Queensland Health

Management of latent tuberculosis in adults

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An electronic version of this document is available at
https://www.health.qld.gov.au/__data/assets/pdf_file/0023/444425/latent-tb-adult.pdf

Please note: Updates after September 2023 are amended in the online Management of Latent Tuberculosis in Adults - Guideline Version 2.0 February 2023 **ONLY** – printed copies may not be current.

Contents

1 Background

Latent tuberculosis (LTB) is defined as a state of persistent immune response to *Mycobacterium tuberculosis* antigens as a result of previously acquired infection and without evidence of clinically manifested active tuberculosis (TB).[1] About a quarter of the world's population has latent TB (LTB).[2] By traditionally accepted estimates, approximately 5–10% of people with LTB will develop active TB in their lifetime, one half within the first 2 years following infection. The period of highest risk is within the first year following an individual's infection.[3]

Early management of TB transmission is an important part of a TB elimination strategy in a low incidence country such as Australia.

Testing for LTB is undertaken in individuals at risk for active TB and who might benefit from preventative therapy. Selective testing and treatment of LTB in high-risk groups, together with active case finding, is part of the strategic plan for control of TB in Australia.

2 Target audience

This guideline documents recommendations of the Tuberculosis Expert Advisory Group for the diagnosis and management of latent tuberculosis in adults. It is intended as a resource to ensure consistent best practice by doctors and nurses who manage tuberculosis in Queensland. Medical practitioners who are inexperienced in TB medicine should adhere to this guideline and are encouraged to discuss individual case management with a medical officer experienced in TB diagnosis and care.

The recommendations are aligned with the World Health Organization (WHO) Guidelines on the management of LTB infection.[6]

3 Who to test for LTB

Testing for latent tuberculosis should be directed at individuals who are likely to have acquired TB infection and who have an increased risk of progressing from latent to active disease. Testing for LTB should be performed with the intention of offering treatment.

Those at increased risk of acquiring TB are:

- close household or other close contacts* of an active case of TB with the highest risk occurring where the index case has smear positive pulmonary TB
- individuals from communities or countries with high TB burden
- residents of certain Aboriginal and Torres Strait Islander communities
- migrants, including refugees from high TB burden countries (defined as a WHO incidence of >40 per 100,000 population)
- some health care workers with direct patient contact, especially where aerosol generating procedures are undertaken

- laboratory workers performing *M. tuberculosis* cultures
- mortuary staff performing high risk procedures.

Persons at increased risk of progression from latent to active TB are:

- those who have acquired their infection recently, within 2 years e.g. household contact of an index case, recent migration from or prolonged travel to, a high TB burden country
- younger age – less than 5 years and especially less than 2 years of age (see Management of Latent Tuberculosis in children under 14 years of age)
- immunocompromised status, including HIV infection and inherited immunodeficiency syndromes
- immune suppressive drug treatment (TNF alpha inhibitor therapy, post organ and bone-marrow transplant, long term corticosteroid therapy i.e., >15mg/d for >1 month)
- other medical conditions (diabetes mellitus, chronic kidney disease, silicosis, surgery (gastrectomy or jejuno-ileal bypass), other disseminated malignancies (haematological, head & neck, lung)
- smokers, malnutrition, alcohol abuse
- CXR abnormalities suggesting healed TB in patients without previous full treatment:
  - fibrotic pulmonary lesions more likely to reactivate; pleural thickening and discrete granulomas (particularly if calcified) are less likely to reactivate.
- all nursing and medical consultations, as well as tests and treatment, are provided without any out of pocket expense in the public health sector.

** Close contact is defined as household contact or 8 hours cumulative contact in same room.*

4 Diagnosis

LTB is diagnosed by detection of cell-mediated, delayed hypersensitivity to *Mycobacterium tuberculosis* via the Tuberculin Skin Test (TST) or by interferon gamma release assay (IGRA). A significant (TST) or positive (IGRA) result for either test must be interpreted based on the pre-test probability of infection with tuberculosis, and the likelihood of progression to disease if infected.

