Policy 3.2  Treatment of Latent Tuberculosis Infection (Adults)

Title  Treatment of Latent Tuberculosis Infection (Adults)
Reference Number WA Tuberculosis Control Program Policy 3.2
Policy Statement This document describes the treatment for latent tuberculosis infection (LTBI) in adults.
Areas Covered Treatment regimens for LTBI treatment including drug doses and adjuvant drugs. Treatment initiation and pre-treatment investigations. Clinical management and follow up.
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Related WA TB Control Program Policies
1.1 Diagnosis of tuberculosis – Laboratory
1.2 Diagnosis of tuberculosis – Clinical
2.1 Medical treatment of tuberculosis (adults)
2.2 Case management of tuberculosis
3.1 Diagnosis of latent tuberculosis infection
3.2 Treatment of latent tuberculosis infection
4.1 Tuberculosis (active and latent) in children
4.2 Management of tuberculosis in prisoners and immigration detainees
4.3 Tuberculosis (active and latent) in pregnant women
4.4 Tuberculosis and HIV
5.1 BCG Vaccination
6.1 Contact tracing for tuberculosis
6.2 Active surveillance for tuberculosis in recent migrants
6.3 Tuberculosis and health care workers
6.4 Active surveillance for tuberculosis prior to anti-TNF alpha treatment
7.1 Notification of tuberculosis and enhanced surveillance data
8.1 Diagnosis and management of Hansen’s disease
9.1 Management of confidential information for the WA Tuberculosis Control Program
9.2 Client record management policy for the WA Tuberculosis Control Program
9.3 Fees and charges associated with tuberculosis and leprosy treatment

Document Control

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Policy 3.2  Treatment of Latent Tuberculosis Infection

1.0 Introduction

This policy describes the drug treatment of latent tuberculosis infection (LTBI) in adults in Western Australia. The diagnosis of LTBI and the management of special groups, including children and pregnant women, and active surveillance for tuberculosis is described in other WA TB Control Program policies detailed above.

The treatment of latent tuberculosis infection (LTBI) is also known as preventive therapy. Preventive therapy reduces the risk of a first episode of TB occurring in people exposed to infection. A Cochrane review of eleven trials involving isoniazid preventive treatment for latent TB in non-HIV affected persons showed that isoniazid was effective in preventing TB in 60% of people. One person can be prevented from getting TB for every 35 people taking isoniazid for six months (Smeja, Marchetti, Cook, & Smail, 1999).

2.0 Rationale

Latent TB infection is that state in which inert viable bacteria remain contained in the body. Persons with latent TB infection do not display symptoms of active TB infection and are not infectious to the general population. However, LTBI has the potential of leading to active tuberculosis.

Diagnosis of LTBI followed by preventive treatment will reduce the risk of developing active TB. An important strategy in TB control, especially in low prevalence countries is the identification of persons with LTBI at risk of progression to active TB disease and treatment of those persons with an effective drug regimen (Communicable Diseases Network Australia, 2002; Apers et al, 2009). This incorporates effective contact tracing of active TB cases, pre-migration screening and treatment, and targeted screening of high-risk groups e.g. prior to anti-TNF alpha treatment.

The rationale for treating latent TB infection is to kill dormant bacilli in order to prevent later reactivation and consequent tuberculosis disease. Treatment for latent TB infection can either be (NICE, 2011):

i) **Primary** – to prevent the acquisition of infection after exposure. Examples are in the treatment of neonates exposed to parents with sputum smear positive tuberculosis or people with HIV exposed to active tuberculosis. Preventive therapy reduces the risk of a first episode of TB occurring in people exposed sputum smear positive tuberculosis.

OR

i. **Secondary** – treatment after latent infection has occurred.
3.0 Indications for treatment

The decision to treat latent TB should be made by balancing the person’s lifetime risk of developing active TB with the risk of developing treatment side effects and compliance with treatment, and the individual’s preference. LTBI treatment will benefit a) those likely to have been recently infected and b) those most at risk of progressing to TB disease.

Recent infection

Of people infected with *M. tuberculosis*, there is a 10-15% chance of developing clinical disease with about half occurring within five years of initial infection (NICE, 2011). This group includes household or close contacts of tuberculosis with a positive screening test, especially contacts of sputum smear-positive tuberculosis patients.

High risk of progressing to active disease

Once infected with *M. tuberculosis* the majority of people do not develop active disease; however, there are certain subgroups of the population who are more at risk to progressing to active TB (Mazurek et al 2010; American Thoracic Society, 2000).

