Quick reference

Tuberculosis Preventive Treatment (TPT): Assessment and Management

Goal for testing

The primary goal of testing for TB infection (TBI or LTBI) is to identify individuals who are at increased risk for the development of TB disease and therefore can benefit from TPT to prevent TB disease.

Persons at low risk

TST/IGRA testing is generally discouraged for those with no elevated risk of infection with TB and no known risk factors for progression to TB disease.

Who should be tested

- Contacts of persons recently diagnosed with infectious TB disease
- People (all ages) born outside of Canada with conditions associated with a very high-risk* of TB reactivation
- Foreign-born persons of all ages from TB endemic countries (TB incidence ≥50/100,000), who have a high-risk* factor for TB reactivation (especially those within 2 years of arrival to Canada) TB incidence rates
- Refugees from TB endemic countries (TB incidence ≥50/100,000) aged ≤65 years as soon as possible after arrival and up to two years after arrival
- People with radiographic evidence of old, healed TB and no history of treatment
- Health care workers who need TBI screening for occupational health requirements
- Persons from Indigenous communities with high rates of TB
- Travelers who may have high-risk contact with TB disease (e.g., working/visiting people/patients in hospitals, refugee camps, shelters, prisons, inner-city areas). See TB Travel Guidelines:

A negative TST/IGRA does not rule out TB disease

A TST is NOT a diagnostic test for active TB disease, and a negative TST or IGRA result in a patient with TB-compatible symptoms does NOT rule out active TB disease. In fact, a negative TST or IGRA in a patient with active TB disease can be a sign of extensive disease and poor outcome.

Contraindications for TST

- Documented positive skin test or IGRA, or tuberculosis disease in the past
- Tuberculin reactions that have severely blistered in the past
- Clear history of treatment for TB infection or disease
- Major viral infections or live-virus vaccinations in the past month, for example, measles, mumps, rubella, varicella, or yellow fever
- Extensive burns or eczema at the usual test site: Choose another site

Not contraindications for TST

- Common cold
- Immunized with any vaccine on the same day
- Recently been vaccinated with non-live virus vaccines
- Pregnant or breastfeeding
- Received Bacillus Calmette-Guérin (BCG) vaccination in the past
- History of positive tuberculin skin test that is not documented

Prioritize patients with at least one of the following medical risks for TB reactivation:

*Very High Risk

- HIV
- Child/adolescent (<18 years of age) TB contact
- Adult (>18 years of age) TB contact
- Silicosis

High Risk

- Chronic kidney disease (stage 4 to 5)
- Transplant recipients (organ or hematopoietic)
- Fibronodular disease
- Receiving immunosuppressing drugs (e.g., tumor necrosis factor α inhibitors or steroids)
- Cancer (lung, sarcoma, leukemia, lymphoma or gastrointestinal)

TST Planting

- 0.1ml (5-TU) of purified protein derivative (PPD)
- Inject intradermally on inner aspect of the forearm
- Injection should raise a small wheal approximately 6–10 millimeters (mm) in diameter, which will disappear in 10–15 minutes.

TST Reading

- Skin test must be read by a trained health professional. Self- reading is inaccurate and should not be done
- Read 48–72 hours after administration
- Use a ruler or caliper to measure **induration** of the transverse diameter (i.e., at right angle to the long axis of the forearm)
- Record in millimeters even if no induration (0 mm)
- Do not measure erythema (redness)

Interpretation

Proper interpretation of the TST should include all the following:

1. Size of the reaction (induration), in mm
2. Predictive value of the test (considering likelihood of true exposure, false-negative and/or false-positive reactions)
3. Risk of progression to TB disease

See online TST interpreter

TST Result	Situation in which reaction is considered positive
<5 mm	In general, this is considered negative
≥5 mm	• People living HIV • Known recent (<2 years) contact with a patient with infectious TB disease • Fibronodular disease (FD) on chest x-ray (evidence of healed, untreated TB) – if TST is <10mm, and prior CXRs are not available there is no need to do a CXR for the sole purpose of identifying FD) • Prior to organ transplantation and receipt of immunosuppressive therapy • Prior to receipt of biologic drugs, such as tumor necrosis factor alpha inhibitors, or disease-modifying anti-rheumatic drugs • Prior to receipt of other immunosuppressive drugs, such as corticosteroids (equivalent of ≥15 mg per day of prednisone for at least one month) • Stage 4 or 5 chronic kidney disease (with or without dialysis)
≥10 mm	• All others

Causes of false-positive TST

- Infection with non-tuberculosis mycobacteria (i.e., environmental Mycobacteria)
- Prior BCG vaccination

Causes of false-negative TST

- Error in administration or reading
- Age <6 months or advanced age
- Immunization within the past 4 weeks with MMR, varicella or yellow fever
- 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)
- Tuberculosis disease or other severe illness

Two-step TST

- A two-step TST only needs to be done if required by occupational health
- If first test is negative, do a second skin test 1 to 4 weeks after the initial plant

BCG vaccination and relationship to TST results

BCG received in infancy	Unlikely to cause a tuberculin reaction of 10mm or greater after 10 years of age or older.
Received at 1 to 5 years of age	10–15% will have a positive TST up to 25 years later.
Received at 6 years or older	40% chance of having persistent positive TST later in life.

