Guidelines on tuberculin testing and treatment of latent TB infection (LTBI) among immunocompetent household contacts of smear-positive pulmonary tuberculosis patients in Hong Kong

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Internal guidelines of
the Tuberculosis & Chest Service 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.

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. A study on a cohort of local children given BCG vaccination at birth from 1978 to 1982 suggested that those who were tuberculin-positive (induration ≥10mm) at an age of 6 to 9 were at a greater risk of developing TB than those who were tuberculin-negative.

4. A higher cut-off point of 15mm or over is more likely to indicate LTBI. Because of the higher prevalence of LTBI among close TB contacts, a tuberculin test response of 15 mm or over among close TB contacts is more likely to indicate LTBI, irrespective of past BCG vaccination.

5. The average risk of progression from TB infection to disease is approximately 10% for an immunocompetent adult. The short-term risk of developing disease is especially high among those recently infected. Treatment of LTBI has been accorded priority only second to treatment of active TB disease.

6. 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. The problem with the former regimen is compliance. Only 50% completed a 6-month course of isoniazid chemoprophylaxis.

7. 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.

8. 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.

9. Isoniazid-associated hepatitis occurs in 0.3% of treated persons from the age of 20 to 34, 1.2% from 35 to 49, 2.3% of those form 50 to 64, and 4.6% over the age of 65.

10. There have been in-service guidelines for tuberculin testing and treatment of latent tuberculosis infection among infants and those aged under five, but not for older subjects. This set of guidelines is intended to provide general guidance for tuberculin testing and treatment of latent tuberculosis infection among older (5 to 64 inclusive), immunocompetent, household contacts of smear-positive pulmonary tuberculosis patients. For the elderly (aged ≥ 65), the higher incidence of isoniazid-related hepatotoxicity and the relative paucity of systematically collected data do not allow recommendation of preventive treatment on a regular basis locally.

Tuberculin testing of older household contacts (aged 5 to 64 inclusive) of smear-positive pulmonary tuberculosis patients

All household contacts aged 5 to 64 (i.e. ≥ 5 or < 65) of smear-positive index tuberculosis patients will be offered tuberculin test (2 unit RT-23) as part of the contact screening work-up except those with past history of confirmed tuberculosis (i.e. TB requiring treatment and not just lung scars).

The existing arrangement for tuberculin testing should be continued. A computerized register should be kept of all household contacts aged 5 to 64 of smear-positive index tuberculosis patients. The tuberculin reaction (in mm) should also be recorded in the register when they are read 48 to 72 hours later. In mobile clinics, where there may be difficulty in arranging the tuberculin testing, the relevant contacts should be offered the options of having CXR examination in the mobile clinic or both CXR and tuberculin test in the closest full-time chest clinic.
All household contacts with tuberculin reaction $\geq 15$ mm should be interviewed by the public health unit. They will be told that they are likely to have been infected by TB and the life-time risk of developing TB disease later is approximately 10%. They should be given health education on the early recognition of symptoms suggestive of TB. They should be referred to see a doctor, preferably, within the same session. The attending doctor should examine the CXR taken for contact screening and discuss treatment for LTBI with the contact if it is appropriate. Irrespective of whether these strongly tuberculin-positive close contacts are put on treatment, they should be offered annual follow-up for two years. During the follow-up visits, CXR will be offered, unless the patient is pregnant.

Treatment of latent tuberculosis infection among tuberculin strongly positive household contacts of smear-positive pulmonary tuberculosis patients

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

1. Subjects aged 5 or above, but below 65
2. Household contacts of patients with smear-positive pulmonary tuberculosis
3. Strongly positive tuberculin skin test response defined as an induration $\geq 15$ mm in response to 2 units of PPD RT23 or documented tuberculin conversion (an increase of the tuberculin reaction size by 10mm or above on repeat testing).

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. Past intolerance of, or contraindication to use of, isoniazid
5. Poor general condition
6. Symptomatic hepatitis or alanine transaminase (ALT) above the upper limit of normal on at least 2 occasions separated by 2 weeks or known case of liver cirrhosis at enrollment
7. Alcoholism (habitual alcohol drinkers with alcohol dependence), even if alcohol use will be discontinued during treatment
8. Concurrently taking other medications commonly associated with clinically significant liver injury
9. Reluctance and/or inability to take medications or attend for follow-up
10. *Mycobacterium tuberculosis* cultured from index patient already known to be resistant to isoniazid

Decision on preventive treatment should be made after discussion with patients. A history of BCG vaccination, with or without a BCG scar should not influence the decision regarding whether to treat LTBI.

*Special situations*

This set of guidelines is not intended for the management of HIV-infected or other immunocompromised contacts. For such situations or for other contacts in whom the risk of the disease is particularly high or the consequence of disease particularly grave, a lower cut-off value for the tuberculin response may have to be used. Reference should be made to other relevant guidelines for up-to-date information, e.g. the latest ATS recommendations and the local guidelines prepared by the Scientific Committee on AIDS for HIV-infected contacts.

No definitive data exist concerning treatment of contacts who have been exposed to patients with probable or confirmed isoniazid-resistant TB. Rifampicin alone for 4
months\textsuperscript{1, 17} is an acceptable alternative and may be offered after careful assessment and discussion with the patient. In situations in which rifampin cannot be used, rifabutin can be substituted.

For contacts of patients with multidrug-resistant tuberculosis (resistant to both isoniazid and rifampicin), the problem has not been evaluated in prospective studies, and consensus is lacking. These patients are unlikely to benefit from treatment with isoniazid and rifampicin. There is, as yet, insufficient evidence to allow recommendation of preventive treatment on a regular basis. Use of a regimen containing other agents active against M. tuberculosis should be considered if treatment of latent tuberculosis infection is to be given. Decision has to be made on a case-to-case basis in full consultation with the patient, and after careful balance of the potential risks and benefits.

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

Chemoprophylaxis Regimen

Six-month course of daily isoniazid (6H) with 180 doses in total.
   - Children aged \leq 16
Isoniazid  5mg/kg daily (max. 300mg)
- Adults
  Isoniazid 300mg daily (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.)

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 follow-up at 1 year (from date of tuberculin test) and 2 year. During the follow-up visits, CXR will be offered, unless the patient is pregnant.

*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 ALT 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 ALT returns to normal.
References


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