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Management of Pulmonary Tuberculosis in 2025: An Update for the Respirologist

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Background

Despite being a curable illness, tuberculosis (TB) remains the most common cause of death from an infectious agent, with a reported 10 million infections and 1.25 million TB-related deaths reported globally in 2023.[1] In Canada, the incidence of TB has remained at approximately 5.1 per 100,000 for many years.[2] However, foreign born and Indigenous populations are disproportionately affected by TB, with the Inuit population experiencing the highest TB incidence in Canada, at a reported rate of 70 per 100,000 in 2020.[3] Drug-resistant TB is reported in less than 10% of TB isolates in Canada, the majority being isoniazid mono-resistant. Multidrug-resistant TB (MDR-TB), defined as resistance to both isoniazid (INH) and rifampin (RIF), is detected in fewer than 4% of drug-resistant TB isolates in Canada.[3]

TB is caused by the *Mycobacterium tuberculosis* (MTB) bacillus, and is spread when people infected with TB aerosolize the bacteria through coughing, laughing, singing, or talking. Following initial infection, the risk of developing active TB disease is greatest in the first 2 years, then decreases significantly, with an estimated lifetime risk of approximately 10%.[4] In addition to several host factors, the risk of TB reactivation increases in the setting of immune suppression, including HIV infection, malignancy, organ or bone marrow transplant, and immunosuppressive treatments such as prednisone and tumour necrosis factor (TNF)-alpha therapy.[5] Prior to initiating treatments that may increase the risk of reactivation, latent TB infection should be considered and appropriate investigations performed.

Diagnosis

TB Infection

An estimated 2 billion people globally have latent tuberculosis infection (LTBI) and are at risk of reactivation of TB disease.[1] Screening is indicated for those who are deemed to have a higher risk of reactivation and in whom there is an intention to treat latent infection if positive. LTBI is diagnosed with either a tuberculin skin test (TST) or an interferon gamma release assay (IGRA). In most Canadian settings, the TST is favoured due to wider availability and lower cost. However, the TST can yield false positive results in individuals who have previously received the bacille Calmette-Guérin (BCG) vaccine,[6] making IGRA the preferred test in this population.[7] BCG vaccination is currently administered to children in over 100 countries and in some Indigenous communities, resulting in a high prevalence in the Canadian foreign-born population and many Indigenous Canadians.

TB Disease

Chest X-ray and other imaging modalities are used to screen for active TB disease. However, the diagnosis of TB disease relies on three technologies: microscopy (sputum smear), molecular testing including nucleic acid amplification testing (NAAT), and culture-based methods.

Sputum smear microscopy remains the standard first-line test for TB disease in Canada. Although its sensitivity is poor, yield improves when multiple samples are collected and sputum induction is used.[8,9] The Canadian TB guidelines recommend that at least three sputum samples be collected, ideally 5–10 mL each, as this increases the yield for both smear and culture.[10] In most Canadian laboratories, a positive sputum smear

TPT Regimen	Dose	Duration of Therapy	Adverse Events
Rifampin monotherapy (4R)	10 mg/kg daily (maximum dose 600 mg/day)	4 months	Bone marrow suppression, rash, drug-drug interactions
Isoniazid monotherapy (9H)	5 mg/kg daily (maximum dose 300 mg/day)	9 months	Peripheral neuropathy, hepatotoxicity
Rifapentine and isoniazid (3HP)	Rifapentine: 10–14 kg – 300 mg weekly 14.1–25 kg – 450 mg weekly 25.1–32 kg – 600 mg weekly 32.1–49.9 kg - 750 mg weekly >= 50 kg - 900 mg weekly (maximum dose 900 mg/week) Isoniazid 15 mg/kg weekly (maximum dose 900 mg/week)	3 months (12 doses)	Hypersensitivity reaction, bone marrow suppression, drug-drug interaction
Isoniazid monotherapy (6H)	5 mg/kg daily (maximum dose 300 mg/day)	6 months	Peripheral neuropathy, hepatotoxicity
Isoniazid and rifampin (3HR)	Isoniazid: 5 mg/kg daily (maximum dose 300 mg/day) Rifampin: 10 mg/kg daily (maximum dose 600 mg/day)	3 months	Peripheral neuropathy, hepatotoxicity, rash, drug-drug interactions