Limitations of TST

Non-specific sensitisation with non-tuberculous mycobacteria (NTM) or previous exposure to the Bacille Calmette-Guerin vaccine (BCG), especially when administered after infancy or more than once, can cause a positive TST response. BCG vaccination does not cause false positive IGRA results, and therefore IGRA may be the preferred test in individuals who have been BCG vaccinated, especially if vaccination has been administered within the previous 15 years, or after the age of one year. Use of IGRA also reduces the number of healthcare visits required for screening.

Both tests have imperfect sensitivity and can't be used to exclude LTB. False negatives may occur where testing has occurred very soon after infection. Either test can be used to diagnose LTB in adults in Queensland with choice of test determined by availability, patient-centred considerations, BCG administration history, and skin integrity (regarding site of TST injection). Acceptable IGRA tests include Quantiferon Gold Plus™ and TSpot test™.

Test limitations in the setting of immunosuppression

The significance of a TST or IGRA result depends on the medical history, risk factors for exposure and likelihood of progression to active disease (see Table 1). The sensitivity of the TST and IGRA may be reduced in the very young and in immunocompromised, particularly those with T cell immunodeficiency such as HIV.

Medications and comorbidities (including severe COVID-19 infection) that cause immunosuppression may result in an indeterminate IGRA test result. Input from a clinician experienced in the management of tuberculosis may be required.

In an immunocompromised patient, consideration should be given to sequentially administering the TST and IGRA test if the initial test is negative. If either of the 2 tests is positive, then further assessment will be required.

5 Clinical assessment

5.1 Rule out active TB disease

Prior to a diagnosis of LTB and before treatment for LTB is commenced, active TB disease must always be ruled out. This will usually require the person to be asymptomatic with either a normal chest x-ray (CXR) or an abnormal CXR that is stable over time (ideally at least 12 months).

Medical assessment and history

Concerning symptoms include:

- cough, for more than 2 weeks
- haemoptysis
- fever
- night sweats
- unexplained weight loss.

An absence of symptoms does not exclude active TB.

Physical examination (e.g., low body weight/cachexia, lymphadenopathy, clinical signs of chronic pneumonia, pleural effusion, fever).

Investigations

CXR

A CXR should be performed for all patients with a significant TST or IGRA result (see Table 1 Interpretation of TST cut-offs for adults and children 5 years of age and older), looking for changes suggestive of active TB. Look for changes of CXR abnormalities over time (if scarring present, ideally be able to demonstrate 12 months of stability of scarring) except where more expedient management is indicated (see below)

Sputum

If there is clinical suspicion or CXR indications of current/previous TB infection, 3 sputum specimens (induced or spontaneous) should be collected on 3 consecutive days including at least one early morning specimen. All specimens should be tested for acid-fast bacillus (AFB) smear and culture +/- Xpert MTB/RIF for molecular detection of TB and the presence of rifampicin resistance.

Other

Other imaging as required (e.g., CT imaging) to assess lung fields, mediastinum or other organs.

5.2 Assessment and management of contacts of TB cases

TST or IGRA are both acceptable as part of the initial risk assessment. IGRA may be preferred where the individual has a history of multiple BCG vaccinations or was vaccinated after the age of one year. If the TST is significant or IGRA is positive, and active TB is excluded, then TB preventive treatment (TPT) should be considered. If initial TST or IGRA is negative, and the contact with active TB was less than 8 weeks ago, repeat testing should be undertaken 8 weeks after contact as early infection may yield a negative TST or IGRA result. If there is TST or IGRA conversion, then TPT should be offered. If TST or IGRA remains negative, the likelihood of LTB is low, and the patient can be reassured and discharged if clinically appropriate.

Pregnancy is not an absolute contraindication to treatment for LTB but the potential risks to mother and foetus from medication must be taken into consideration. A medical assessment should be considered to assess the risk of exposure in this setting as routine treatment of LTB is not recommended. Re-evaluation and consideration of TPT may be considered in the post-partum period (see Management of tuberculosis in pregnant women and newborn infants).

The drug susceptibility profile of the index case with active TB should be confirmed prior to selecting the antimicrobial agent for TPT, as the presence of resistance to isoniazid or rifampicin in the index case will guide the therapeutic choice for the contact with LTB.

