Diagnosis and management of latent tuberculosis infection

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Latent tuberculosis infection (LTBI) is an important management issue, particularly in patients born in countries with a high prevalence of TB. Early treatment can prevent active TB presenting and new techniques are now available to assist with the diagnosis of LTBI.

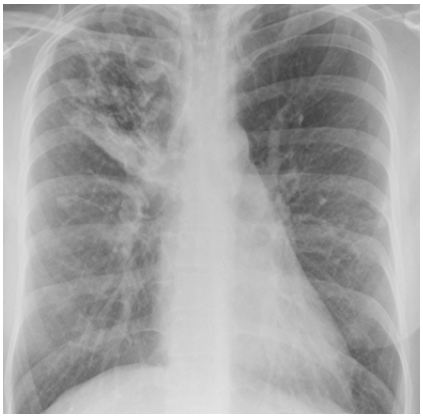

Figure. Chest x-ray showing active pulmonary tuberculosis.

Although the incidence of active tuberculosis (TB) in Australia has fallen dramatically since the 1960s, it has slowly increased over the past decade, predominantly occurring in people born overseas.[1] Worldwide, an estimated 8.8 million cases of and an estimated 1.6 million deaths related to TB occur each year.[2] However, these figures are dwarfed by the estimated two billion people who have clinically silent infection with *Mycobacterium tuberculosis*. This number represents about one-third of the world's population, the great majority of whom come from developing countries.

Patients with latent TB infection (LTBI) are at risk of developing active TB in the future, and treatment with a single antituberculous drug (usually isoniazid) can reduce this risk. Diagnosis and treatment of LTBI is often not feasible in the developing world, but it is undertaken in selected populations in more affluent countries. The local relevance of LTBI is that ongoing immigration from countries with a high prevalence of TB means that significant numbers of people enter Australia with LTBI, and LTBI screening may be required for groups such as healthcare workers. Accordingly, an understanding of the principles of the pathogenesis, diagnosis and treatment of LTBI, an awareness of indications for LTBI screening and the available tests, and an understanding of when to refer for ongoing specialist management is needed.

What is latent tuberculosis infection?

Infection with *M. tuberculosis* results from the inhalation of tubercle bacteria produced by a person with active pulmonary TB. Once inhaled, tubercle bacilli enter the lungs and spread to other sites in the body. If this primary infection is not controlled by an effective immune response, symptomatic pulmonary or extrapulmonary TB may occur at this time, but this is uncommon. The more usual course of events is that a successful immune response leads to formation of an encasing complex (granuloma) and scar that stops further replication and spread of organisms and prevents the development of clinical illness. Within the granuloma, tubercle bacilli can stay dormant for decades, a stage known as LTBI. The flowchart on page 73 shows the natural history of TB infection.

Although the great majority of people with LTBI (more than 90%) will remain asymptomatic for life, LTBI can reactivate into clinically active TB at any stage, particularly in the setting of immunosuppression or advancing age. This means that even patients with a childhood exposure to TB remain at risk throughout their lives, highlighting the importance of appropriate diagnosis and management of patients with LTBI.

Who should be tested for latent tuberculosis infection?

There are several situations that may warrant investigation for LTBI, some of which occur in the general practice setting. Some people may be screened because of an increased risk of contracting TB, while others may need screening for procedural reasons, such as pre-occupational requirements.

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Migrants and refugees from countries with endemic tuberculosis

People in Australia who are most likely to have a high risk of past TB exposure are those who have emigrated from or spent considerable time in countries known to have a high prevalence of TB. As part of the Australian immigration health screening process, migrants, refugees and applicants for certain categories of visa are required to have a chest x-ray for exclusion of active pulmonary TB (Figure). However, routine premigration screening for LTBI is not currently undertaken in any person applying to enter Australia as a resident.

Newly arrived refugees are one group for whom LTBI screening should be considered because their living conditions prior to arrival in Australia often place them at particularly high risk of TB exposure. Guidelines recently issued by the Australasian Society for Infectious Diseases recommend routine LTBI screening for refugees, ideally within two months of their arrival in Australia.[3] GPs are often the first point of contact for newly arrived refugees, and are ideally placed to offer testing for LTBI or organise appropriate referral.

Healthcare workers and students

Now that Bacille Calmette Guérin (BCG) vaccination is no longer routinely given to healthcare students or healthcare workers, universities and employers such as hospitals may require these groups to undergo routine screening for LTBI prior to commencement of studies or employment. A program of regular LTBI testing may also be required for those hospital staff who are at risk of ongoing occupational exposure to TB. Screening may be conducted by the institutional health service or institutions may enter into agreements with local GPs to provide this service.

