Guidelines on tuberculin testing and treatment of latent TB infection among silicotic patients in Hong Kong (2004)

Internal guidelines of the Pneumoconiosis Clinic of the Department of Health of the Government of the Hong Kong SAR
Background

1. The Centers for Diseases Control of the United States published a detailed set of guidelines on tuberculin testing and treatment of latent tuberculosis infection in 2000\(^1\).

2. Anti-TB chemoprophylaxis has not been widely practiced in Hong Kong, partly because of the difficulty in interpreting a positive tuberculin response within a community where BCG revaccination was widely practiced, and partly because of potential problems with drug compliance and drug reaction with prolonged course of treatment.

3. Silicotic subjects are at high risk of developing tuberculosis (TB). Two local studies have quantified the annual risk of TB in silicotic subjects, which is in the range of approximately 3-5% per annum\(^2,3\). The development of tuberculosis has often been associated with accelerated lung tissue injury, further deterioration in lung function and increase in mortality.

4. Tuberculin test has been in regular use for the diagnosis of LTBI for many years. A positive reaction can result from infection by *Mycobacterium tuberculosis*, previous BCG vaccination or cross-reaction caused by non-tuberculous mycobacteria. A higher cut-off point of 15 mm or over is more likely to indicate LTBI than reaction of smaller sizes\(^4,5\). Most of our silicotic patients are over the age of 60. They are unlikely to have received BCG vaccination, because the practice was started only in the 1950s. However, it is uncertain whether infection with other environmental mycobacteria may lead to a false-positive tuberculin response.

5. A daily 12-month regimen of isoniazid was shown to be more effective than a 6-month regimen of isoniazid for preventing TB in persons with fibrotic lung disease\(^6\). The problems with the former regimen are client acceptance and compliance. Recent data from Centres for Disease Control indicate that only 60% of patients complete at least 6 mo of treatment\(^1\).

6. In United States, isoniazid daily regimen for 9 months is recommended\(^1\) because, in subgroup analyses of several trials, the maximal beneficial effect of isoniazid is likely achieved by 9 months\(^7-9\). A 6-mo regimen also provides substantial protection
and has been shown to be superior to placebo in both HIV-negative and HIV-positive persons. In some situations, treatment for 6 months rather than 9 months may provide a more favorable outcome from a cost-effectiveness standpoint.

7. In a previous study in Hong Kong, 6 months of isoniazid, 3 months of isoniazid plus rifampicin, and 3 months of rifampicin gave comparable results, and reduced the incidence of TB by about 50%.

8. Despite an earlier favourable report in the use of the 2-month rifampicin plus pyrazinamide regimen in the treatment of latent tuberculosis among the HIV-infected subjects, such regimen was associated with a high incidence of hepatotoxicity in a recent local study on the treatment of latent tuberculosis infection among the silicotic subjects. There have also been similar reports from other places.

9. In a previous study of anti-tuberculosis drug-related liver dysfunction in Hong Kong, age and HBsAg status were found to be the predictors of drug-related liver dysfunction. In a retrospective study on TB in older people in Hong Kong, the incidence of liver dysfunction among those patients aged 65 or above was found to be 17.7%, in contrast with only 9.2% among younger patients. The recent study by Jasmer et al on the treatment of LTBI also found that patients older than 35 years had a higher risk of grade 3 or 4 hepatotoxicity.

10. Isoniazid-associated hepatitis occurs in 0.3% of treated persons from the age of 20 to 34, 1.2% from 35 to 49, and 2.3% of those from 50 to 64.

11. This set of guidelines is intended to provide general guidance for tuberculin testing and treatment of latent tuberculosis infection among silicotic patients in Hong Kong.
**Tuberculin testing**

Tuberculin test will be offered to all silicotic patients without a history of confirmed tuberculosis. Retesting will also be offered if the last tuberculin test was less than 10mm and taken more than 5 years ago.

If the client agrees to tuberculin testing, BCG history should be obtained. The number of previous BCG scars should be recorded while the test is being administered. The tuberculin reaction (in mm) should be read 48 to 72 hours later, and entered into the medical records.

Patients with tuberculin reaction at 10 mm or above should be assessed to exclude active TB before treatment for LTBI is offered. Stable clinical condition, absence of systemic symptoms, stable radiological feature (apart from natural disease progression), and negative sputum smears (and cultures if available) are useful to exclude active disease.

For those with tuberculin reaction less than 10mm, there is no need to retest for booster phenomenon. Instead, retesting will be offered after 5 years.

Irrespective of tuberculin status, all silicotic patients should be given health education on early recognition of symptoms suggestive of TB.
Treatment of latent tuberculosis infection

Who to treat

In view of a considerable risk of developing tuberculosis after infection, treatment of latent tuberculosis infection with isoniazid should be considered, irrespective of previous BCG vaccination, if all of the following conditions are met:

1. Silicosis confirmed by the Pneumoconiosis Medical Board.
2. Profusion of category 1 or above
3. A positive tuberculin skin test response defined as an induration $\geq 10$ mm in response to 2 units of PPD RT23.