Older age is not a contraindication to treatment for LTB. The potential for treatment-related toxicity needs to be balanced against the risk of progression to active disease, on a case-by-case basis. Whilst rifampicin may be the preferred treatment option in many cases, use may be precluded on the basis of drug interactions with other essential medications. The risk of hepatotoxicity from isoniazid increases with advanced age, so the benefit of treatment with isoniazid must then be weighed up against the risk of toxicity in older individuals. In particular, hepatoxicity (see below) with isoniazid is rare in patients <35 years of age, more common but still low risk in those between the ages of 35 and 50 and increases beyond 50 years of age.

Immunocompromised patients

Close contacts* of smear positive pulmonary TB should be offered LTB treatment.

TST and/or IGRA should be considered, however, are not necessarily required for immunocompromised close contacts of individuals with smear positive pulmonary TB. TPT may be offered to highly vulnerable contacts without TST or IGRA following careful risk assessment, taking into account the exposure intensity, index case characteristics, and patient factors.

** Close contact is defined as household contact or eight hours cumulative contact in same room.*

5.3 Assessment and management of patients who have lived in high TB burden countries (without identifiable contact)

Persons who have migrated from high TB burden countries (including refugees) or have lived in such countries for a prolonged period (>3 months) may have acquired latent TB. There may be a significant risk of progression to active TB disease, especially in the first 2–3 years after arrival or return to Australia, but a small yearly risk persists thereafter.

Diagnostic tests for LTB should be used as outlined above. The decision to test and treat migrant persons depends not only on the chance of infection based on TB burden of country of origin (or previous residence), but also on the presence of risks for progression to active disease, and the likely benefit from preventive treatment based on the comorbidities and age of the individual.

Several validated risk calculators are available online, and may assist with risk assessment, patient counselling, and decision making.*

Programmatic activities to perform LTB screening in migrants needs to consider such factors to ensure any initiatives are likely to be cost effective.

**Whilst there are several online calculators available, the McGill University Health Centre Online TST/IGRA interpreter https://www.tstin3d.com/en/calc.html can be recommended.*

5.4 Tuberculosis Preventative Therapy (TPT)

The risk of developing active TB may be reduced by treatment for LTB. Treatment choice should be based on individual patient preference, comorbidities, current medications, and likelihood of adherence to a daily treatment regimen. Shorter treatment courses are associated with improved adherence rates.

Rifamycin-based treatment courses are shorter, associated with improved completion rates, and potentially reduced healthcare cost due to fewer clinic visits for treatment supervision. Such regimens are rifampicin monotherapy daily for 4 months and combination rifapentine and isoniazid weekly for 12 weeks. Isoniazid monotherapy for 6 months has a long history of being an effective preventative regimen but with an increased risk of adverse reactions in older age groups compared to rifampicin. Some clinicians favour a 9 month isoniazid regimen duration although the incremental benefit over the 6 month duration may be limited in most cases. Isoniazid is favoured when drug-drug interactions with rifampicin are problematic (e.g., warfarin, protease inhibitors, hormonal contraception, and many others).

TPT options are outlined below. Drug doses listed are for adult patients only; please refer to the Queensland Health paediatric treatment guidelines Management of Latent Tuberculosis in children under 14 years for paediatric treatment and dosing recommendations.

Published product information should always be consulted to ensure a complete list of adverse events, drug interactions and contraindications for any of the agents recommended in this guideline.

4R	Rifampicin monotherapy, daily administration, for 4 months
3HP	Rifapentine plus isoniazid weekly for 3 months
3HR	Isoniazid plus rifampicin, daily administration, for 3 months
6H	Isoniazid monotherapy, daily administration, for 6 months

Rifampicin monotherapy, daily administration, for 4 months [4R]

Rifampicin is prescribed at a dose of 10mg/kg to a maximum of 600mg daily. Rifampicin monotherapy is associated with a reduced risk of hepatotoxicity, in comparison with isoniazid based TPT options. Rifampicin monotherapy may be the preferred option where a shorter treatment course is favoured, or in the presence of factors that confer an increased risk of hepatotoxicity with isoniazid use (age >35, history of liver disease, regular use of alcohol, chronic liver disease). Side-effects from rifampicin may include a flu-like syndrome, hypersensitivity reactions, gastrointestinal intolerance, bone marrow suppression, and hepatotoxicity.