Table 1. TB Preventive Therapy (TPT) regimens and side effects; *courtesy of Natasha Sabur, MD, MPH, FRCPC*

triggers NAAT testing to confirm the presence of MTB DNA. In many Canadian settings, the high prevalence of nontuberculous mycobacteria may further reduce the specificity of sputum smear sampling for pulmonary TB,[11] making NAAT testing critical for rapidly identifying those who may require respiratory isolation. Globally, the Xpert MTB/RIF technology (Cepheid Inc, Sunnyvale, California, USA), an automated NAAT that has demonstrated superior accuracy compared to smear microscopy and additionally provides rapid genotypic drug resistance information, is recommended by the World Health Organization (WHO) as the first-line test for patients with suspected TB.[12] Although not widely available across Canada, Xpert MTB/RIF technology is used in many Northern communities, and other forms of NAAT technology are used in many Canadian mycobacterial laboratories.

Automated liquid culture is generally regarded as the gold-standard confirmatory test for diagnosing active TB disease. Once a TB isolate has been cultured, phenotypic drug susceptibility to all first-line TB medications can be performed. However, many laboratories employ other methods to detect mutations known to confer drug resistance (genotypic drug susceptibility testing), as these methods provide detection of drug resistance more quickly than phenotypic methods. The Canadian TB guidelines recommend rapid molecular testing to predict drug-resistant TB for all samples with a new positive NAAT or culture for TB.[10]

TB Preventive Therapy (TPT)

TPT, or treatment for latent TB infection, reduces the risk of progression from infection to active disease and is recommended for individuals at high risk for reactivation. A landmark randomized controlled trial in the 1960's established the efficacy of isoniazid (INH) monotherapy for TPT,[13] and for decades, 9 months of INH monotherapy was considered the gold standard for TPT. However, INH monotherapy has notable limitations, including poor treatment completion rates and a significant adverse event profile. **Table 1** provides information on TPT regimens and side effects.

Subsequent studies have successfully evaluated other LTBI regimens— including 4 months of daily rifampin (RIF)[14] and 3 months of weekly high-dose INH and rifapentine[15] — for non-inferiority against 9 months of INH, and these are now recommended for TPT. Although the Canadian TB guidelines recommend 3HP (INH

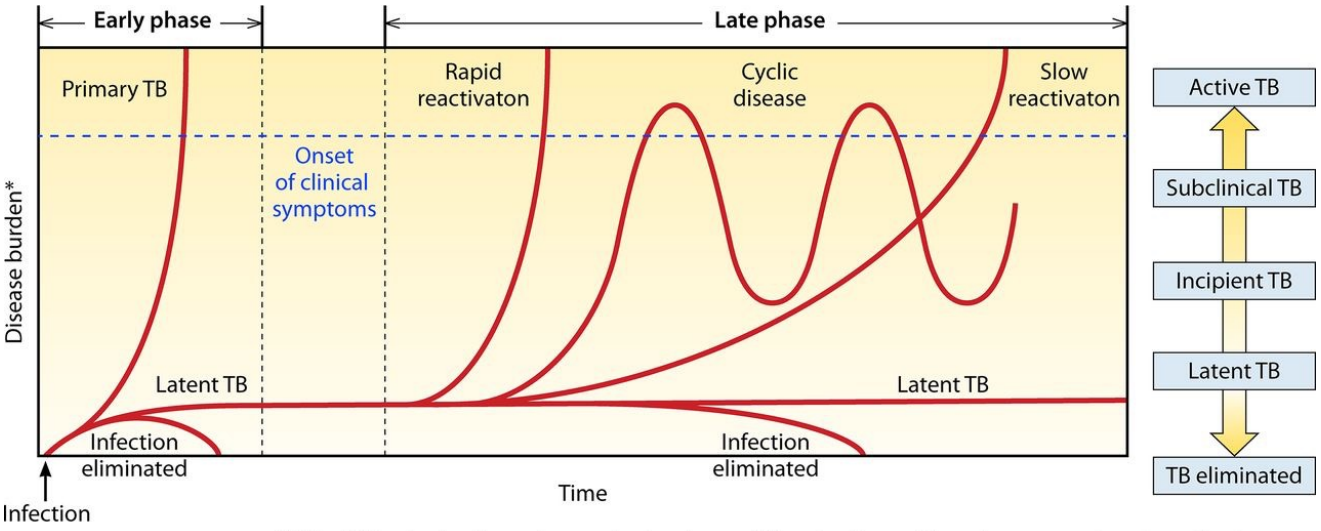

Figure 1. Pathways of tuberculosis disease progression. After initial exposure, *M. tuberculosis* may be eliminated by the host immune response, persist as a latent infection, or progress to primary active disease. Following the establishment of latent infection, disease may persist in a latent form, naturally progress in a slow or rapid fashion to active tuberculosis, or cycle through incipient and subclinical states before developing into symptomatic disease or eventual disease resolution. Although not all possibilities for regression of disease burden are depicted, spontaneous recovery may occur in any of these clinical trajectories; *used with permission from Drain, P. et al., 2018*

