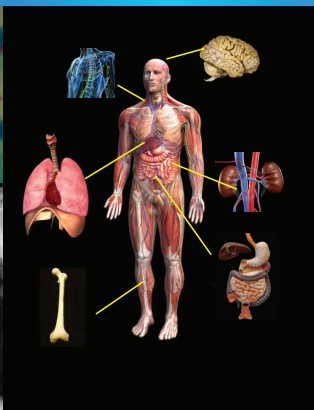
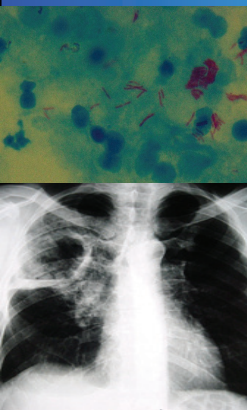


QUICK REFERENCE FOR HEALTHCARE PROVIDERS

MANAGEMENT OF **TUBERCULOSIS** (3rd EDITION)



Ministry of Health Malaysia



Academy of Medicine Malaysia



Malaysian Thoracic Society

KEY MESSAGES

1. Tuberculosis (TB) is a notifiable infectious disease. Timely diagnosis, prompt treatment & adherence to medication are key factors in combating TB.
2. Screening of TB should be done in high risk groups including all close contacts (especially household contacts).
3. Patients with symptoms of TB should have sputum smear for acid fast bacilli (AFB), mycobacterium culture & sensitivity (C&S), & chest x-ray (CXR) done. Nucleic Acid Amplification Tests (NAAT) plays a role in rapid detection of *Mycobacterium tuberculosis* & multidrug-resistant TB (MDR-TB).
4. TB serology should not be used to diagnose pulmonary TB (PTB) or extrapulmonary tuberculosis (EPTB).
5. For latent TB infection (LTBI), tuberculin skin test (TST) is the preferred method for diagnosis. Interferon Gamma Release Assay may be used as an alternative. Treatment should be considered for high risk patients.
6. A daily antiTB regimen is recommended for both intensive & maintenance phases. A proper defaulter tracing system should be in place to detect early interruption in treatment and follow-up. Poorly managed TB will lead to drug-resistant TB.
7. Fixed-Dose Combinations are preferred to separate-drugs combination for the treatment of TB.
8. Infants & children under 5 years of age with close contact are at high risk of developing active TB.
9. Active TB should be ruled out in all HIV-positive patients.
10. Preventive measures should be employed to reduce TB risk among healthcare workers.

This Quick Reference provides key messages and a summary of the main recommendations in the Clinical Practice Guidelines (CPG) Management of Tuberculosis (3rd Edition).

Details of the evidence supporting these recommendations can be found in the above CPG, available on the following websites:

Ministry of Health Malaysia: www.moh.gov.my

Academy of Medicine Malaysia: www.acadmed.org.my

Malaysian Thoracic Society: www.mts.org.my

CLINICAL PRACTICE GUIDELINES SECRETARIAT

Health Technology Assessment Section

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HIGH RISK GROUPS

- Close TB contacts especially infants & children under 5 years of age
- Immunocompromised patients such as those with diabetes mellitus, HIV infection, end-stage renal disease, malnutrition, use of immunosuppressant drugs, etc.
- Intravenous drug users
- People living in overcrowded conditions

INVESTIGATIONS

- PTB
 - o CXR (PA) should be taken in symptomatic & high risk patients. Any abnormality warrants further diagnostic investigation.
 - o A minimum of 2 sputum samples (including 1 early morning sample) should be sent for TB microscopy. One sample should be subjected to *M. tuberculosis* C&S testing.
 - o Spontaneously produced sputum is generally used for laboratory testing; however sputum induction could be carried out if patient is unable to expectorate.
 - o NAAT can be carried out for the rapid identification of *M. tuberculosis* and detection of MDR-TB. This test can be carried out in a TB risk level 2 laboratory.
- EPTB
 - o Patient with EPTB should have a CXR to exclude or confirm co-existing PTB. Imaging (ultrasound, computerised tomography & magnetic resonance imaging) may be carried on the area of interest to demonstrate features suggestive of TB.
 - o Body fluids or tissue samples suspected of TB should be subjected to TB C&S.
 - o NAAT testing can be carried out on positive TB cultures.