Ignore prior history of BCG vaccination for:

- Close contacts of persons with respiratory TB disease
- Immigrants from countries with a high burden of TB – BCG World Atlas available online at bcgatlas
- Persons from Indigenous communities with high rates of TB
- BCG vaccination in infancy and the person tested is now age 10 years or older
- Immunocompromised, including HIV and renal failure
- Diabetes
- Chest x-ray consistent with old, healed TB

Interferon Gamma Release Assays (IGRAs)

The IGRA blood test screens for exposure to TB by measuring the body's immune response to antigens derived from the TB bacteria, unlike the TST. The IGRA test does not cross react with the BCG. IGRA is preferred in people who have received 1 or more BCG vaccines after the age of one year. For full recommendations on the use of IGRAs – see: Canadian TB Standards: IGRA

The IGRA test commonly available in Ontario – but not currently covered by OHIP –- is the QuantiFERON-TB Gold (QFT)

IGRA testing is available through:

- Lifelabs IGRA-QFT (1-877-849-3637)
- Dynacare IGRA-QFT (1-800-565-5721)

Management of a positive TST or IGRA

- All positive TST/IGRA results should be notified to your local public health department.
- All persons with a positive TST/IGRA should be further evaluated to rule out TB disease.

If active TB disease is ruled out, counsel on TBI treatment.

Evaluation

A TB evaluation includes the following: Clinical assessment, interpretation of radiographic findings and sputum collection, if necessary.

1. Clinical assessment (history, risk factors, and physical examination for signs and symptoms of TB disease).
2. Chest x-ray (CXR), anterior/posterior (AP) and lateral views.
3. If symptomatic OR CXR findings consistent with TB: collect 3 sputum specimens to send for AFB Smear and Culture. Sputum specimens (either spontaneous or induced) can be collected on the same day, at least 1 hour apart.

1. Clinical assessment

- New or worsening cough that is greater than >2 to 3 weeks)
- Fatigue
- Anorexia
- Unexplained weight loss
- Hemoptysis
- Chest pain
- Dyspnea
- *Fever, *chills, *Night sweats (*may be absent in the very young and elderly)
- Enlarged lymph nodes

Many patients with pulmonary tuberculosis may have a normal physical exam, even if symptomatic.

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

2. Interpretation of radiographic findings

- Chest x-rays should always be interpreted in the context of clinical and laboratory findings – note +ve TST/IGRA on CXR requisition.
- The interpretation of chest x-rays is highly variable between readers.
- 10% of persons with HIV infection and pulmonary TB disease will have a normal chest x-ray.

3. Sputum collection and timelines for results

- Collect 3 sputum specimens (either spontaneous or induced). How to collect sputum
- The specimens can be collected on the same day at any time, a minimum of 1 hour apart.
- Collect 5 to 10 cc of sputum per specimen.
- If immediate delivery to lab (within one hour) is not possible, protect specimens from light in a paper bag and refrigerate at 4°C pending transport to the lab. Deliver to the lab as soon as possible to avoid overgrowth of normal flora.
  Public Health Ontario lab requisition
- All specimens submitted for TB will automatically be tested for AFB smear and culture: positive smears will automatically have PCR done; positive TB cultures will automatically be tested for drug sensitivity

Consultation or referral to a TB specialist is recommended for persons who are:

- HIV positive
- Contacts of multidrug-resistant TB
- Children under 12 years of age
- Pregnant women at high risk of TB
- Have an abnormal CXR (other than simple granulomas)

Management of TB infection if treatment is refused, contraindicated, or stopped before completion

Patients who do not start or complete TPT treatment should be informed of the symptoms of TB disease and instructed to return for medical assessment if those symptoms arise. Repeat CXR or follow up 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). For further information, contact your local health unit.

Tuberculosis Preventive Treatment (TPT)

- TPT reduces an individual's risk of developing TB disease. Rule out TB disease first, before starting TPT.
- Approximately 10% of persons infected with TB will go on to develop TB disease: 5% within 2 years of infection and 5% over the remainder of life.

