Management of Latent Tuberculosis in Adults

Guideline

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Queensland Government

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1. Background

Latent tuberculosis (LTB), defined as a state of persistent immune response to prior-acquired *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active tuberculosis (TB)[1], affects about one-third of the world's population[2]. Approximately 10 per cent of people with LTB will develop active TB disease in their lifetime, with the majority developing it within the first five years after initial infection[3].

The period of highest risk is within the first year following primary infection[4]. Detection of LTB is undertaken in individuals at risk for active TB in whom active disease has been excluded and for whom preventive therapy is indicated. Early management of TB transmission is an important part of a TB elimination strategy in a low incidence country such as 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 but also 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
    a. certain Aboriginal and Torres Strait Islander communities
    b. migrants, including refugees from high TB burden countries (generally defined as a WHO incidence of >40 per 100,000 population)
- health care workers
- Mycobacteriology lab workers, mortuary staff performing autopsies.

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 Guidelines for management of LTB in children)
- 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 relapse; pleural thickening and discrete granulomas (particularly if calcified) are less likely to relapse.

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). The interpretation of the TST or IGRA reaction is based on the likelihood of the person being infected with TB as well as the likelihood of progression to disease if infected. The risk of true TB infection, rather than non-specific sensitisation with non-tuberculous mycobacteria (NTM) or Bacille Calmette-Guerin (BCG) vaccination is assessed individually taking into account the person's likelihood of exposure to TB.

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. TST remains the recommended test for diagnosis of LTB in Queensland. IGRA tests (Quantiferon Gold in tube™ and TSpot test™) are acceptable alternatives. Unlike the TST, BCG vaccination does not cause false positive results with IGRA tests. IGRA tests may be the preferred test in individuals who have been BCG vaccinated, especially if vaccination has occurred within the previous 15 years[7]

The significance of a TST result depends on the medical history, risk factors for exposure and likelihood of progression to active disease (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. In immunocompromised, consideration should be given to sequential TST and IGRA testing if the initial TST is negative. If either test is positive, then further assessment will be required.

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).

5. Clinical Assessment

5.1. Rule out active TB disease

- Medical assessment and history. Concerning symptoms include:
  - cough, for more than 2 weeks
  - haemoptysis
  - fever
  - night sweats
  - unexplained weight loss.
- Physical examination (e.g. low body weight/cachexia, lymphadenopathy, pleural effusion, fever)
- Investigations:
  - CXR

    A CXR should be performed for all patients with a significant TST or IGRA result (see Table 1), 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, three sputum specimens (induced or spontaneous) should be collected on three 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 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 should be done as part of the initial risk assessment. If the TST/IGRA is positive, and active TB is excluded, then LTB treatment should be offered. If initial TST/IGRA is negative, and the contact with active TB was less than eight weeks ago, repeat testing should be undertaken in eight weeks after contact as early infection may yield a false negative TST or IGRA result. If there is TST or IGRA conversion, then LTB treatment 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.

Older age is not an absolute contraindication to treatment for LTB, but should be considered taking into account the higher risk of toxicity with advanced age. The benefits of treatment 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[13]. This needs to be balanced against the exposure risk in conjunction with the risk of progression to active disease, on a case by case basis.

Immunocompromised patients

Close contacts* of smear positive pulmonary TB should be offered LTB treatment. TST/IGRA testing is not necessarily required depending on the clinical assessment of risk. Sequential IGRA/TST may be of benefit where contact is casual or index case has extrapulmonary disease only.

* 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. Diagnostic tests for LTB should be used as outlined above. Testing and treatment for migrant persons depends not only on the chance of infection based on TB burden of country of origin (or previous residence) but on the presence of risks for progression to active disease. Any programmatic activities to perform LTB screening in migrants needs to consider such factors to ensure any initiatives are likely to be cost effective.

5.4 Treatment for LTB

The risk of developing active TB may be reduced by treatment for LTB.

The preferred treatment is 9 months of **isoniazid** (5mg/kg up to a maximum 300mg daily). In Queensland all patients are also offered supplementation with pyridoxine (vitamin B6) 25mg to be taken daily with isoniazid.

6 months of isoniazid monotherapy can also be used as an alternative, though less efficacious regimen.

Isoniazid + Rifampicin in combination for 3 months is another acceptable alternative with probable similar efficacy to isoniazid in terms of effectiveness and safety[9-12].

Rifampicin monotherapy is an alternative regimen (Rifampicin 10mg/kg, up to 600mg/d) for 4 months. Evidence is limited to observational data and a single trial in silicosis patients[8] but this regimen may be useful in those with intolerance of isoniazid, or in contacts of patients with known isoniazid resistant infection.

Rifapentine is not currently available in Australia hence a 3 month course of isoniazid plus rifapentine, administered weekly (12 doses), is not a therapeutic option.

Prior to initiating treatment for LTB, baseline liver function tests (LFTs) are recommended. If abnormal at baseline, a hepatitis screen should be performed. After the baseline testing follow-up LFT is then recommended within 4 weeks of commencing therapy, with further monitoring after this as indicated (e.g. high risk of hepatotoxicity, advanced age).

The main side effect of isoniazid-based treatment is hepatotoxicity. The important symptoms of drug toxicity (including nausea, vomiting, abdominal pain, jaundice or unexplained fatigue) must be explained to the patients prior to obtaining consent to commence treatment. Drug interactions and contraindications are complex and available from MIMS and other resources.

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.

All nursing and medical consultations, as well as tests and treatment, are provided free of charge in Queensland.

Missed doses: In the event of treatment interruption, extend treatment by the time missed to compensate.

- Interruption of <1 month is probably not significant. Ensure the complete course is taken.
- Interruption for >1 month in the first three months of treatment: recommence the whole course again and ensure future compliance.

5.5 Monitoring during treatment for LTB

Patients on treatment for LTB should be reviewed by a no later than four weeks after commencement of treatment. Subsequent appointments should then be after 2 to 3 months (0, 1, 3, 6, and 9 months) for low risk candidates.

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.

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.

Note: If a patient is symptomatic, treatment should be discontinued if aminotransferase values are **three times** the upper limit of normal. If the patient is asymptomatic, therapy should be ceased if aminotransferases exceed five times the upper limit of normal. When hepatotoxicity has abated, a four 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.

6. Surveillance

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.

If patients decline the recommended LTB prophylactic therapy they need to be 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). This is recommended 6 monthly (clinical review and CXR) to complete a minimum of 2 years of follow-up.

7. Re-exposure following LTB treatment

If patients 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 per cent protection against development of disease following re-exposure[14], irrespective of previous LTB therapy. Therefore a second course of LTB treatment is generally not recommended, even if the exposure was close/intense[15]. However, in children under five 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 LTB therapy.

8. Classification of significant TST reactions

Table 1 Interpretation of TST cut-offs for adults and children five 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/regardless of BCG
Immunosuppressed #	Travel to a high incidence country for a period of >3 months^	
	Those at increased risk of TB exposure or greater host susceptibility+	

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 three 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.

9. Supporting and related 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

Revision history

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	March 2016	March 2018	

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