TREATMENT FOR NEW TB CASES

- For newly-diagnosed PTB, the standard antiTB treatment is a 6-month regimen consisting of daily 2-month of EHRZ followed by daily 4-month of HR.

Dosages of First-Line AntiTB Drugs

Drug	Recommended dose			
	Daily		3 times per week	
	Dose (range) in mg/kg body weight	Maximum in mg	Dose (range) in mg/kg body weight	Daily maximum in mg
Isoniazid (H)*	5 (4 - 6)	300	10 (8 - 12)	900
Rifampicin (R)	10 (8 - 12)	600	10 (8 - 12)	600
Pyrazinamide (Z)	25 (20 - 30)	2000	35 (30 - 40)**	3000**
Ethambutol (E)	15 (15 - 20)	1600	30 (25 - 35)**	2400**
Streptomycin (S)	15 (12 - 18)	1000	15 (12 - 18)**	1500**

*Pyridoxine 10 - 50 mg daily needs to be added. **Daily treatment is the preferred regimen.

Fixed-Dose Combination Dosing

Drug	Body weight	Dose
Akurit-4	30 - 37 kg	2 tablets daily
	38 - 54 kg	3 tablets daily
	55 - 70 kg	4 tablets daily
	More than 70 kg	5 tablets daily

- Any deviation from the standard regimen or previously treated TB should be referred to specialist with experience in TB management.
- Duration of treatment may be prolonged in certain circumstances:-
 - o Persistently AFB smear positive after 2 months
 - o EPTB
 - o Extensive cavitation on CXR

LATENT TB INFECTION

- Only individuals who are at high risk of acquiring LTBI or developing TB reactivation should be investigated. Treatment might be considered for those who are positive for LTBI.

Positive TST for LTBI

Positive TST Reaction	Types of Individual
≥5 mm	<ul style="list-style-type: none"> • HIV-infected persons • Organ transplant recipients • Persons who are immunosuppressed for other reasons
≥15 mm	<ul style="list-style-type: none"> • Individuals from countries with low incidence of TB
≥10 mm	<ul style="list-style-type: none"> • Close contacts • Recent immigrants • Injecting drug users • Residents & employees of high risk congregate settings (such as correctional facilities, nursing homes, homeless shelters, hospitals & other healthcare facilities) • Persons with fibrotic changes on CXR

TB IN CHILDREN

Recommended treatment regimens & dosages for TB in children are as the following:-

TB cases	Regimen	
	Intensive phase	Maintenance phase
<ul style="list-style-type: none"> • New smear positive or negative PTB • Less severe EPTB 	2HRZ	4HR
<ul style="list-style-type: none"> • Severe concomitant HIV disease 	2HRZE	4HR
<ul style="list-style-type: none"> • Severe form of EPTB • TB meningitis/spine/bone 	2HRZE	10HR
<ul style="list-style-type: none"> • Previously treated smear positive PTB including relapse & treatment after interruption 	3HRZE	5HRE

Drug	Dose (range) in mg/kg	Maximum dose
Isoniazid*	10 (10 - 15)	300 mg
Rifampicin	15 (10 - 20)	600 mg
Pyrazinamide	35 (30 - 40)	2 g
Ethambutol	20 (15 - 25)	1 g

*Pyridoxine 5 - 10 mg daily needs to be added if isoniazid is prescribed.

- For asymptomatic children with history of TB contact, CXR & TST should be performed.
- Treatment for LTBI in children is either daily 6 months of isoniazid or daily 3 months of isoniazid + rifampicin

TB IN PREGNANCY, LACTATION & USE OF ORAL CONTRACEPTIVE

- First-line anti TB drugs except streptomycin are safe for pregnancy & breastfeeding.
- Defer BCG at birth for newborns of mothers with active TB <2 months before delivery.
- Patients on rifampicin should use an alternative contraceptive method other than oral contraceptive pills.