1) Infants and children <2 years old, especially if they are contacts of active TB patients (Marais, Schaaf, & Donald, 2009);
2) Persons recently infected with *M. tuberculosis* (within 2 years);
3) Cigarette smokers;
4) Persons with a history of untreated or inadequately treated active TB, including persons with fibrotic changes or upper lobe infiltrates on chest x-ray consistent with prior active TB; and
5) Persons with associated medical conditions or treatments (Table 1).

Table 1: Co-morbid conditions which increase the risk of developing active TB

- HIV infection
- Immunosuppressive therapy such as anti-tumour necrosis factor alpha (TNFα), post organ transplantation immunosuppressant therapy and immunosuppressant therapy equivalent to prednisolone 15mg/day for 1 month
- Silicosis
- Diabetes mellitus
- Chronic renal failure/haemodialysis
- Leukemia or lymphoma
- Cancers of the head, neck or lung
- Persons who have had gastrectomy or jejunoileal bypass
- Malnutrition
- Medical conditions as a consequence of excessive alcohol use or illicit drug use
HIV - Co-infection with HIV increases the lifetime risk of progression of latent infection of *M. tuberculosis* to TB disease from 5-10% lifetime risk in non-HIV infected individuals to 50% lifetime risk in HIV positive individuals (World Health Organisation, 2004).

**Immunosuppressive treatment** - e.g. solid organ transplant recipients, use of TNF-α antagonists. Individuals being considered for immunosuppressive treatments and diagnosed with LTBI should be offered treatment before they commence the immunosuppressive treatment (see WA TB Control Program policy 6.4 *Active surveillance for tuberculosis prior to anti-TNF alpha treatment*).

**3.1 Precautions for LTBI treatment**

Caution should be exercised in prescribing preventive therapy in certain groups of patients with increased risk of treatment side effects. This includes patients with pre-existing hepatic impairment, alcoholism, viral hepatitis and patients of an older age group.

When LTBI is diagnosed as part of cross sectional screening e.g. active surveillance in migrant populations (see WA TB Control Program policy 6.2 *Active surveillance for tuberculosis in recent migrants*) preventive treatment is not routinely offered to individuals aged over 35 years as the risk of adverse events may start to outweigh the benefits of treatment. This differs to situations where there is a high risk of progression from latent TB to active TB when age is less of a factor e.g. contact of active TB, HIV co-infection or immunosuppression.

In pregnant women treatment can be delayed until after delivery unless there is a high risk of active disease (see section 5.4 below).

The above are not absolute contraindications to preventive therapy but the risk of treatment side effects should be weighted against the benefit of treatment. These patients may be reviewed more regularly with more frequent monitoring of liver function.

**3.2 Contraindications for LTBI treatment**

Preventive therapy is *not* recommended in:

- **Contacts of Multidrug-resistant TB (MDR-TB)** – preventive therapy can and should still be considered in high-risk exposure. The choice of drug depends on the susceptibilities of the MTB isolate and drugs to which the index case is sensitive to should be used. However, there is no evidence on which to base this potentially toxic therapy.
- Those patients with a history of previous completed treatment for active TB or previous completed treatment for latent TB. Chest x-ray follow up for 2 years is preferred in this group.
- **Suspicion of active TB**.
3.3 Primary preventive therapy

A group that requires special consideration are those individuals at high risk of developing primary TB infection following exposure to an infectious case. Commencement of preventative treatment immediately following the exposure to prevent the development of primary TB infection should be considered.

This type of treatment should be considered for the following at risk groups:

1) Children under the age of 2 years exposed to TB,
2) A neonate who’s mother has active pulmonary TB, or
3) Immunosuppressed individuals (e.g. HIV infection, transplant recipients).

4.0 Pre-treatment investigations

Treatment of latent TB infection should only be considered once active TB has been excluded by chest x-ray (CXR) and clinical assessment. The following should be performed prior to the commencement of preventive therapy:

Chest radiograph

- The CXR needs to be current i.e. within 6 months, or within 1 month if patient is symptomatic.
- In pregnancy CXR is not performed until after delivery unless there is a strong clinical suspicion of active pulmonary TB.
- If the CXR is abnormal and suggestive of active TB disease then other investigations including sputum acid-fast bacilli examination are required and preventive therapy should not be commenced until active TB disease is excluded.
- If the CXR is abnormal but represents old TB changes, then preventative therapy can be commenced if there is no prior history of previous completed TB treatment.
- An end-of-treatment CXR is recommended except in children <15 years of age.

