Assessment and Treatment of Latent Tuberculosis Infection

Reference for Health Care Providers

Southwestern Public Health
Oxford • Elgin • St.Thomas

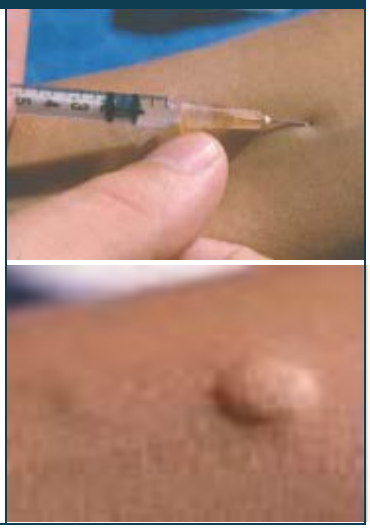
Indications for tuberculin skin testing (TST)

- To diagnose latent tuberculosis infection (LTBI) in persons at increased risk for progression to active tuberculosis disease
- A TST is not reliable for the diagnosis of active disease

Who should be tested?

- Contacts of persons recently diagnosed with active 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

Note: TSTs are generally discouraged for those with no elevated risk of infection with TB and no known risk factors for progression to active disease.



Interpretation: Deciding that the TB Skin Test is Positive

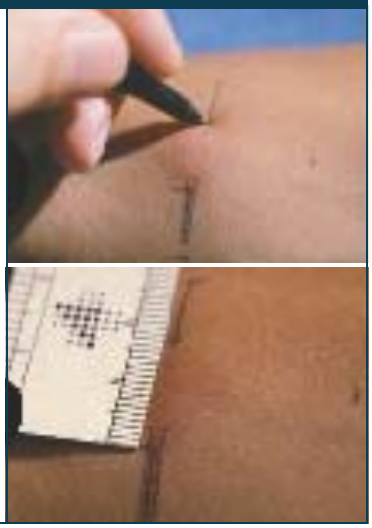
This decision is based on:

a) 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)

A web-based interactive algorithm, "The Online TST/IGRA Interpreter", is available at www.tstin3d.com to assist in TST/IGRA interpretations



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 • Exception: children under 5 years of age at high risk of TB infection
≥ 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) • Organ transplantation (related to immune suppressant therapy) • TNF alpha inhibitors • 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)

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:
  • 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, Aboriginal 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

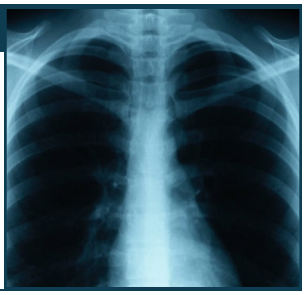
Risk Factors for Progression to Active Disease	
High Risk	HIV, AIDS, transplantation (related to immune suppressant therapy), silicosis, chronic renal failure (requiring hemodialysis), carcinoma of the head and neck, recent TB infection (≤ 2 years), abnormal chest x-ray (fibronodular disease)
Moderate Risk	TNF alpha inhibitors, diabetes mellitus (all types), treatment with glucocorticoids (≥ 15 mg/day of prednisone for ≥ 1 month), young age when infected (0-4 years)
Slightly Increased Risk	Heavy alcohol consumption (≥3 drinks/day), underweight (90% of ideal body weight), cigarette smoker (≥ 1 pack/day), abnormal chest x-ray (granuloma)
Low Risk	Person with a positive TST with no known risk factors, normal chest x-ray ("low risk reactor")
Very Low Risk	Person with a positive two-step (no other), no other known risk factor and normal chest x-ray

Clinical Picture

- 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.

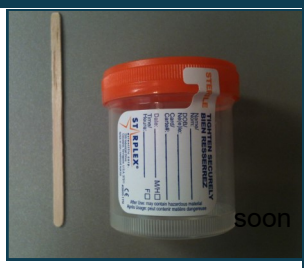
Note: TB can occur in any part of the body with site-specific symptoms. Lymph node TB is the most common extra-pulmonary site. Few cases of extrapulmonary TB are considered communicable.

Radiograph



- 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 4ºC pending transport to the lab. Delivery to the lab should occur as as possible to avoid overgrowth of normal flora.

Note: Instructions for patient sputum collection can be obtained from Elgin St. Thomas Public Health.