TB-HIV CO-INFECTION

- Isoniazid prophylaxis therapy for 6 months should be offered to all HIV patients after **active TB is ruled out**.
- Highly Active Antiretroviral Therapy (HAART) during TB treatment reduces mortality & results in earlier sputum smear/culture conversion.

CD4 count (cells/ μ l)	Timing of HAART initiation
<50	2 weeks after starting intensive phase of antiTB treatment
>50	After completion of intensive phase of antiTB treatment
>350	Continue antiTB treatment & monitor CD4. Commence HAART if CD4 drops <350 cells/ μ l.

- Efavirenz is the preferred Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) in combination with 2 Nucleoside Reverse Transcriptase Inhibitors for HIV-TB co-infection.
- Immune Reconstitution Inflammatory Syndrome (IRIS) usually occurs within 3 months of antiTB treatment, typically within 2 - 12 weeks after starting HAART:
 - Especially in patients with CD4 <50 cells/ μ l, anaemia or EPTB
 - Major manifestations are fever or lymphadenitis
- Co-trimoxazole prophylaxis should be given for TB-HIV co-infection & throughout antiTB treatment.

FLOW CHART FOR THE RECOMMENDED 6-MONTHS TREATMENT OF PTB

Visit	Duration	Regimen	Investigations
1.	Start of treatment	EHRZ/SHRZ	FBC, RBS, RP, LFT, HIV Sputum AFB direct smear Sputum MTB C&S, CXR
2.	2 - 4 weeks	EHRZ/SHRZ	LFT
3.	2 months	HR H ³ R ³	LFT if necessary Sputum AFB direct smear* Sputum MTB C&S if smear remains positive, CXR
4.	4 months	HR H ³ R ³	Sputum AFB direct smear & CXR only if there is no clinical improvement
5.	6 months	Completion of 6 months treatment	Sputum AFB direct smear CXR

Patients with initial sputum smear negative should have repeat sputum smear at 2 months of antiTB 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, & repeat sputum AFB & sputum MTB C&S at 3 months.

H³R³=thrice weekly of isoniazid & rifampicin

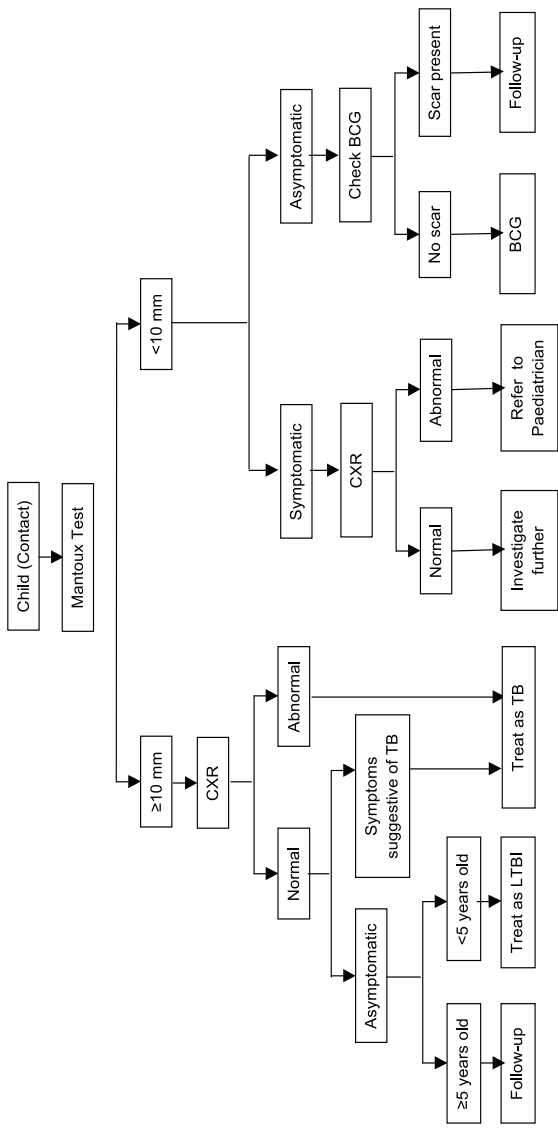
E - Ethambutol	FBC - Full blood count, RBS - Random blood sugar
H - Isoniazid	RP - Renal profile, CXR - Chest x-ray
R - Rifampicin	LFT - Liver function Test, HIV - HIV screening test
Z - Pyrazinamide	MTB C&S - <i>Mycobacterium tuberculosis</i> culture & sensitivity

- Follow-up may not be conducted routinely after completion of antiTB treatment. Patients should be well-informed on symptoms of TB recurrence.

