Other

National position statement for the management of latent tuberculosis infection

David Stock and the National Tuberculosis Advisory Committee (NTAC)

Background

The primary role of any tuberculosis (TB) control program is to ensure the prompt identification and effective treatment of active disease. The host immune system often succeeds in containing the initial (or primary) infection with *Mycobacterium tuberculosis* (Mtb), but may fail to eliminate the pathogen. The persistence of viable organisms explains the potential for the development of active disease years or even decades after infection. This is known as latent tuberculosis infection (LTBI) although, rather than a distinct entity, this probably represents part of a dynamic spectrum.[1] Individuals with LTBI are asymptomatic and it is therefore clinically undetectable.

The World Health Organization (WHO) estimates that one-third of the global population has been infected with Mtb[2], with highest prevalence of LTBI in countries/regions with the highest prevalence of active disease.[3] In 2013, 88% of 1322 notifications in Australia were in the overseas-born population (incidence 19.5 per 100,000 v. 1.0 per 100,000), with this proportion rising over the course of the last decade.[4] Combined with epidemiological evidence of low local transmission, this strongly implies that the vast majority resulted from reactivation of latent infection acquired prior to immigration.[5, 6] Contrasting trends in TB incidence in other developed countries probably reflect differences in policy regarding LTBI.[7]

Conclusion: The diagnosis and treatment of LTBI represents an important opportunity for intervention by jurisdictional TB control programs.

Targeted testing

The development of initiatives with the ultimate goal of eliminating TB on a global scale could lead one to conclude that highly inclusive, if not universal, testing should be undertaken in order to optimise capture of LTBI. However, such an undertaking would be prohibitively expensive, impractical and inevitably compromise the positive predictive value of the chosen test(s). We must therefore focus our resources on at-risk groups who would benefit from treatment.

Given the very low rates of transmission within Australia, it is clear that progressing toward TB elimination is largely contingent on the implementation of strategies to detect and treat LTBI in migrants from high incidence countries.

The 2 key factors to take into account when identifying an individual or population at risk are the pre-test probability (PTP) of LTBI and the risk of progression to active disease.

High PTP:

- Close (household) contacts of pulmonary TB
- Migrants# from countries with a high incidence of TB*
- Healthcare workers from settings with high TB incidence[8]

Migrants comprises those who have moved to Australia with the intent of staying long-term and those whose residence is time-limited, e.g. overseas students
*A cohort study from the United Kingdom showed that programmatic testing of migrants from countries with a range of TB incidence thresholds from 40 to 250 per 100,000 would be cost-effective and identify the majority of individuals with LTBI.[9] Lowering the threshold to 40 in 100,000, as recommended by the National Institute of Clinical Excellence (NICE)[10], while also cost-effective, substantially increases the cohort size, consequently increasing the workload for local TB services[11]. A recent publication supports the implementation of a similar, targeted strategy across Australia[12], although there is, as yet, no local cost-effectiveness data.

Increased risk of progression to active disease:

- Evidence of recent infection
- Fibrotic change consistent with TB on chest radiograph without history of previous treatment
- Human immunodeficiency virus (HIV) infection

- Other co-morbidities, including silicosis, renal failure (chronic kidney disease stage V), poorly controlled diabetes mellitus, certain malignancies (haematological, head & neck, lung), previous gastrectomy or jejuno-ileal bypass surgery, malnutrition and alcohol abuse
- Treatment with anti-tumour necrosis factor (anti-TNFα) inhibitors
- Solid organ transplant recipients
- Other immunosuppressive therapy, including long-term oral corticosteroids (prednisolone ≥15mg/day or equivalent)
- Young children, especially those aged <5 years

NTAC recommends that the following groups are tested for LTBI:

- Those identified by contact tracing within Australia
- Migrants (from any country) with a history of TB contact within the last 2 years
- Migrants from countries with a high incidence of TB*
  - Aged 35 or under
  - Aged over 35 with one or more risk factors for reactivation

  Prioritisation of recent migrants and those staying permanently is advisable.

