterium avium complex (MAC) DNA is performed on all AFB smear positive specimens from new, untreated patients. Turnaround time is up to 4 days from receipt by the laboratory.
- Culture for Mycobacterium Tuberculosis – results may be available anywhere from 4 days to 7 weeks.
- Susceptibility testing to first line anti-tuberculosis drugs is done on all positive cultures – first-line results are available within 12 days after the culture report. Full panel second-line drug sensitivity testing is done if resistance is detected to Rifampin or 2 or more drugs – results are available up to 12 days after first line test results are reported.

Treatment of Latent Tuberculosis Infection

- Approximately 10% of patients infected with TB will go on to develop active TB disease: 5% within 2 years of infection and 5% over the balance of their life expectancy.
- The decision to begin treatment should be based on:

1. A positive TST
2. Risk of progression to active disease
3. Medical contraindications (see table 5). Patients under 65 years old with no comorbidities have low rates of hepatotoxicity
4. Evaluation of risks/benefits with patient
5. Likelihood of adherence to full length of LTBI treatment:
   - patient ability to take medication as instructed and to tolerate side effects, etc.
   - provider ability to continue monthly follow up
6. Active TB has been ruled out (history, risk factors, and physical examination; negative sputum samples if patient is symptomatic or has abnormal CXR.

Table 4: Recommended Treatment Regimens (Canadian TB Standards, 2022)

First Line	Duration	Dose	Frequency	Common adverse effects
Rifampin (4R)	4 months (120 doses)	10mg/kg Maximum: 600 mg	Daily	Rash, drug interactions
Rifapentine and isoniazid (3HP) ***Directly observed preventive therapy (DOPT)**	3 months (12 doses)	Isoniazid: 15 mg/kg Maximum: 900 mg Rifapentine: 10-14.0 kg: 300 mg 14.1-25.0 kg: 450 mg 25.1-32.0 kg: 600 mg 32.1-49.9 kg: 750 mg ≥50.0 kg: 900 mg Maximum: 900 mg	Once Weekly	Flu-like reactions, drug interactions **50 mg Pyridoxine (Vitamin B6) should be given at each dose to minimize the risk of neuropathy**
Second Line	**Duration**	**Dose**	**Frequency**	**Common adverse effects**
Isoniazid (9H)	9 months (270 doses)	5mg/kg Maximum: 300 mg	Daily	Hepatoxicity, peripheral neuropathy **25 mg Pyridoxine (Vitamin B6) should be given daily at each dose to minimize the risk of neuropathy**
Alternative	**Duration**	**Dose**	**Frequency**	**Common adverse effects**
Isoniazid (6H)	6 months (180 doses)	5mg/kg Maximum: 300 mg	Daily	Hepatoxicity, peripheral neuropathy
Intermittent isoniazid for 9 months	9 months (78 doses)	15mg/kg Maximum: 900 mg	Twice weekly	Hepatoxicity, peripheral neuropathy
Isoniazid and rifampin (3HR)	3 months (90 doses)	Isoniazid: 5mg/kg Maximum: 300 mg Rifampin: 10mg/kg Maximum: 600 mg	Daily	Hepatoxicity, peripheral neuropathy, drug interactions

Table 5: LTBI Treatment - Recommendations for Follow-Up & Monitoring

Drug	Adverse Reaction	Monitoring	Comments

Rifampin (RMP)	• CNS
	• Dermatologic
	• Hypersensitivity
	• Hepatitis
	• Gastrointestinal
	• Hematological
	• Renal
	Many drug interactions:
	Refer to the Compendium of Pharmaceuticals and Specialties
		• Baseline testing for all patients undergoing tuberculosis preventive treatment is recommended, including, CBC, liver enzymes, bilirubin, Hepatitis B and C serologies, and HIV.
		• Evaluation after the first month of treatment provides an opportunity to assess medication tolerability and to encourage adherence. ALT and bilirubin testing is recommended 1 month into treatment for all regimens. A CBC should also be completed for those on a rifamycin medication.
		• Additional testing not necessary unless:
		  • Baseline results are abnormal
		  • Patient has symptoms of an adverse reaction
			• Colours bodily fluids reddish orange
			• May permanently discolour contact lenses
			• By accelerating estrogen production, RMP may interfere with the effectiveness of birth control pills; alternative contraception method should be advised
			• Contraindicated in severe chronic liver disease
			• **RMP given alone to persons with active TB disease can lead to resistance**

Isoniazid (INH)	• Liver enzyme elevation
	• Hepatitis
	• Peripheral neuropathy
	• CNS
	• Gastrointestinal
	• Hematological
	• Hypersensitivity
	For drug interactions:
	Refer to the Compendium of Pharmaceuticals and Specialties
		• Baseline testing for all patients undergoing tuberculosis preventive treatment is recommended, including, CBC, liver enzymes, bilirubin, Hepatitis B and C serologies, and HIV.
		• Evaluation after the first month of treatment provides an opportunity to assess medication tolerability and to encourage adherence. ALT and bilirubin testing is recommended 1 month into treatment for all regimens.
		• Monthly ALT and bilirubin is recommended for those with risk factors for hepatotoxicity, and should be considered for those without risk factors:
		  • Pre-existing liver disease (particularly hepatitis C)
		  • Age ≥35 years
		  • History of alcohol abuse or prior drug-induced hepatitis
		  • Pregnant or within 3 months post-partum
		• If AST level >5 times baseline level, or if symptoms of hepatotoxicity develop (i.e. anorexia, nausea, vomiting, abdominal discomfort, dark coloured urine, jaundice or sclera icterus), then INH should be stopped and a TB specialist consulted.
			Hepatitis risk correlated with age:
			Age Group **Risk**
			<20 0.1-0.2%
			20-34 0.3%
			35-49 0.5%
			50-64 1.0-3.0%
			≥65 2.0-5.0%
			• Hepatitis risk increases with daily alcohol consumption, or viral hepatitis
			• INH-induced hepatitis is almost always reversible
			• **INH given alone to persons with active TB disease can lead to INH-resistant TB**

Follow-up after Treatment is Complete or Refused

- There is no need for routine follow-up after treatment is complete
- If treatment is refused or not completed, the patient should be advised of the symptoms of active TB and instructed to return for evaluation if those symptoms develop
  - Routine chest radiography is not recommended unless the risk of TB disease is high. In this situation consider regular follow-up for 2 years, as this is the period of highest risk (e.g. at 6, 12 and 24 months)

References:

Canadian Tuberculosis Standards, 8th Ed., 2022. https://www.tandfonline.com/toc/ucts20/6/sup1

Canadian Tuberculosis Standards, 7th Ed., 2013.

The Ontario Lung Association

Toronto Public Health, Quick Reference: Assessment and Treatment of Latent Tuberculosis Infection, 2013