

Tuberculosis in adults

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Abstract

Tuberculosis (TB) in Malaysia is rising due to multiple factors and issues related to its management are addressed in the updated evidence-based clinical practice guidelines. Screening for active TB should be considered in high risk groups. Light emitting diode-based fluorescence microscopy and nucleic acid amplification tests are recommended investigations. Health education and standardised 6-month daily antituberculosis (antiTB) regimen are among important elements for successful treatment. Latent TB infection screening should only be performed on high risk individuals. AntiTB regimen offered to HIV-positive adults should be the same as for HIV-negative adults and timing to initiate highly active antiretroviral therapy in patients with TB is based on CD4 count. All patients on antiTB treatment should be monitored to assess their response to treatment and to identify problems associated with it.

Introduction

The number of tuberculosis (TB) cases in Malaysia is continuously rising unabated, leading to high morbidity and mortality rates. This problem has been compounded by the human immunodeficiency virus (HIV) pandemic, complacency, negligence towards the disease and international travel. Although the incidence of multidrug-resistant TB (MDR-TB) is still under control, extensively drug-resistant TB has been detected.

Delayed presentation, inaccurate diagnosis, inappropriate empirical treatment, high treatment default rates in some settings, newer diagnostic tools and latent TB are just some of the issues in the management of TB in the local context. The management of TB needs to be standardised to improve patient outcomes, assist monitoring and evaluation efforts and to prevent the emergence of MDR-TB.

Locally, the number of new TB cases has increased from 15,000 per annum in 2005 to 19,251 per annum in 2011. While pulmonary TB (PTB) is the most common form of TB, extrapulmonary TB (EPTB) still poses a threat. The majority of patients are in the 21–60 years age group (69.5%) with a male predominance of 65%. Foreigners accounted for 13.9% of cases. The smear positive rate among new patients suffering from PTB is 72%.

Patients with active PTB typically present with a history of chest symptoms and nonspecific constitutional symptoms. Those presenting with unexplained cough lasting more than

2 weeks with or without constitutional symptoms should be investigated for PTB. Typical symptoms may be absent in the immunocompromised or elderly patients. Symptoms and signs due to EPTB vary according to the organs involved and may be nonspecific.

Screening

Early detection and treatment of active PTB prevent its spread and improve outcomes. Active screening is therefore an important strategy in controlling TB. Those high risk groups that should be considered to be screened for active TB are:

- Close TB contacts (both household and non-household contacts)
- Immunocompromised patients such as those suffering from diabetes mellitus and HIV infection
- Substance abusers and cigarette smokers
- People living in overcrowded conditions such as incarceration and institutionalisation

In addition, HIV screening should be offered to all patients with TB.

Investigations

The diagnosis of TB is confirmed by isolating *Mycobacterium tuberculosis* from clinical samples. In situations where clinical samples are difficult to obtain and in EPTB, certain procedures such as sputum induction, gastric

lavage, bronchoscopy and tissue biopsy should be performed to establish the diagnosis.

All patients suspected of having PTB should submit at least two sputum specimens for microscopic examination in a quality-assured laboratory. If possible, at least one specimen should be obtained early in the morning, as sputum collected at this time has the highest yield. Light emitting diode-based fluorescence microscopy should be used as the preferred method over the conventional Ziehl–Neelsen light microscopy in diagnosing PTB in both high and low volume laboratories.

Nucleic acid amplification tests (molecular methods endorsed by World Health Organization) can be performed for detection of *Mycobacterium tuberculosis* in clinical specimens. Currently available commercial serological assay should not be used to diagnose TB. In EPTB, the usage of adenosine deaminase in pleural TB and TB meningitis may aid diagnosis.

The radiologic features of TB may mimic those of many other diseases; thus, a high degree of clinical suspicion is required when interpreting the imaging manifestations. Chest radiography should be used as the primary imaging modality to aid diagnosis and management of PTB and EPTB. Computerised tomography may be considered in cases of normal chest radiography but with high clinical suspicion or in the management of PTB complications.

Treatment of PTB in adults

The aims of TB treatment are to cure the disease and to reduce its transmission. In general, individuals with pulmonary and laryngeal TB are infectious, whereas those with EPTB are regarded as non-infectious. The infectiousness increases when the sputum smear is positive or multiple pulmonary cavities are seen on the chest radiograph. The chances of infection also increase in immunocompromised individuals and if the contact has been in a close proximity and spent a longer time together with the index case.

Health education must be provided to patients and family members/carers at the time of starting the treatment.