  NTAC acknowledges that implementing this recommendation may require an increase in resources and the relative importance of competing demands would need to be carefully considered at a jurisdictional level.
- People living with HIV infection
- Patients commencing anti-TNFα therapy
- Patients being assessed for solid organ transplantation
- Australian residents returning from a prolonged period working in a healthcare setting in a high incidence country, and migrants from high incidence settings intending to work in Australian healthcare settings

Testing should generally be performed on an intention-to-treat basis, i.e. on the understanding that a diagnosis of LTBI will result in an offer of treatment. An individual risk-benefit assessment should be undertaken to inform this decision.

Testing

Two types of tests are currently in use for the diagnosis of LTBI in Australia, the tuberculin skin test (TST) and interferon-gamma release assay (IGRA). Both TST and IGRA are indirect tests, demonstrating immune sensitisation to Mtb. They cannot, therefore, distinguish between elimination and persistence of Mtb following primary infection. There is also the potential for test failure in the setting of impaired host immunity. Furthermore, neither test can distinguish between recent and distant infection, nor reliably predict progression to active disease.

The principal advantage of IGRA over TST is in terms of specificity. Unlike TST, the test outcome is unaffected by previous testing, Bacille Calmette-Guerin (BCG) vaccination (typically high coverage in at risk populations) or exposure to non-tuberculous mycobacteria (NTM), with the exception of *M. marinum, M. szulgai and M. kansasii*. The major drawbacks have been the relative unfamiliarity and higher cost of the test. There is also a possibility that an indeterminate result may be returned due to failure of the positive or negative control.

Both TST and IGRA are acceptable for the diagnosis of LTBI. This is consistent with recently published WHO guidelines[13] on testing in high income, low prevalence countries. For further information please refer to the following NTAC document: *Position Statement on Interferon-γ Release Immunoassays in the Detection of Latent Tuberculosis Infection*[**].

The following represents a reasonable approach to the interpretation of TST results:

Regard as TST-positive if

a. ≥15mm

* ≥ 100 per 100,000 based on WHO estimates (http://who.int/tb/country/data/profiles/en/). This threshold has been chosen by consensus, considering both epidemiological risk of LTBI and cohort size. Targeted testing for migrants from countries of incidence 40 – 99 per 100,000 should be considered where resourcing is favourable or where underlying medical conditions suggest a significant risk of disease progression or severe manifestations of disease not otherwise specified in the above recommendations.

** http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-cdi3601i.htm Please note this position statement is currently under review and an updated version will be published shortly.

b. ≥ 10mm but < 15mm with a history of close contact or an abnormal chest radiograph (calcified nodules, upper lobe fibrosis). Consider performing IGRA as a supplementary test

c. ≥ 5 but < 10mm in those age < 5 years with high PTP AND increased risk of progression to active disease. If age ≥ 2 years consider performing IGRA as a supplementary test, noting that indeterminant IGRA results may be more likely in very young children[14]

d. ≥ 5mm and immunosuppressed (IGRA can be performed concurrently – treat if either is positive)

Treatment can be offered to HIV-infected and preschool age contacts of an infectious case without prior testing in recognition of their susceptibility to meningitis and disseminated infection[15]

Preventive treatment

A diagnosis of LTBI requires ensuring that active disease is excluded. Prior to initiation of LTBI treatment, patients should have a chest x-ray performed, sputum (induced if necessary) cultured for TB where feasible, and be reviewed by a clinician with experience in the diagnosis and management of TB.

Isoniazid

This is the most widely used and evidence-based regimen, although there is debate as to the most appropriate duration of treatment. A risk reduction in excess of 90% can be achieved after 12 months of daily self-administration but, as one would expect, field effectiveness is compromised by declining adherence.[16] Extrapolation from trial data had suggested that treatment for 9 months is optimal[17], but subsequent meta-analyses concluded that there is no demonstrable benefit in continuing beyond 6 months.[18, 19] There are no head-to-head studies of 6 versus 9 months isoniazid (INH).