Screening test for LTBI

For further information on screening tests for LTBI please see the WA TB Control Program policy 3.1 Diagnosis of latent tuberculosis infection.

Baseline blood tests

A full blood count (FBC) and liver function test (LFT) should be done prior to treatment commencement as a minimum.
5.0 Treatment of LTBI

Standard full treatment for tuberculosis disease should be considered if any doubt exists about the presence of active TB exists (see the WA TB Control Program policy 2.1 Medical treatment of tuberculosis (adults)).

5.1 Treatment regimens

Single drug preventive treatment is generally used in treating LTBI. The regimens used at the WA TB control program are:

5.1.1 Isoniazid monotherapy (6H)

Single agent isoniazid has been used to treat LTBI for at least 35 years (Smeja et al, 1999). A six-month course of isoniazid monotherapy is the treatment of choice for adults in the WA TB Control Program. In most instances isoniazid monotherapy for 6 months is adequate treatment for LTBI in adults (including children >12 years old) with efficacy in the order of 60% to 80% depending on compliance (Smeja et al, 1999). Durations of isoniazid longer than six months have slight additional efficacy over that of the six month treatment regimen, but the potential extra benefit is out-weighted by the poorer compliance associated with more prolonged treatment and a smaller increased risk of hepatic toxicity.

Isoniazid Dose: 5-10mg/kg to a maximum of 300mg daily

5.1.2 Rifampicin monotherapy (4R)

A four-month course of Rifampicin monotherapy is used for those individuals who are known contacts of patients with active pulmonary tuberculosis resistant to isoniazid. It is also used as an alternative regime for those patients intolerant of isoniazid e.g. hepatic toxicity. Rifampicin should be used with caution in HIV infected persons being treated with certain combinations of antiretroviral drugs and joint management with an HIV specialist is essential.

Rifampicin Dose: ≥ 50 kg body weight give 600mg daily
< 50mg body weight give 450mg daily

Rifampicin 450mg is preferably given as 3 x 150mg capsules.

5.1.3 Combination therapy (3RH)

Combination therapy with rifampicin and isoniazid for three months (3RH) has been shown to be equivalent to isoniazid monotherapy in terms of effectiveness and safety (National Institute for Health and Clinical Excellence (NICE, 2011; Ena & Valls, 2005). However, meta-analysis of trials using 3RH combination was of various qualities and the duration of
follow up of participants differed widely. Therefore this treatment regimen is not widely used except in the paediatric setting.

A regimen using rifampicin and pyrazinamide for two months has been found to have significant rates of hepatotoxicity and even fatal liver injury (American Thoracic Society, 2001; Blumberg et al, 2005). This combination therapy is no longer recommended to treat latent TB infection.

5.2 Isoniazid side effects

Side effects of isoniazid therapy include lethargy, nausea, a loss of appetite, vomiting, skin rash, dizziness, drowsiness, and fever. The most serious side effect is hepatitis.

Liver enzyme abnormalities

Asymptomatic liver enzyme abnormalities (up to 3 times upper limit of normal) are common and occur in approximately 20% of people. The symptomatic hepatitis rate is 1 to 3 per 1000 persons (Blumberg et al, 2005; Fountain et al, 2005). Age over 35 years and daily alcohol ingestion has been associated with higher rates of hepatitis (NICE, 2011). The risk may also be increased in persons with underlying liver disease, those with hepatitis B and C infection, HIV infection in those with a history of heavy alcohol consumption, pregnant women and in the postpartum period i.e. within 3 months of delivery.

Prodromal symptoms of hepatotoxicity may include malaise, anorexia, nausea and vomiting. Dark urine, jaundice, abdominal pain and tenderness may develop. However patients may be asymptomatic and more frequent monitoring of liver function is recommended in those groups at higher risk of hepatotoxicity.

Neuropathy

The development of neuropathy is uncommon (less than 0.2%). The risk is increased in individuals with nutritional deficiency, diabetes, HIV infection, renal failure, and alcoholism, as well as pregnant and breastfeeding women. The risk can be minimised by administering pyridoxine.