A careful medication history is required prior to prescription of rifampicin, due to the potential for significant drug-drug interactions. Female patients of childbearing age should be advised that hormonal forms of contraception including the oral contraceptive pill, Mirena® (levonorgestrel-releasing intrauterine system) and Implanon NXT® contraceptive implant are unreliable during use and for 3 weeks following cessation of Rifampicin.

Rifapentine plus isoniazid weekly for 3 months [3HP]

This regimen offers effective convenient therapy especially when administered in fixed dose combination formulation. At the time of guideline publication, rifapentine is not registered on the Australian Register of Therapeutic Goods and hence requires approval under the Special Access Scheme administered by the TGA. While loose tablets of isoniazid (9 x 100mg = 9 tablets) and rifapentine (6 x 150mg = 6 tablets; for adults >= 50kg) present a significant pill burden per dose, combination tablets are available from the Global Drug Facility with each tablet containing 300mg rifapentine and 300mg isoniazid. Doses for body weight less than 50kg are published by the US CDC (Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020 | MMWR). Adverse effects are similar to rifampicin and isoniazid when used in other regimens. Weekly administration may be given with direct observation, or as self-administered therapy depending on an assessment of likely adherence.

Isoniazid plus rifampicin, daily administration, for 3 months [3HR]

Dosing of isoniazid and rifampicin is the same as for monotherapy.

Isoniazid monotherapy, daily administration, for 6 months [6H]

Isoniazid is prescribed at a dose of 5mg/kg up to a maximum 300mg daily.

Isoniazid monotherapy may be the preferred regimen where important drug-drug interactions are expected to contraindicate or complicate rifampicin use. Clinical trial data suggests there is a small additional risk reduction where the treatment course is extended from 6 – 12 months in subjects with stable scarring on CXR. It has long been accepted from a re-analysis of that data that 9 months may be the preferred duration. However, in most instances, 6 months duration is effective and safe.

The main side effect of Isoniazid treatment is hepatotoxicity, which ranges in severity from asymptomatic derangement of liver enzymes (common) to fulminant hepatic failure (rare). The important symptoms of drug toxicity (including nausea, vomiting, abdominal pain, jaundice or unexplained fatigue) must be explained to the patients prior to commencing treatment.

Universal prescription of vitamin B6 for individuals taking isoniazid is no longer recommended. Patients taking isoniazid who have an increased risk of peripheral neuropathy should be offered vitamin B6 at a dose of 25mg daily. This includes patients with diabetes mellitus, HIV infection, renal failure, chronic excessive alcohol consumption, and those who are pregnant and/or breastfeeding. Rarely, other neurological manifestations can occur including optic neuropathy.

5.5 Monitoring during treatment for LTB

Routine blood test monitoring is not universally indicated for patients receiving TPT, but the need for baseline and monitoring tests should be considered on an individual patient basis.

Patients with a history of liver disease, regular use of alcohol, chronic liver disease, HIV infection, age >35 years, pregnancy or in the immediate postpartum period (within 3 months of delivery) should have baseline liver function tests. If abnormal at baseline, a hepatitis screen should be performed.

Patients receiving rifampicin should have a baseline liver function test where the above risks exist, and consideration given to full blood count baseline and monitoring.

Patients should receive verbal and written counselling detailing possible side effects, when to stop treatment, and when to contact clinic staff. Patients should be provided with contact details for the clinic that has facilitated TPT.

Patients on treatment for LTB should be reviewed no later than 4 weeks after commencement of treatment. Regular reviews should occur thereafter at the discretion of the treating clinician based on clinical need up to and including treatment completion.

At each outpatient clinic:

- assess adherence
- evaluate for signs and symptoms of active TB and drug reactions
- remind patients of signs and symptoms of hepatotoxicity and peripheral neuropathy
- perform LFTs if there is clinical concern for hepatotoxicity
- ensure that patients have contact details for the prescribing clinic.

Patients who should be considered for more frequent review include those:

- aged over 35 years (especially if age > 50 years)[13]
- a history of daily alcohol intake, abnormal baseline LFT, chronic liver disease, or in receipt of hepatotoxic medications
- where there are concerns regarding adherence
- HIV infection or other immunocompromised status
- where the patient develops side effects from the medication(s).