Contacts of a patient with pulmonary tuberculosis

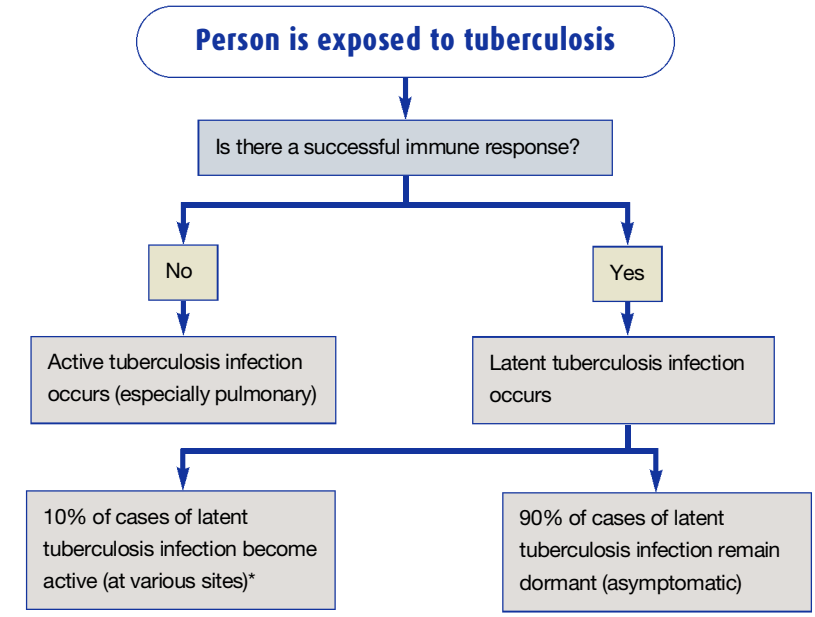
Screening for LTBI in people who are known or suspected to have been recently exposed to TB is a key element of the public health TB response. Those requiring screening may include household contacts of active pulmonary TB cases, as well as healthcare workers with exposure to patients with suspected active TB. LTBI screening in these situations is the responsibility of public health authorities (or involved hospitals).

People who present to a GP requesting screening after a potential TB exposure should be referred to the public health TB program via the departments of health in each state. This ensures that a consistent approach to contact tracing is adopted for each case.

Immunosuppressed patients

Immunosuppression is associated with an increased risk of TB reactivation and screening for LTBI may be considered in patients who are already immunosuppressed (e.g. those with HIV infection) or who are preparing for immunosuppression (e.g. before chemotherapy, taking high-dose corticosteroids or undergoing therapy with tumour necrosis factor inhibitors). This screening will normally be performed at specialist centres in conjunction with management of the immunosuppressive condition, and is unlikely to be required in a general practice setting.

The natural history of tuberculosis infection



* Approximate lifetime rates quoted. Increased rates of activation occur in patients with immunosuppression (e.g. HIV infection, advanced age, chemotherapy).

What tests are available to diagnose latent tuberculosis?

It is important to realise from the outset that there is no 'gold standard' test for the diagnosis of LTBI. No single investigation is sufficient to diagnose or exclude TB infection.

Tuberculin skin test

Since the early 1900s, the diagnosis of LTBI has been made by testing patients' immunological response to tuberculous antigens. The tuberculin

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Table 1. Pros and cons of tuberculin skin test and interferon-gamma release assay

Tuberculin skin test	Interferon-gamma release assay
Pros	
• Long experience of use • No pathology laboratory required • Inexpensive	• Specific for *Mycobacterium tuberculosis* • Objective result • Can be repeated without affecting result • Single clinic visit only • Mitogen and control allow assessment of immune adequacy
Cons	
• False positives with previous BCG vaccination, exposure to other mycobacteria • False negatives with immunosuppression or active disease • Needs follow-up visit • Multiple tests may induce 'booster effect'	• Need for venepuncture • Limited experience of use in some groups (e.g. children) • Requires laboratory access • Increased cost

ABBREVIATION: BCG = Bacille Calmette Guérin.

skin test (TST), applied by the Mantoux method, consists of an intradermal injection of tuberculin purified protein derivative, with the strength of immunological reaction measured by the size of induration generated at the injection site.