Decision to start TPT should be based on:

1. Interpretation of TST/IGRA in context of patient's history:

- Size of the TST reaction (induration), in mm
- Predictive value of the test (considering likelihood of true exposure, false-negative, false-positive reactions)
- Risk of progression to TB disease
- *Refer to online TST interpreter

2. TB disease has been ruled out (history, risk factors, and physical examination; negative sputum cultures for TB if patient is symptomatic or has abnormal CXR)
3. Assessment of risks/benefits of treatment options
4. Likelihood of adherence to full length of TPT

- Patient ability and commitment
- Provider ability to continue monthly follow-up for adherence, side effects, etc.

5. Discussion of risks/benefits with patient

Tuberculosis Preventive Treatment Recommendations for ≥12 years of age

TB medications are free when ordered through your local public health department

First-line regimens

Benefits of first line regimens: reduced risk of hepatotoxicity, improved treatment completion, more cost-effective than 9 months of Isoniazid

Regimen	Frequency & Duration	Oral Dose	Criteria for completion	Monitoring
Rifampin (4R)	Daily for 4 months (120 doses)	10mg/kg Maximum: 600 mg	A minimum of 120 doses completed within 6 months can be considered adequate treatment.	**Baseline testing** • Complete blood count (CBC), alanine aminotransferase (ALT), bilirubin, Hepatitis B&C and HIV serologies **Monthly clinical assessment including** • CBC, ALT, bilirubin at 1 month • Repeat bloodwork: - monthly if baseline or 1 month results are abnormal - if symptoms of an adverse reaction
Rifapentine and Isoniazid* (3HP) **Currently available through TB clinics**	Once weekly for 3 months (12 doses) *Prescribe with Vitamin B6 50mg to prevent neurotoxic effects of INH	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	12 doses within 16 weeks	**Baseline testing** • CBC, alanine aminotransferase, bilirubin, Hepatitis B&C and HIV serologies **Monthly clinical assessment including** • CBC, ALT, bilirubin at 1 month • Repeat bloodwork : - monthly if baseline or 1 month results are abnormal - if symptoms of an adverse reaction

Second-line regimen

If both first-line regimens are not tolerated, not feasible or contraindicated, the following regimens can be considered as alternatives.

Regimen	Frequency & Duration	Oral Dose	Criteria for completion	Monitoring
Isoniazid (9H)*	Daily for 9 months (270 doses) *Prescribe with Vitamin B6 25mg to prevent neurotoxic effects of INH	5 mg/kg Maximum: 300 mg	9 months is equivalent to 270 doses. Completing 270 doses within a 12-month period can be considered adequate treatment	**Baseline testing** • CBC, ALT, aspartate aminotransferase (AST), bilirubin **Monthly clinical assessment including** • ALT, AST, bilirubin at 1 month • Repeat bloodwork: - monthly if hepatic disease, or baseline results are abnormal - if symptoms of an adverse reaction • If AST level is > 5 times the baseline level, or if symptoms of hepatotoxicity develop (i.e., anorexia, nausea, vomiting, abdominal discomfort, dark-coloured urine, jaundice or scleral icterus), then INH should be stopped and a TB specialist consulted

For Alternative regimens not routinely recommended see, Canadian TB Standards, Chapter 6

Adverse Drug Reactions

Drug	Common Adverse Reactions	Comments
Rifampin (RMP)	• Rash • Hepatoxicity * Many drug interactions – refer to Compendium of pharmaceuticals and specialties (CPS) / Lexicomp and Micromedex	• Colours bodily fluids orange-red • May permanently discolour contact lenses/dentures • May interfere with effectiveness of birth control pills: supplementary contraceptive method should be advised • Contraindicated in severe chronic liver disease
Rifapentine (RPT)	• Rash • Hepatoxicity * Many drug interactions – refer to CPS / Lexicomp and Micromedex	• Colours bodily fluids orange-red • May permanently discolour contact lenses/dentures • May interfere with effectiveness of birth control pills: supplementary contraceptive method should be advised • Contraindicated in severe chronic liver disease
Isoniazid (INH)	• Hepatoxicity • Peripheral neuropathy * Many drug interactions – refer to CPS / Lexicomp and Micromedex	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 TB disease can lead to INH-resistant TB

Paediatric Tuberculosis Infection Treatment Guidelines for children under 12 years of age

References:

Canadian Tuberculosis Standard, 8th edition, Canadian Journal of Respiratory, Critical Care and Sleep medicine, 2022, Volume 6, Issue sup 1.

Canadian Pharmacists Association, (2023), RXTX (formerly, Compendium of pharmaceuticals and specialties [e-CPS])