FIRST-LINE ANTI-TB MEDICATIONS: COMMON SIDE EFFECTS, DRUG-DRUG INTERACTIONS & HAART CONCERN

Drug	Common Side Effects	Drug-Drug Interactions	Anti-TB & HAART Concern
Isoniazid	Skin rash, jaundice, hepatitis, drowsiness, anorexia, nausea, abdominal pain, burning, numbness or tingling sensation in the hands or feet	<ul style="list-style-type: none"> Reduction in phenytoin & diazepam level Increase in the toxicity of anticonvulsants, benzodiazepines, paracetamol, serotonergic antidepressants, warfarin & theophylline 	Care is needed when taking it with HAART medications that can cause peripheral neuropathy, particularly stavudine (d4T) & didanosine (ddl)
Rifampicin	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain, orange or red urine & flu syndrome (fever, chills, malaise, headache, bone pain)	Reduction in plasma level of anti-infectives, hormone therapy (including ethinylestradiol, norethindrone, tamoxifen, levothyroxine), methadone, warfarin, cyclosporine, corticosteroid, anticonvulsants, cardiovascular agents, theophylline, sulfonyleurea, HMG-CoA reductase inhibitors, antipsychotics, benzodiazepines & possible reduction in efficacy of azole antifungal drug	Reduces levels of protease inhibitors & NNRTIs
Pyrazinamide	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain & joint pain	Excretion may be blocked by probenecid	Should be taken 2 hours before didanosine (ddl)
Ethambutol	Visual impairment	Absorption delayed or reduced by aluminium hydroxide	-
Streptomycin	Skin rash, deafness (no wax on otoscopy), dizziness (vertigo & nystagmus), decreased urine output	May increase ototoxicity & nephrotoxicity when use with aminoglycoside, amphotericin B, cephalosporins, cyclosporin, cisplatin, frusemide & vancomycin	-

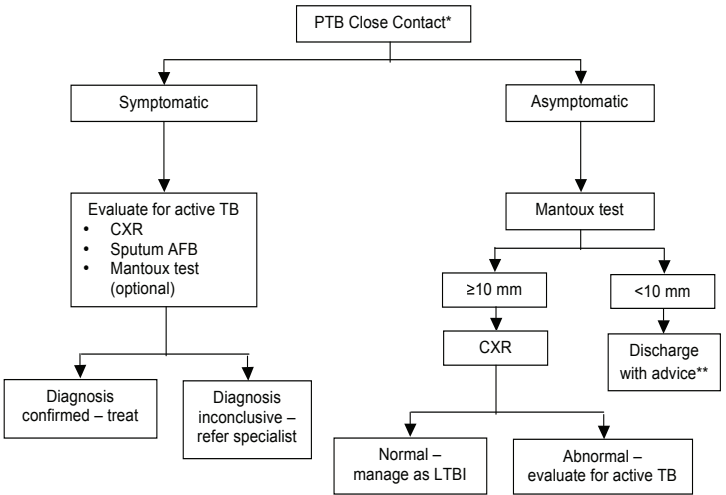
ALGORITHM ON MANAGEMENT OF CHILDREN WITH POSITIVE HISTORY OF CONTACT WITH TB



Note:

- Mantoux test may be negative in children who are malnourished and immunocompromised.
- Contact tracing and investigations in children are to be done **within 6 weeks** of diagnosis of the index patient.

ALGORITHM ON INVESTIGATIONS FOR TB CONTACT TRACING IN ADULTS



*Immunocompetent close contacts

**To seek medical advice if patient has symptoms suggestive of TB such as fever, cough etc. for more than 2 weeks.

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 antiTB drugs
 - MDR-TB & extensively drug-resistant TB
 - EPTB except for tuberculous lymphadenitis
 - Renal &/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