Tuberculosis (TB)

Note: *The scope of this guidance document includes active TB disease and not latent TB infection.*

MICROBIOLOGY

- *Mycobacterium tuberculosis*, the primary etiologic agent of tuberculosis, is an acid-fast bacillus (AFB) with lipid-rich cell wall. Humans are the only reservoir.
- Other species in the *M. tuberculosis* complex (e.g., *Mycobacterium bovis*) are rare cause of disease.
- Nontuberculous mycobacteria (NTM) are a separate group of organisms which are ubiquitous in the environment and rarely cause infections in susceptible hosts.

Risk factors for TB

- Recent exposure to a person with infectious TB
- History of a positive test result for *M. tuberculosis* infection
- Substance use disorder
- Born in or travel to a region with a high TB incidence (for country profiles see: https://www.who.int/teams/global-tuberculosis-programme/data)
- Residents and employees of high TB-risk congregate settings based on local epidemiology, such as homeless shelters and prisons
- Member of a medically underserved and/or low-income population with high rates of TB

DIAGNOSIS

- Clinical assessment, chest radiography, and microbiologic testing are all necessary to diagnose TB.
- Pulmonary TB involving the lung parenchyma and/or tracheobronchial tree is the most common form of TB.
- Extrapulmonary TB can affect nearly any body site/organ. Common locations are lymphadenitis, pleural, abdominal, and central nervous system.

Chest Radiography

- Chest X-ray should be done in all patients with suspected TB.
    - Classic presentation includes upper zone disease with or without cavitation
    - Intrathoracic adenopathy may be seen
    - Calcified nodules may be consistent with granuloma and indicate remote TB infection
    - Less typical patterns include pleural effusion, lower zone infiltrates, diffuse miliary pattern, and rarely a normal chest radiograph (particularly in advanced HIV and severe immunosuppression).
- CT is not usually necessary but may be considered in atypical presentations or suspected false negative chest X-ray.

Microbiologic Testing

1. Smear microscopy for AFB
    - Widely used and inexpensive.
    - Unconcentrated AFB smears (done in FH) are 10-fold less sensitive than concentrated smears (done at BCCDC). Unconcentrated AFB smears cannot be used for discontinuing airborne precautions.
    - AFB smear positive specimens can indicate TB, NTM, or rarely other bacteria like *Nocardia*.
2. Mycobacterial culture
    - Gold standard for TB diagnosis. Can differentiate TB from NTM and provide phenotypic drug susceptibility testing.
    - *M. tuberculosis* can take 2 to 8 weeks to grow in culture. Initial susceptibility testing takes an additional 2 to 4 weeks.
    - If sample volume is limited, mycobacterial culture should take precedence over microscopy and PCR.
3. Polymerase chain reaction (PCR)
    - PCR is more sensitive than smear microscopy but less sensitive than culture.

- PCR should not be used to monitor TB treatment response as it cannot differentiate live or dead bacteria
- The FH PCR can detect mutations which may be associated with rifampin resistance.
- Requests for TB PCR should be discussed with Medical Microbiology.

4. Interferon-gamma release assays (IGRA)
    - IGRAs are in vitro blood tests of cell-mediated immune response to *M. tuberculosis* specific antigens.
    - IGRAs are NOT RECOMMENDED for the diagnosis of active TB disease. Furthermore, anergy during TB disease can cause false negative results.

Extrapulmonary TB

Note: All extrapulmonary TB should be concurrently investigated for pulmonary TB (chest radiography and sputum AFB)

- Pleural infection
    - Pleural infection is often AFB and culture negative. Pleural fluid is lymphocyte predominant, exudative, glucose is low or normal, and pH is usually above 7.3.
    - Pleural fluid should also be sent for AFB smear and mycobacterial culture.
- Gastrointestinal TB
    - Gastrointestinal TB can mimic Crohn's disease.
    - Stool can be sent for AFB smear and mycobacterial culture.
    - Endoscopy can be done with samples sent for histopathology as well as AFB smear and mycobacterial culture.
- Peritoneal TB
    - Peritoneal TB can mimic peritoneal carcinomatosis.
    - Peritoneal TB is usually AFB negative, but often culture positive. Peritoneal fluid is usually proteinaceous (>30 g/L), lymphocytic (>70%), and low serum ascites albumin gradient (<11 g/L).
    - Peritoneal biopsy can be sent for histopathology as well as AFB smear and mycobacterial culture.
- Urinary Tract TB
    - Urine can be sent for AFB smear and mycobacterial culture, which will often confirm diagnosis.
- CNS infection
    - CNS TB is usually AFB smear negative. Large volume CSF sampling (≥10 cc) for mycobacterial culture can improve yield.
    - CSF analysis usually shows elevated opening pressure, moderate lymphocytic pleocytosis (100-500 WBC/mL), low glucose (<2.5 mmol/L), and elevated protein (>0.5 g/L).
    - Neuroimaging may show basilar meningitis, focal lesions (tuberculomas), or hydrocephalus.
- Disseminated & Miliary TB
    - Disseminated TB is disease in two or more noncontiguous organs, or isolation of TB in blood, bone marrow, or liver biopsy.
    - Miliary TB is a subset of disseminated TB with characteristic micronodules on chest radiography. Patients can present with shock and acute respiratory distress syndrome.
    - Sputum and urine for AFB smear and mycobacterial culture should be sent. Other potentially involved extrapulmonary sites of infection should also be investigated as appropriate.