Liver function test derangement on therapy

If a patient is symptomatic, treatment should be discontinued if aminotransferase values are 3 times the upper limit of normal. If the patient is asymptomatic, therapy should be ceased if aminotransferases exceed 5 times the upper limit of normal. When hepatotoxicity has abated, a 4 month regimen of rifampicin monotherapy would be appropriate if the hepatotoxicity was associated with isoniazid administration. If rifampicin was used initially, singly or with isoniazid, cautious reintroduction can be considered.

Patients with LTB who are close contacts of individuals with MDR TB

If the index case of a close contact has MDR TB, there is no national or international consensus on whether to treat or what agents to use. In those individuals at greatest risk for disease progression, preventative treatment should be considered with reference to the document Management of contacts of multidrug-resistant tuberculosis.

Missed doses

In the event of treatment interruption, extend treatment by the time missed to compensate if interruption is less than one month. If Interruption is > 1 month in the first 3 months of treatment, recommence the whole course again and ensure future compliance.

6 Surveillance

6.1 Following completion of TPT

Patients who have completed a satisfactory course of treatment for LTB do not require ongoing surveillance. They should be educated regarding symptoms of TB disease, given that even where there has been excellent adherence to TPT, risk of TB disease is not totally eliminated.

6.2 Patients who decline TPT or are not suitable

It is important that these patients are educated regarding symptoms of TB disease. In this situation surveillance is recommended with clinical and radiological checks to monitor for early symptoms and signs of TB for the period of highest risk (2 years) following TB contact or arrival from a high TB burden country. This is recommended 6 monthly (clinical review and CXR) to complete a minimum of 2 years of follow-up. There is a lower yield to follow up beyond 2 years. There should be clear communication with general practitioners to ensure that the diagnosis of LTB is clearly documented in the patient's clinical record.

7 Re-exposure following TPT

If patients diagnosed with latent TB are re-exposed through contact with a case of active TB, there is no value in repeating the tests for LTB. In immune-competent adults, there is evidence that a first episode of TB infection (not disease) provides approximately 80% protection against development of disease following re-exposure,[14] irrespective of previous LTB therapy. Therefore, a second course of TPT is generally not recommended, even if the exposure was close/intense.[15] However, in children under 5 years of age or those with HIV infection (there may not be any effective immunity conferred by prior TB infection), then it is recommended to repeat the full course of TPT.

8 Serial TST testing and conversions

Serial testing occurs to identify a new TB infection after a recent exposure in the context of a contact investigation or in populations with increased risk of exposure e.g., healthcare workers in certain settings.

A TST conversion is indicated when the initial TST reaction is insignificant and the repeat TST reaction is significant (see Table 1). When change in TST diameter is incorporated into the overall assessment a change of at least 6mm is considered significant. Anyone with a TST > 10mm has a higher likelihood of TB infection.[16]

As IGRA testing is more specific for TB infection it may be a useful supplementary test.

9 Classification of significant TST reactions

Table 1 Interpretation of TST cut-offs for adults and children 5 years of age and older

≥5 mm	≥10 mm*	≥15 mm
HIV infected	Close contact of active TB case regardless of BCG	No TB risk factors/normal host
Immunosuppressed#	Travel to a high incidence country for a period of > 3 months^	
	Those at increased risk of TB exposure or greater host susceptibility+	

(National Tuberculosis Advisory Committee (NTAC), 2017)

 # Receiving immunomodulators, chemotherapy, ≥ 15mg prednisone/day for more than one month, or organ transplantation.

**In those who are BCG naive or are at increased risk for TB exposure or infection, and patients are reluctant for LTB treatment, consider IGRA as a supplementary test.*

^Travel—someone who has travelled to a high incidence country, or countries, for a period of more than 3 months (> 40/100,000). For country profiles see: http://www.who.int/tb/publications/global_report/en/

+ Increased likelihood of infection due to immigration from high incidence country (> 40/100,000), or host factors, such as, diabetes, chronic renal failure, neoplastic disease and malnutrition.

10 Supporting documents

World Health Organisation

Guidelines on the management of latent tuberculosis infection

Communicable Diseases Network Australia

CDNA National Guidelines for the Public Health Management of TB

CDC

Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020 MMWR Feb 14 2020

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Approval and implementation

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2.0	May 2023	May 2025		Minor updates in terminology reference LTB and TPT. Inclusion on new regimens. Update on LTB testing types