The information should include:

- Nature of the disease
- Necessity of strict adherence to the prolonged treatment

c. Risks of defaulting treatment

d. Side effects of medications

e. Risks of transmission and need for respiratory hygiene as well as cough/sneeze etiquette

A standardised TB treatment regimen is of utmost importance in controlling PTB (refer to Table 1). Presently, a 6-month regimen consisting of 2 months of daily (intensive regimen) EHRZ (2EHRZ) followed by 4 months of daily (maintenance regimen) HR (4HR) is the recommended and preferred treatment for patients with newly diagnosed PTB. The regimen should contain 6 months of rifampicin, which should be rounded to higher recommended dose if tolerated. If ethambutol is contraindicated, streptomycin can be substituted.

Table 1. Dosages of first-line antituberculosis (AntiTB) drugs

Drug	Recommended daily dose	
	Dose (range) (mg/kg body weight)	Maximum (mg)
Isoniazid (H)	5 (4–6)	300
Rifampicin (R)	10 (8–12)	600
Pyrazinamide (Z)	25 (20–30)	2000
Ethambutol (E)	15 (15–20)	1600
Streptomycin (S)	15 (12–18)	1000

Pyridoxine 10–50 mg daily needs to be added if isoniazid is prescribed.

In previously treated TB patients including those treated as new cases who have taken treatment for more than 1 month and are currently smear- or culture-positive again (i.e. failure, relapse or return after default), physicians with experience in TB management should be consulted for retreatment of TB.

Fixed-dose combinations (FDC) are preferred to separate-drug combination for the treatment of TB to help patients adhere to treatment. This is done by incorporating two or more drugs in a single tablet. In patients who develop toxicity, intolerance or contraindication to specific drug component, FDCs can be substituted with separate-drug regimens.

Direct observed therapy, short course (DOTS) combines drug treatment with political commitment, sputum smear microscopy for diagnosis and directly observed therapy (DOT) to ensure adherence and good management practice. When possible, DOT,

either by healthcare worker or family member, should be adopted to improve compliance in TB management. It should be patient-centred and incorporate negotiations, considering patient's characteristics and preferences. Prompt reminders should be sent to TB patients who default treatment. Failing that, home visit by healthcare workers should be carried out.

All EPTB cases should be treated with anti-TB for a minimum of 6 months except for bone (including spine) and joint tuberculosis, which require 6–9 months, and tuberculous meningitis, which require 9–12 months. Streptomycin should be used instead of ethambutol in adult TB meningitis.

Latent TB infection

Latent TB infection (LTBI) is defined as an infection with *Mycobacterium tuberculosis* complex, where the bacteria may be alive but in the state of dormancy and not currently causing any active diseases/symptoms. The lifetime risk of developing TB reactivation among those with LTBI is about 5–10%. This reactivation tends to occur within the first 2 years after exposure. However, the risk of reactivation is much higher in immunocompromised individuals.

LTBI should be diagnosed based on the absence of symptoms, normal/static chest X-ray findings and positive tuberculin skin test (TST)/interferon-gamma release assays (IGRA). However, the interpretation of the TST result is compounded by the cross-reactivity of the reagent (tuberculin) with BCG and nontuberculous mycobacteria, giving rise to false positive results. TST of ≥ 10 mm should be considered as a positive test for LTBI for most individuals investigated in this country except for categories listed in Table 2.

Table 2. Positive TST for LTBI

Positive TST reaction (measurement)	Type of individual
TST reaction of ≥ 5 mm	HIV-infected persons Organ transplant recipients Persons who are immunosuppressed for other reasons
TST reaction of ≥ 15 mm	Individuals from countries with low incidence of TB
TST reaction of ≥ 10 mm	All other individuals

LTBI screening should only be performed on high risk individuals. If LTBI testing is inconclusive, the patient should be referred to a specialist with experience in TB management. Patients with LTBI may be offered treatment.

TB–HIV co-infection

TB and HIV infections have a bidirectional interaction, resulting in an accelerated development of both diseases. HIV infection accelerates the development of TB from infection to advanced disease. In turn, TB depletes the CD4 T-lymphocyte count and intensifies the immunodepressant effect of HIV.

At least one-third of HIV-positive persons worldwide are infected with *Mycobacterium tuberculosis* and 8–10% of them develop clinical disease every year. For the past 3 years, the local registry showed that HIV–TB co-infections in Malaysia have stabilised. PTB is still the major type of presenting disease in HIV–TB co-infections. TB rates are higher in individuals who are highly active antiretroviral therapy (HAART)-naïve compared to those who are on HAART. Risk of mortality is 2.6 times higher in HIV-positive patients who develop TB compared to those who do not. In view of these, active TB should be ruled out in all HIV-positive patients. In all HIV-positive patients suspected of PTB, sputum TB culture should be done regardless of smear AFB status.