Tissue

- AFB can be detected in tissue sent for histopathology. Similar to smear microscopy, this cannot differentiate between TB, NTM, or other bacteria like *Nocardia*.
- Fresh tissue specimens should be sent for AFB smear microscopy and mycobacterial culture.

INFECTION CONTROL

Suspected TB cases

- Initiate airborne precautions for anyone being evaluated for TB.
- Nontuberculous mycobacteria do not require airborne precautions.

When to discontinue airborne precautions for someone under investigation for TB

- Request sputum x3 for AFB and mycobacterial culture
  - Specimens should be collected at least 8 hours apart with at least one early morning specimen.
  - Specimens may include sputum, induced sputum, tracheal aspirates, or bronchoscopy washings/bronchoalveolar lavage.
  - If bronchoscopy is performed, consider post-bronchoscopy expectorated sputum for improved yield.
  - Induced sputum with nebulized 3% hypertonic saline is an option with equivalent yield as bronchoscopy
- If 3 negative sputum AFB smears or 2 negative sputum for TB PCR
  - Discontinue airborne precautions (if alternative diagnosis to explain patient presentation)
- If AFB smear positive and TB PCR positive, or TB culture positive
  - Consult ID/Respirology.
  - See "When to remove airborne precautions for someone with confirmed TB".
- If AFB smear positive but TB PCR negative
  - Review risk factors for TB vs NTM infection (see risk factors for TB).
  - If suspicious of TB infection → Continue airborne precautions and consult ID/Respirology
  - If no risk factors/not suspecting TB infection → Discontinue airborne precautions as NTM more likely.

Discontinuing airborne precautions in patients with confirmed TB

Concentrated AFB Smear	Rifampin Susceptibility	Criteria to discontinue airborne precautions
Negative	Susceptible	Minimum **2 weeks** effective therapy AND Clinical evidence of improvement
Positive	Susceptible	Minimum **2 weeks** effective therapy AND Clinical evidence of improvement AND 3 x consecutive negative concentrated AFB smears
Persistent Positive (≥2 weeks effective therapy)	Susceptible	Minimum **4 weeks** effective therapy AND Clinical evidence of improvement
Negative	Suspected or confirmed resistance	Minimum **4 weeks** effective therapy AND Clinical evidence of improvement AND Second-line drug susceptibility results available
Positive	Suspected or confirmed resistance	Minimum **4 weeks** effective therapy AND Clinical evidence of improvement AND 3 x consecutive negative concentrated AFB smears AND Second-line drug susceptibility results available

Note: For persistently smear positive or any drug resistant TB, consult with ID prior to discontinuing airborne precautions.

Home isolation

Discharge to home isolation for patients still on airborne precautions can be done in collaboration with TB services. Generally, all the following criteria need to be met:

- Patient tolerating treatment regimen with appropriate TB services follow-up
- Patient does not share common airspace with non-household members (e.g., rooming house) and household air is not being recirculated to other housing units (e.g., some apartment complexes)
- All household members have been previously exposed to the patient.
- Any children under the age of 5 or persons with immunocompromising conditions present in the home are receiving treatment for active TB disease or latent TB infection.

Patient information is available at: https://www.healthlinkbc.ca/healthlinkbc-files/home-isolation-tuberculosis

TREATMENT

General Principles

- Drug therapy for TB disease is given in 2 phases: an initial *intensive phase* to rapidly kill TB organisms and prevent selection of drug-resistant organisms; then a follow-on *continuation phase*.

- Treatment of drug-susceptible TB disease should include 2 effective drugs at all times, and at least 3 effective drugs in the intensive phase (first 2 months).