However, such treatment is not appropriate for confirmed cases of active tuberculosis and may not be appropriate in the following situations:

1. Clinical suspicion of active pulmonary tuberculosis
2. Clinical suspicion of extrapulmonary tuberculosis
3. History of receiving more than two months of continuous anti-tuberculosis treatment in the past
4. Symptomatic hepatitis or known case of liver cirrhosis at enrollment
5. Alanine transaminase (ALT) above the upper limit of normal on at least 2 occasions separated by 2 weeks. (If the patient has been started on treatment with a single pretreatment ALT above the upper limit of normal (but $<1.5X$), the treatment should be closely monitored, with the criteria for stopping treatment as stated in the section on management of drug-induced liver dysfunction below).
6. Alcoholism (habitual alcohol drinkers with alcohol dependence), even if alcohol use will be discontinued during treatment
7. Concurrently taking other medications commonly associated with clinically significant liver injury
8. Poor general condition
9. Reluctance and/or inability to take medications or attend for follow-up
Pretreatment Investigations

1. Baseline blood tests for patients aged 16 or above or on any clinical indications, e.g. patients whose initial evaluation suggests a liver disorder, patients infected with HIV, pregnant women and those in the immediate postpartum period (i.e., within 3 mo of delivery), persons with a history of liver disease (e.g., hepatitis B or C, alcoholic hepatitis), persons who use alcohol regularly, and others who are at risk for chronic liver disease:
   a. Complete blood picture (CBP),
   b. Liver function test (LFT) including albumin and total protein,
   c. Renal function test (RFT)
   d. Hepatitis B surface antigen (HBsAg)
2. Sputum examination: two sputum sample collected on two different days are collected for acid-fast bacilli (AFB) smear and culture for mycobacteria.
3. Urinalysis for glucose and protein

Regimen for latent TB infection

A course of isoniazid 300 mg daily for 6 months (180 doses) will be offered. A lower dose of 200mg daily may be considered for patients with chronic renal failure. Pyridoxine supplementation at 10 mg daily should be considered for those with malnutrition or at risk of neuropathy, e.g. diabetes mellitus, habitual alcohol use, chronic renal failure, and HIV infection. An alternative regimen of rifampicin (450 mg for those weighed < 50kg, 600mg for those weighed ≥ 50 kg) daily for 4 months will be offered if there is past intolerance or probable resistance to isoniazid.
Patient Education and Dispensing of Medication

The drug should be dispensed on a monthly basis with a drug calendar. Health education and counselling will be provided before treatment and at each monthly visit. Patients should be clearly informed of the potential side effects and advised to report them promptly. They should be encouraged to comply with the prescription and record every consumed dose in the calendar honestly. The monthly drug calendar is to be returned in the next follow-up visit. Help of relatives should be enlisted if available.

Monitoring

1. All patients will be followed up at least monthly during treatment.
2. At all treatment visits, patients will be assessed clinically for adverse side effects. For those HBsAg-positive, with abnormal baseline LFT or otherwise at risk of hepatic disease, LFT should be checked biweekly at 2, 4 and 6 weeks, and 2 months. Any other investigation will be done according to clinical suspicion. Treatment should be withheld according to the management of drug-induced hepatitis protocol.
3. Biweekly LFT during the initial two months is also recommended for those aged 35 or above. In those situations where the patient is unable or unwilling to come to the chest clinics every two weeks, LFT should be checked at least monthly in the initial two months and whenever there is clinical suspicion of hepatitis.
4. The drug calendar will be reviewed at each visit to assess compliance with treatment.
5. Treatment will be terminated for any adverse drug reactions that entail treatment interruption for more than 1 month.
6. If the patient fails to complete the 180 doses of treatment within 6 months, treatment may be extended to allow completion of the regimen, up to a maximum of 3 more months.
7. CXR, sputum and / or other investigations will be checked upon clinical suspicion. If active TB develops during treatment of LTBI, chemoprophylaxis must be replaced by appropriate anti-TB treatment.
8. After treatment, all patients should be offered regular follow-up as usual for their silicosis. Besides periodic CXR assessment, further investigations for TB will be performed upon clinical suspicion.

**Management of drug-induced liver dysfunction**

If patient has asymptomatic biochemical liver dysfunction with ALT < 3 X the upper limit of normal and bilirubin < 2 X the upper limit of normal, treatment may be continued under close clinical and biochemical monitoring. LFT has to be monitored every 2 weeks or more frequently as appropriate until LFT returns to normal.

**Definition of symptomatic hepatitis:**
It is defined as the presence of symptoms of hepatitis, such as malaise, reduced appetite, nausea, vomiting, yellowing of sclera, lethargy and/or right upper quadrant discomfort, together with the presence of liver dysfunction irrespective of the severity of the biochemical abnormalities.

**Management of drug-induced hepatitis:**
Treatment should be stopped and not resumed for any of these findings:
1. ALT > normal range when accompanied by symptoms of hepatitis, or
2. ALT > 3 X the upper limit of normal range in an asymptomatic person,
3. Serum bilirubin > normal range when accompanied by symptoms of hepatitis
4. Serum bilirubin > 2 X the upper limit of normal in an asymptomatic person.

After withholding treatment, LFT will be repeated weekly until LFT returns to normal.
References