+ rifapentine) as the first-line TPT regimen,[16] rifapentine has not been approved by Health Canada, and significant drug access issues persist in many parts of Canada. An alternative regimen of 4 months of RIF is more widely used, with other treatment regimens considered when necessary.

Subclinical TB

Disease progression after infection has historically been divided into two forms: latent TB infection (asymptomatic, non-replicating bacteria, culture negative, non-infectious) and active TB disease (symptomatic, replicating bacteria, culture positive, infectious). We now have a better understanding of a more nuanced spectrum of TB infection, including a subclinical form of disease where patients are asymptomatic but harbour actively replicating TB bacilli with positive sputum cultures **(Figure 1)**. Radiographic findings in subclinical TB tend to be more subtle due to its paucibacillary nature, and since patients are asymptomatic, they may have more difficulty producing sputum for diagnosis. Furthermore, sputum smear and NAAT testing may have reduced sensitivity in subclinical TB resulting in delayed diagnosis.[17,18] TB prevalence data suggest that subclinical TB accounts for up to 50% of cases in endemic areas,[19] though its incidence in low burden settings such as Canada remains unknown. Emerging evidence suggests that subclinical TB may be intermittently infectious,[20] therefore contributing to community transmission and hampering global TB elimination efforts.

Treatment of TB disease

Drug-sensitive TB (DS-TB)

The recommended treatment regimen for drug-sensitive TB, developed more than four decades ago, consists of 6 months of rifampin (R) and isoniazid (H) with pyrazinamide (Z) added for the first 2 months and ethambutol (E) included until the isolate is known to be fully susceptible to first-line medications (commonly referred to as the HZRE regimen).

Although the standard 6 month regimen is safe and effective, its length is associated with nonadherence and loss to follow up, prompting efforts to shorten the duration of treatment for DS-TB. Several trials have attempted to reduce treatment duration with the addition of fluoroquinolones or with higher doses of RIF, however, none have shown non-inferiority to the HZRE regimen.[21-24] Rifapentine, a cyclopentyl derivative of rifampin with a longer half-life, has been evaluated in the context of treatment shortening. The TBTC Study 31/A5349, a randomized, open-label, phase 3 non-inferiority trial, demonstrated that a 4-month regimen consisting of isoniazid, rifapentine (P), moxifloxacin (M), and pyrazinamide (HPMZ) was non-inferior to the standard 6-month HZRE regimen in patients with DS-TB.[25] This regimen has been endorsed in international clinical practice guidelines as the first-line treatment for patients with drug-sensitive pulmonary TB in 2024.[26] In the Canadian setting, limited access to rifapentine has hindered broad uptake of this shorter-course treatment regimen. Additionally, there have been concerns regarding the high pill burden and poor tolerability of this regimen in clinical practice.[27] While research in this area continues, the standard 6-month HRZE regimen remains the gold-standard treatment for DS-TB.

Multidrug-resistant TB (MDR-TB)

Significant gains have been made in the treatment of MDR-TB. Previously, the standard treatment for MDR-TB consisted of up to 18 months of therapy, with significant toxicity and high rates of adverse events. Today, most cases of pulmonary MDR-TB can be treated with a 6-month, all-oral regimen known as the BPAL-M regimen, comprised of bedaquiline, pretomanid, linezolid, and moxifloxacin. This regimen is now endorsed by the WHO as the first-line treatment for MDR-TB.[28] Pulmonary MDR-TB is a rare disease in Canada, and treatment should be undertaken in consultation with a TB program experienced in managing drug-resistant TB.

Conclusions

TB continues to have a major impact on global health, and in Canada, continues to disproportionally affect the foreign born, Indigenous communities, and other vulnerable populations. Accumulating evidence suggests that subclinical TB may be an important contributor to TB transmission, though more research in this area is needed. Recent advances in the treatment of both drug-sensitive and drug-resistant TB may offer a more nuanced approach to treatment of pulmonary TB in years to come.

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