5.3 Pyridoxine administration

Pyridoxine at a dose of 25mg daily should be given concurrently to persons on INH therapy who are predisposed to neuropathy e.g. persons with diabetes, chronic renal impairment, malnutrition, HIV infection and those with seizure disorders. It is not required for otherwise healthy adults on preventive therapy.
5.4 Special treatment groups

HIV co-infection
Co-infection with HIV increases the lifetime risk of progression of latent infection of *M. tuberculosis* to tuberculosis (TB) disease from 5-10% lifetime risk in non-HIV infected individuals to 50% lifetime risk in HIV positive individuals (World Health Organisation, 2004). Treatment needs to be prolonged for 9 months. Isoniazid monotherapy is the preferred treatment regimen and pyridoxine 25mg daily should be prescribed concurrently. For further detail on tuberculosis in HIV-affected individuals, see the WA TB Control Program policy 4.4 *Tuberculosis and HIV*.

Pregnancy
The preferred regimen for preventive therapy is isoniazid 300mg/day for 6 months with pyridoxine 25mg/day supplementation. Isoniazid is a category A drug and is safe to use in pregnancy. The decision to treat should be made in conjunction with the patient's preference. Treatment should be encouraged during pregnancy when there is a high risk of progression to active disease. That is, if the woman:
- Is a recent close contact with active TB; or
- Has HIV infection or is severely immunocompromised; or
- Has other medical conditions which increases the risk of reactivation of latent tuberculosis.

If preventive treatment is to be deferred until after delivery then the pregnant woman should be closely monitored for signs of active disease.

Neonates
Refer to the WA TB Control Program policy 4.1 *Tuberculosis (active and latent) in children* and policy 4.3 *Tuberculosis (active and latent) in pregnant women*.

Children
Refer to the WA TB Control Program policy 4.1 *Tuberculosis (active and latent) in children*.

Isoniazid resistance
Contacts of people with isoniazid resistant TB should be offered four months of rifampicin (4R).

MDR-TB
For contacts of Multidrug-resistant TB (MDR-TB), preventive therapy can and should still be considered in high-risk exposure. The choice of drug depends on the susceptibilities of the MTB isolate and drugs to which the index case is sensitive to should be used. However, there is no evidence on which to base this potentially toxic therapy. Consultation with a specialist physician experienced in TB management should be sought.
Older persons
Preventive treatment is not routinely offered to individuals aged over 35 years as part of population cross sectional screening as the risk of adverse events may start to outweigh the benefits of treatment. However, benefit may outweigh the risk of adverse events however in situations where there is a high risk of progression to active TB e.g. close contact of active TB or HIV co-infection.

Refusal of preventive treatment
Those patients who are eligible for treatment of LTBI but decline the medication should be given information regarding TB symptoms and be followed up with a chest x-ray every 6 months for 2 years.

6.0 Clinic Management and Follow up

Follow up at the WA TB control clinic is essential to ensure compliance and to manage any side effects. After patients have been assessed as suitable for preventive treatment and baseline investigations performed, they are assigned a case manager who will provide support, education and guide the patient through the duration of their treatment.

Patients should be followed up at 2-4 weekly intervals and monitored for side effects of medication, compliance with medication and monitoring of blood chemistry as appropriate. LFTs should be checked again at least once after starting the medication. More frequent biochemistry should be considered with HIV-infected individuals, pregnant women or women within three months of giving birth, individuals with chronic liver disease, those who consume alcohol regularly, individuals with co-morbidities and on other medications likely to interact with INH, and those over 35 years of age.

6.1 Treatment completion

Treatment for latent TB would be considered complete when a minimum 80% of the intended dose has been administered within the allocated timeframe. The duration of treatment may be extended within reason if doses have been missed or treatment interrupted temporarily.

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<td>6 months daily isoniazid</td>
<td>180 doses within 8 months</td>
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<tr>
<td>4 months daily rifampicin</td>
<td>120 doses within 6 months</td>
</tr>
<tr>
<td>9 months daily isoniazid</td>
<td>270 doses within 12 months</td>
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When restarting therapy for patients who have interrupted treatment, clinicians may continue the regimen originally prescribed as long as the criteria for completion mentioned above is achievable. If interruptions were frequent or prolonged, the entire regimen needs to be restarted. In either situation, when therapy is restored after an interruption of more than 2 months, a medical examination to rule out active TB disease is indicated (American Thoracic Society, 2000).
No further follow up is required after a satisfactory course of treatment is completed.

7.0 Works Cited


**Feedback or comments related to this policy should be addressed to the Medical Director, WA TB Control Program Justin.Waring@health.wa.gov.au**