There is evidence of an extremely durable treatment response in a low-prevalence setting.[20] The principal safety concern has been the hepatotoxic potential of this drug[21], although more recent data has shown very low rates of significant hepatitis, perhaps as a result of better patient selection and treatment monitoring[22].

Dose: 10mg/kg daily, up to a maximum of 300mg***.

The challenges faced by both physicians and patients in trying to maintain treatment adherence over many months led to a search for equally effective but shorter regimens.

Rifampicin (RIF)

Evidence in the literature is limited to a single trial in silicosis patients[23] and some observational data[24, 25]. The Centers for Disease Control and Prevention (CDC) in the United States recommend treatment for 4 months as an alternative to INH.[26] Acceptable safety and completion rates have been established for this regimen[27] and a trial is currently recruiting in an attempt to address the lack of efficacy data[28]. RIF is a cytochrome P450 inducer and the potential for drug interactions may need to be carefully considered.

Dose: 10mg/kg daily, up to 600mg.

Rifampicin-isoniazid (RIF-INH)

This combination has been shown to have an equivalent efficacy and safety profile to INH.[29] Evidence supporting its use in the treatment of LTBI comes predominantly from studies conducted in children.[30, 31, 32] Daily treatment for 3 months is recommended as an alternative to INH monotherapy by NICE[10] but is not in widespread use in Australia.

Isoniazid-rifapentine (INH-RPT)

Rifapentine is a potent, long-acting rifamycin. An open-label study of weekly, directly observed therapy (DOT) with this combination for 12 weeks showed non-inferiority to 9 months of daily, self-administered INH.[33] It also appears to be efficacious and well-tolerated in HIV-infected adults.[34] Durability of response and performance in certain settings (e.g. no DOT, age < 2yrs) are yet to be established. This regimen is now recommended by the CDC.[35] It is not currently registered for use in Australia but is the subject of considerable interest.

Important - Rifampicin-pyrazinamide (RIF-PZA) is not generally recommended due to an unacceptable risk of significant hepatotoxicity in non-HIV infected individuals[26].

NTAC recommends that:

- INH for 6-9 months is the standard of care

*** Pyridoxine (Vitamin B6) 25mg daily may be co-prescribed in adults for all regimens containing isoniazid to minimise the risk of peripheral neuropathy.

for the treatment of LTBI in adults

- RIF-INH for 3 months is an acceptable alternative, especially when treating LTBI in children
- Rifampicin for 4 months can be used in the event of intolerance of INH or infection by a suspected/known INH-resistant organism

Infection with a multi-drug resistant (MDR) organism

Isoniazid and rifamycins are unlikely to be effective in the setting of MDR-TB infection. As is the case for fully-drug susceptible organisms, the great majority will not progress to active disease. The potential consequences of MDR-TB transmission are, however, substantial and contacts should therefore be managed by an experienced TB physician. Fluoroquinolone-based preventative therapy has been used in Australia and internationally, with accumulating evidence relating to the magnitude of protection provided[36, 37]. Regardless of preventative therapy administered, contacts should be closely monitored for signs of active disease for at least 2 years.[38]

Monitoring

Routine monitoring of liver function is not necessary in the under 35's without risk factors (regular alcohol consumption, pre-existing liver disease). Otherwise these should be checked monthly for a minimum of 3 months. Transaminases over 5 times the upper limit of normal (ULN) according to your local laboratory reference range should prompt cessation of treatment, with a lower cut-off of 3 times the ULN if symptoms are present.

All patients should be educated about symptoms of hepatitis and advised to stop treatment pending assessment by a doctor if they are concerned.

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Corresponding author:

Dr David Stock
Staff Specialist Respiratory and General Medicine
Royal Hobart Hospital
david.stock@ths.tas.gov.au

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