TST has been used for the diagnosis of LTBI for over a century but has a number of limitations. False positives can be caused by previous BCG vaccination or exposure to environmental (atypical) mycobacteria. False negatives are seen with severe systemic illness (including TB itself) and immunosuppression.[4]

Interferon-gamma release assay

The limitations of the TST have led to the development of alternative immunological methods to test for TB exposure, in particular the interferon-gamma release assays (IGRA).

The most widely available IGRA in Australia is the Quantiferon Gold In-Tube assay. In this test, a patient's blood sample is collected in tubes coated with TB-specific or control antigens, and the immunological response is measured by the amount of interferon-gamma released from peripheral blood mononuclear cells after incubation.

IGRA testing has a number of advantages over TST in the diagnosis of LTBI. The antigens used are specific for *M. tuberculosis*, eliminating false-positive results from BCG vaccination or exposure to other mycobacteria. The test can be performed on a single visit, without the follow up that is required to read the TST, and local complications of TST are eliminated. In addition, an easily quantifiable result is produced, rather than the significant inter-reporter variability associated with measurement of the TST. Finally, the inclusion of control tubes means that false-negative results due to immunosuppression can be identified, reducing the uncertainty associated with negative TST results in immunosuppressed patients.

Although neither TST nor IGRA provides a definitive diagnosis of LTBI, the tests are similar in terms of sensitivity in most situations. Table 1 lists advantages and disadvantages associated with each method. Overall, the convenience and ease of use of IGRAs means that they are increasingly being used as an alternative to TST in many settings, although TST continues to be used widely.

We now routinely use IGRA in the investigation of LTBI, and are comfortable in substituting it where pre-existing guidelines recommend TST. However, a significant disadvantage of the Quantiferon Gold In-Tube test is that a Medicare rebate is not currently available unless the patient is immunocompromised. Both TSTs and IGRAs usually remain positive following treatment of either LTBI or active TB and therefore should not be used as 'tests of cure'.

Radiology

Patients with a negative TST or IGRA results do not usually require a chest x-ray, unless they are at particularly high risk of TB. In patients with LTBI, the chest x-ray is usually normal or shows minor changes such as nodules, linear scars or pleural thickening.

How should a patient with a positive screening test be managed?

As indicated above, a positive screening test does not in itself prove that the patient

Table 2. Typical features of active versus latent tuberculosis infection

Typical features	Active tuberculosis (pulmonary)	Latent tuberculosis infection
Symptoms	Cough, fever, haemoptysis	None
Chest x-ray	Abnormal	Normal or scars/granulomas
Sputum acid-fast bacillus smear/culture	Positive	Negative
Infectiousness	Yes	No
Treatment	Multiple drugs	Single drug (in selected cases)

has LTBI. Most importantly, the presence of active TB must be excluded before a diagnosis of LTBI can be confirmed. Therefore, all patients with a positive TST or IGRA should be assessed clinically and with a chest x-ray for evidence of active TB.

Features that suggest active TB infection is present in a patient with a positive screening test include:

- fever, cough, sputum production and haemoptysis
- weight loss
- lymphadenopathy
- night sweats
- radiological evidence – pulmonary opacity, intrathoracic lymphadenopathy or pleural effusion
- elevated inflammatory markers (C-reactive protein, erythrocyte sedimentation rate and white cell count).

Table 2 shows a comparison of major features of active and latent infections.

Clinical assessment

Clinical assessment is usually straightforward. Patients should be asked about a past history of LTBI or active TB, and about classic symptoms of TB such as cough, haemoptysis, fevers, sweats and weight loss.

Physical examination should include examination of the respiratory system, and other systems as directed by any features on the clinical history. The possibility of extrapulmonary TB also needs to be considered.

Radiological assessment

A chest x-ray should be performed routinely in patients with a positive screening test. In some situations, it is difficult to know whether the findings from the chest x-ray indicate latent infection or active disease, and further investigation may be indicated, especially in patients with cough or other symptoms suggestive of TB; referral for specialist investigation (such as bronchoscopy or biopsy) is usually necessary for such patients. Occasionally, additional radiological studies may be conducted if extrapulmonary TB is suspected.

How should a patient with latent tuberculosis infection be treated?

Making a diagnosis of LTBI does not necessarily mean that treatment is indicated: this decision is made by weighing up the pros and cons of treatment. Treatment of patients with LTBI significantly reduces the risk of later active TB infection occurring (by 70 to 90%), but treatment of patients with LTBI is lengthy and involves some risk of side effects. Although the decision to treat is usually made at a specialist centre, patients are often seen in general practice during treatment and GPs should be familiar with common management issues. Table 3 highlights some indications for specialist consultation in patients presenting for management of LTBI.