Timelines for Test Results:

- Smear for AFB – results are available in 1 business day from arrival at the lab.
- Amplified Mycobacterium Tuberculosis Direct (AMTD) - distinguishes between TB and other types of mycobacteria, for example, Mycobacterium Avium Complex (MAC). AMTD is performed automatically on AFB smear positive specimens from new patients. Results are available in 2-3 business day from arrival at the lab.
- Culture for Mycobacterium Tuberculosis – results maybe available anywhere from 4 days to 7 weeks.
- Sensitivity testing for susceptibility to first line anti-tuberculosis drugs (4-7 days after the organism has grown in culture), is done automatically on all positive cultures – first-line results are available in 8-10 business days. Full panel second-line drug sensitivity testing is automatically done if resistance is detected to Rifampin or 2 or more drugs – results are available in 4-15 business days.

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, has abnormal CXR or is being treated with Rifampin)

Table 4: Recommended Treatment Regimens

First Line Regimen	Interval & Duration	Oral Dose	Criteria for Completion	Comments	Effectiveness
Isoniazid (INH)	Daily for 9 months	5 mg/kg/day to a maximum of 300 mg/day	9 months is equivalent to 270 doses. Completing 270 doses within a 12 month period can be considered adequate treatment	Recommended treatment regimen Provides optimal protection in preventing progression to active disease For children, especially those < 5 years old, consult a Specialist	Assuming good adherence to treatment: INH, when taken for 9 months, is up to 90% effective in preventing progression to active disease and is the recommended duration of treatment.
VitaminB6 (Pyridoxine)	Daily with INH	25 mg		Protects against neurotoxic effects of INH; Usually prescribed, particularly important or clients with diabetes, renal failure, malnutrition, substance abuse or seizure disorders, or for women who are pregnant or breastfeeding	
Second Line/ Alternative Regimen	**Interval & Duration**	**Oral Dose**	**Criteria for Completion**	**Comments**	**Effectiveness**
Isoniazid & Rifampin (INH/ RMP)	Daily for 3-4 months	Adult: INH – 5 mg/kg/ day to a maximum of 300 mg/day RMP – 10 mg/ kg/day to a maximum of 600 mg/day	For the preferred 4 month regimen, a minimum of 120 doses completed within 6 months can be considered adequate treatment.	Use this regimen in consultation with a specialist. *Consider collecting sputum and pending for culture results prior to initiation to avoid inducing drug resistance Alternate regimen for persons: who are unlikely to be able to complete 9 months of INH (i.e., adherence concerns)	Published efficacy of 3 months of INH/RMP is 64%; 4 months is expected to have higher efficacy Efficacy and safety is similar to 6-9 months of INH
Rifampin (RMP)	Daily for 4 months	Adult: 10 mg/kg to a maximum of 600 mg/day	A minimum of 120 doses completed within 6 months can be considered adequate treatment.	Use this regimen in consultation with a specialist: *Consider collecting sputum and pending for culture results prior to initiation to avoid inducing drug resistance Alternate regimen for persons: who cannot tolerate INH; who are contacts of INH resistant TB Risk of side effects is higher if Rifampin is not taken consistently	Published efficacy rates 63% equivalent to 6 months INH. Excellent safety and high completion rates

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

Drug	Adverse Reaction	Monitoring	Comments

Isoniazid (INH)	• Liver enzyme elevation
	• Hepatitis
	• Peripheral neuropathy
	• CNS
	• Gastrointestinal
	• Hematological
	• Hypersensitivity
	For drug interactions -
	Refer to the Compendium of Pharmaceuticals and Specialties
		• Baseline serum aminotransferases
		• Monitor monthly
		• Monthly ALT, AST for patients with:
		  • 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.
		• Repeat monitoring of liver enzymes for patients with symptoms consistent with hepatic side effects.
			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**

Rifampin (RMP)	• CNS
	• Dermatologic
	• Hypersensitivity
	• Hepatitis
	• Gastrointestinal
	• Hematological
	• Renal
	Many drug interactions:
	Refer to the Compendium of Pharmaceuticals and Specialties
		• Baseline bilirubin, serum creatinine, CBC, platelets and liver enzymes
		• Repeat measurement if:
		  • 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**

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, 7th Ed., 2013
The Ontario Lung Association & Toronto Public Health, Quick Reference: Assessment and Treatment of Latent Tuberculosis Infection, 2013