Anti-TB regimen offered to HIV-positive adults should be the same as for HIV-negative adults. Daily treatment should be offered in the maintenance phase. The minimum duration of anti-TB treatment to be considered in HIV-infected adults is 6 months for PTB. Co-administration of rifampicin and protease inhibitors should not be used in HIV–TB co-infections. Isoniazid prophylaxis therapy for 6 months should be offered to all HIV patients with LTBI after ruling out active TB. In terms of timing to initiate HAART in patients with TB and HIV:

- If CD4 < 50 cells/ μ L, initiate HAART 2 weeks after starting intensive phase of anti-TB treatment.
- If CD4 > 50 cells/ μ L, defer initiating HAART until completion of intensive phase of anti-TB treatment.
- If CD4 > 350 cells/ μ L, complete anti-TB treatment and consider HAART if CD4 drops below 350 cells/ μ L.

Immune reconstitution inflammatory syndrome (IRIS) should be suspected if there is paradoxical worsening of symptoms especially in patients with CD4 <50 cells/ μ L, anaemia or EPTB, who have recently started on HAART. Co-trimoxazole prophylaxis should be given to patients with TB-HIV co-infection.

Follow-up

All patients on anti-TB treatment should be monitored to assess their response to treatment and to identify problems associated with it. All patients should be aware of symptoms indicative of PTB and adverse drug reactions. At each clinic visit, patients taking ethambutol should be questioned regarding possible visual disturbances. Patients should be well-informed on symptoms of TB recurrence. The following table provides recommendations on investigations during PTB treatment (Table 3).

Table 3. The recommended 6-month daily treatment of PTB

Visit duration	Regimen	Investigations
0 month	EHRZ/SHRZ	FBC, RBS, RP, LFT, HIV, Sputum AFB direct smear, Sputum MTB C&S, CXR
2–4 weeks	EHRZ/SHRZ	LFT
2 months	HR	LFT if necessary, CXR, Sputum AFB direct smears, Sputum MTB C&S if smear remains positive
4 months	HR	Sputum AFB direct smear and CXR only if there is no clinical improvement
6 months	Completion of 6 months treatment	Sputum AFB direct smear, CXR

S, streptomycin; RBS, random blood sugar; E, ethambutol; FBC, full blood count; AFB, acid fast bacilli; H, isoniazid; RP, renal profile; MTB C&S, *Mycobacterium tuberculosis* culture and sensitivity; R, rifampicin; LFT, liver function test; CXR, chest X-ray; Z, pyrazinamide; HIV, HIV screening test.

Patients with initial negative sputum smear should repeat sputum smear after 2 months of anti-TB treatment. If still negative, no further sputum sample is required.

If smear AFB remains positive at 2 months, refer to specialists with experience in TB management, and repeat sputum AFB and sputum MTB C&S at 3 months.

MDR-TB is defined as *Mycobacterium tuberculosis* infection resistant to both isoniazid and rifampicin with or without resistance to other drugs.

Prevention

All TB cases must be notified by written notification within a week after diagnosis made using the standard notification forms. Failure to comply is liable to be compounded under the Prevention and Control of Infectious Disease Act 1988 (Act 342). All healthcare facilities should have administrative, engineering and personal protective measures in place to reduce tuberculosis occupational risk of healthcare workers.

Referral criteria

The following conditions should be referred to specialists with experience in TB management:

- Unsure of TB diagnosis
- Retreatment of TB
- Adverse events following anti-TB drugs
- Multidrug-resistant and extremely drug-resistant TB
- EPTB except for tuberculous lymphadenitis
- Renal and/or liver impairment with TB
- HIV-TB co-infection
- Smear negative TB
- Smear positive after 2 months of treatment
- All children diagnosed with TB
- Maternal TB
- Complex TB cases requiring surgical intervention

Details of the evidence supporting these recommendations can be found in the CPG on Management of Tuberculosis (3rd Edition), available on the following websites: Ministry of Health Malaysia: <http://www.moh.gov.my> and Academy of Medicine: <http://www.acadmed.org.my>. Corresponding organisation: CPG Secretariat, Health Technology Assessment Section, Medical Development Division, Ministry of Health Malaysia and contactable at htamalaysia@moh.gov.my.