Factors that influence decisions about LTBI treatment include patient age, duration of infection and comorbidities, especially immunosuppression. Younger patients and those with recently acquired LTBI are usually treated because their cumulative risk of reactivation is relatively high. Elderly patients with infection acquired in the distant past are often not treated because their risk of reactivation is lower and they are at higher risk of side effects from treatment. The threshold for LTBI treatment is usually low in immunosuppressed patients, such as those treated with high-dose prednisolone or chemotherapy or those with underlying HIV infection, because they are at higher risk of future TB reactivation.[5]

Any patient diagnosed with LTBI who is not treated should be aware of the risk of future reactivation. The possibility of active TB should be considered if they develop pneumonia or another clinical pattern suggestive of active TB at a later stage. This discussion of risk should be clearly documented in practice medical records, including the reasons why treatment was not initiated.

Isoniazid

Isoniazid is the most common antituberculous medication used for the treatment of patients with LTBI. Occasionally, therapy other than isoniazid may be used, such as following exposure to drug-resistant TB or in patients with known isoniazid hypersensitivity.

In adults, isoniazid is given at a dose of 300 mg per day. Duration of therapy is usually six or nine months.

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Table 3. Latent tuberculosis infection – when to refer or seek specialist advice

- Investigation and treatment of latent tuberculosis infection in patients younger then 16 years
- Initiation of treatment for latent tuberculosis infection being considered
- Significant side effects in a patient taking isoniazid
- Suspected or proven active tuberculosis infection
- Patients seeking post-exposure screening

Side effects

The most well-recognised complication of isoniazid therapy is hepatitis. Mild and transient abnormalities of liver function are common, and up to 20% of patients may develop elevations of alanine aminotransferase (ALT) after starting therapy.[6] If the ALT level is less than three times the upper limit of normal and the patient is asymptomatic, no change to therapy is required. More severe hepatitis is less common, but occurs at increased frequency in older patients or those with abnormal baseline liver function tests (LFTs). Patients under 50 years of age have a risk of 1 to 2% of significant hepatitis during a course of isoniazid, with an increased risk of 2 to 3% in patients older than 50 years. If patients have symptomatic hepatitis with an ALT level three to five times the upper limit of normal or an ALT level more than five times the upper limit of normal, isoniazid should be discontinued and specialist advice sought before rechallenge or introduction of alternative anti-LTBI therapy.

Other side effects of isoniazid are uncommon. Peripheral neuropathy may occur in poorly nourished individuals, in pregnant or breastfeeding women, or in those at risk of neuropathy because of other causes such as alcohol excess, diabetes or HIV infection. Administration of pyridoxine (vitamin B_6) 25 mg daily for those at higher risk of side effects prevents this complication. Drug allergy, with itch, skin rash and fever, may occur, as may exacerbation of acne and (rarely) a drug-induced lupus syndrome. Isoniazid interacts with phenytoin and carbamazepine and may enhance their effects.

Monitoring

Before starting treatment for LTBI, all patients should have baseline investigations including a full blood examination and LFTs. Testing for hepatitis B and C serology is usually indicated, especially in overseas-born patients.

In those patients whose baseline liver function is normal it is not necessary to routinely monitor LFTs unless they are known to have underlying liver disease or HIV infection, are older than 35 years or are being treated with other hepatotoxic medications. All patients should be educated about the symptoms of hepatitis (e.g. abdominal pain, jaundice, dark urine) and instructed to cease isoniazid and present for investigation should these symptoms occur. This information should be reinforced in writing, and repeated at follow-up visits. Patients whose LFTs are abnormal at baseline, especially those with active hepatitis, are at higher risk of developing isoniazid-associated hepatotoxicity and more frequent specialist review should be considered.

Completing therapy and follow up

At the end of a treatment course for LTBI, a detailed record should be made regarding the type and duration of treatment, the compliance and the side effects.

Determining whether treatment has been effective is currently not possible. GPs should be aware that neither testing with TST nor IGRA reliably become negative following treatment, and treatment success cannot be based on repeat testing. Although treatment of LTBI has been shown to greatly reduce the risk of subsequent reactivation of TB, patients and medical staff should be alert to the fact that active TB cannot be completely excluded as a future diagnosis.

Conclusions

The management of LTBI is an important part of good long-term medical care for many patients, and has the potential to prevent serious illness. Although aspects of managing patients with LTBI may require specialist involvement and consultation, many elements may be effectively carried out in a general practice setting. MT

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COMPETING INTERESTS: None.