First-line drug therapy for suspected drug-susceptible TB

- **Consultation with Infectious Diseases/Respirology strongly recommended**
- Initial standard regimen includes rifampin, isoniazid, pyrazinamide, and ethambutol
- Recommended drug doses for daily therapy:

Drug	Daily dose by weight	Daily dose	Notes
Rifampin	10 mg/kg (Maximum 35 mg/kg)	Typically 600 mg	-Tablets: 150, 300 mg -Most important TB drug -Frequent drug-drug interactions -Orange body fluid discolouration -Rash common -Hematologic effects, GI symptoms, hepatotoxicity less common
Isoniazid	5 mg/kg	Maximum 300 mg	-Tablets: 50, 100, 300 mg -Hepatotoxicity most common -Peripheral neuropathy common, reduced by taking pyridoxine -GI symptoms, rash, and hematologic effects less common
Pyrazinamide	(25 mg/kg) 40 to 55 kg 56 to 75 kg 76 to 90 kg	 1000 mg 1500 mg 2000 mg	-Tablets: 500 mg -Hepatotoxicity and rash most common -Gout, GI symptoms and hematologic effects less common
Ethambutol	(15 mg/kg) 40 to 55 kg 56 to 75 kg 76 to 90 kg	 800 mg 1200 mg 1600 mg	-Tablets: 100, 400 mg -Optic neuropathy most common -Rash, hematologic effects, GI symptoms, and neurologic effects less common

- Pyridoxine (vitamin B6) 25 to 50 mg PO daily should also be prescribed to reduce risk of isoniazid peripheral neuropathy

Central Nervous System TB

- Higher dose rifampin (20 up to 35 mg/kg/day) is recommended in CNS TB
- Concurrent corticosteroids reduce mortality and are recommended in CNS TB
    - Corticosteroid regimens:

Clinical Status	Altered LOC (GCS<15) +/- focal neurological deficits	Normal LOC (GCS 15) with no focal neurological deficits
Total Course	8 weeks	6 weeks
Week 1	Dexamethasone 0.4 mg/kg IV daily	Dexamethasone 0.3 mg/kg IV daily
Week 2	Dexamethasone 0.3 mg/kg IV daily	Dexamethasone 0.2 mg/kg IV daily
Week 3	Dexamethasone 0.2 mg/kg IV daily	Dexamethasone 0.1 mg/kg IV daily
Week 4	Dexamethasone 0.1 mg/kg IV daily	Dexamethasone 3 mg PO daily
Week 5+	Dexamethasone 4 mg PO daily decrease by 1 mg/week	Dexamethasone 2 mg PO daily decrease by 1 mg/week

Note: doses may need to be reduced if not on rifampin.

Pericardial TB

- Concurrent corticosteroids are recommended in pericardial TB in HIV negative patients.
    - Corticosteroid regimen

Clinical Status	HIV-negative
Total Course	6 weeks
Week 1	Prednisolone 120 mg PO daily
Week 2	Prednisolone 90 mg PO daily
Week 3	Prednisolone 60 mg PO daily
Week 4	Prednisolone 30 mg PO daily
Week 5	Prednisolone 15 mg PO daily
Week 6	Prednisolone 5 mg PO daily

FOLLOW-UP

1. **Clinical**
   - Monthly patient weight
   - Monthly vision testing while on ethambutol
2. **Radiology**
   - Chest x-ray at two months and at the end of therapy
3. **Laboratory**
   - Monthly CBC, creatinine, AST or ALT, and bilirubin
4. **Microbiology**
   - Sputum AFB smear x3 at least 8 hours apart every 2 weeks until AFB smears negative.
   - Once AFB smears negative, repeat sputum mycobacterial culture x3 every month until culture negative.
   - Repeat drug susceptibility testing if sputum culture remains positive at 3 months. Consult ID.
5. **Medications**
   - Patient requires a referral to either New Westminster or Vancouver TB Clinic prior to discharge to provide outpatient medications and for ongoing follow-up.
   - Rifampin, isoniazid, pyrazinamide, ethambutol and pyridoxine are provided free to outpatients by TB services.
   - Please arrange for a clinic appointment day after discharge so there is no treatment interruption. If clinic appointment is delayed, please consult pharmacist to arrange interim medication supply.

Therapeutic Drug Monitoring

- Therapeutic drug monitoring may be considered in select cases. Therapeutic drug monitoring should be done in conjunction with Infectious Diseases and TB Services.

DURATION

- Final treatment duration will be determined by TB Services during follow-up. These durations are provided as a general guideline for patient counselling.
- Standard regimen for drug-susceptible pulmonary TB is 6 months in duration: rifampin, isoniazid, pyrazinamide, and ethambutol for two months of intensive therapy, followed by rifampin and isoniazid for 4 months.
- Typical treatment duration for drug-susceptible extrapulmonary TB:

Organ Site	**Duration**
Lymphadenitis	6 months
Pleural	6 months
Abdominal	6 months
Bone and Joint	6 months (may be extended to 9 to 12 months)
Central Nervous System	9 to 12 months
Disseminated	6 months (may be extended to 9 to 12 months)
Genitourinary	6 months (9 months for BCG disease)
Pericardial	6 months

- Treatment duration with non-standard regimens or for drug-resistant TB are complicated and must be determined with specialist guidance.

REFERENCES

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