MOH CLINICAL PRACTICE GUIDELINES 1/2016

PREVENTION, DIAGNOSIS AND MANAGEMENT OF TUBERCULOSIS

EXECUTIVE SUMMARY

MINISTRY OF HEALTH
SINGAPORE

Academy of Medicine
Singapore

College of Family
Physicians, Singapore

Singapore Medical
Association

Chapter of Infectious
Disease Physicians
College of Physicians,
Singapore

Chapter of Respiratory
Physicians
College of Physicians,
Singapore

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Introduction

This is the executive summary of the MOH Clinical Practice Guidelines (CPG) on Prevention, Diagnosis and Management of Tuberculosis. It is intended to be used with reference to the full version of the CPG, which is freely available on the MOH website at this link:
https://www.moh.gov.sg/content/moh_web/healthprofessionalsportal/doctors/guidelines/cpg_medical.html

Target audience

The target audience is all healthcare practitioners in Singapore. These guidelines aim to

1. Increase knowledge and awareness of tuberculosis as to facilitate the early detection of active tuberculosis
2. Serve as an evidence-based resource to provide guidance on the use of tuberculosis diagnostic tools and treatment regimens
3. Inform regarding the public health measures necessary for the control of tuberculosis control in Singapore

How to use this document

All recommendations made in the CPG are summarised in this document.

Please note the following:

a. The page numbers of the full CPG document where each recommendation is explained are provided.

b. Each recommendation has a corresponding Grade of Recommendation and Level of Evidence (refer to page 4 for details).

Key recommendations are highlighted in green.

Levels of evidence

Level	Type of Evidence
1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GPP	Good Practice Points: Recommended best practice based on the clinical experience of the guideline development group.

1. Tuberculosis transmission and pathogenesis

No.	Recommendation	Grade, Level of evidence	CPG Page No.
1	Healthcare providers must be aware of the individual and group risk factors for tuberculosis to ensure early diagnosis of tuberculosis.	GPP	24

2. Clinical diagnosis of tuberculosis

No.	Recommendation	Grade, Level of evidence	CPG Page No.
2	In patients presenting with unexplained cough of more than 3 weeks, pulmonary tuberculosis should be considered.	Grade A, Level 1+	26
3	Persons with prolonged cough of more than 3 weeks should undergo chest radiographic examination.	Grade D, Level 4	26
4	Persons presenting with cough and abnormal chest radiograph are often prescribed an empirical course of antibiotics for chest infection. As fluoroquinolones may mask or delay the diagnosis of pulmonary tuberculosis, these drugs should be avoided as empirical treatment for chest infection.	Grade B, Level 2++	26
5	Medical practitioners in primary care are urged to refer suspected tuberculosis cases to the Tuberculosis Control Unit or specialists with experience in tuberculosis management.	GPP	26
6	Two sputum samples – including one early morning sample– should be obtained for both microscopy and mycobacterial cultures for patients with suspected pulmonary tuberculosis. Recommendations for sputum collection are in Appendix 1 (page 17; CPG Page 91).	Grade D Level 4	27

No.	Recommendation	Grade, Level of evidence	CPG Page No.
7	In patients in whom it is difficult to obtain sputum specimens, e.g. children and stroke patients, other means of obtaining sputum should be utilised, including sputum induction and gastric lavage.	Grade D, Level 3	27
8	In patients presenting with extrapulmonary disease, a chest radiograph should also be done to determine if there is concomitant pulmonary tuberculosis and sputum samples obtained to determine if the case is infectious.	Grade D, Level 3	28
9	Patients with newly diagnosed tuberculosis should be screened for human immunodeficiency virus (HIV) and diabetes mellitus.	Grade D, Level 3	32

3. Imaging in tuberculosis

No.	Recommendation	Grade, Level of evidence	CPG Page No.
10	Patients with chest radiographic findings that suggest active* or inactive† disease should be referred without delay for further evaluation including two sputum samples for acid-fast bacilli (AFB) smear and culture.	*Grade D, Level 4 †GPP	36
11	A chest radiograph may be performed on pregnant patients (with lead shield protection) when it is required for tuberculosis contact investigations and for evaluation of active disease.	Grade D, Level 4	38

4. Tuberculosis laboratory diagnosis

No.	Recommendation	Grade, Level of evidence	CPG Page No.
12	All tuberculosis suspects should have relevant clinical specimen(s) obtained and sent for mycobacterial cultures, regardless of the AFB smear results.	Grade B, Level 1++	43

No.	Recommendation	Grade, Level of evidence	CPG Page No.
Nucleic acid amplification tests (NAATs)			
13	In pulmonary tuberculosis, nucleic acid amplification tests (NAATs) need not be routinely performed on sputum in the Singapore context, when the clinical, radiological and epidemiological features are consistent with pulmonary tuberculosis.	GPP	44
14	Rapid molecular tests like the Genotype MTBDR*plus* and Xpert MTB/RIF should be used as the initial test on respiratory samples from individuals suspected of multidrug-resistant tuberculosis. Specimens should still be sent for mycobacterial culture and phenotypic drug susceptibility testing to first and second-line anti-TB drugs.	Grade A, Level 1++	45
15	The presence of *rpo*B gene mutation as detected by the Xpert MTB/RIF assay should be taken as a surrogate for the presence of multidrug-resistant tuberculosis (MDR-TB) until proven otherwise by phenotypic drug-susceptibility testing.	Grade D, Level 4	45
16	For extrapulmonary tuberculosis, nucleic acid amplification tests performed on the appropriate fluid and/or tissue samples are useful adjunctive tests for cases where the clinical suspicion of active tuberculosis is high.	Grade B, Level 1+	46
Adenosine deaminase (ADA)			
17	Testing for adenosine deaminase (ADA) in pleural and ascitic fluids may be useful in tuberculous pleurisy and peritonitis*. ADA testing in sputum samples **is not recommended** for pulmonary tuberculosis†.	*Grade A, Level 1++ †Grade D, Level 3	46

5. Treatment of tuberculosis

No.	Recommendation	Grade, Level of evidence	CPG Page No.
Initiation of treatment			
18	Patients with chest radiographic findings that suggest active disease may be commenced on tuberculosis treatment even before bacteriological results are available.	GPP	50
19	Tuberculosis treatment should be seriously considered in symptomatic patients despite the X-ray appearances of inactivity.	GPP	50
20	Before starting tuberculosis treatment, baseline liver enzymes should be performed in those over 15 years old. Adult patients to be commenced on ethambutol must have their visual acuity and colour vision checked at baseline.	GPP	50
Treatment regimens for pulmonary tuberculosis			
21	**6-month standard regimen** The 6-month standard treatment regimen comprising a 2-month intensive phase of ethambutol, isoniazid, rifampicin and pyrazinamide followed by a 4-month continuation phase of rifampicin and isoniazid is the regimen of choice for pulmonary tuberculosis.	Grade A, Level 1++	51
22	**9-month regimen** For patients who are unlikely to tolerate pyrazinamide (e.g. the elderly, those with liver disease), a 9-month regimen comprising ethambutol, rifampicin and isoniazid for 2 months followed by rifampicin and isoniazid for 7 months may be used.	Grade A, Level 1+	51
Treatment of extrapulmonary tuberculosis			
Note: Extrapulmonary tuberculosis is generally treated with the same regimen (6- or 9-month) as pulmonary tuberculosis. Please refer to additional recommendations below:			
	Tuberculous meningitis		
23	Tuberculous meningitis should be treated with the standard tuberculosis regimen but extended to 12 months. Steroids should be used as an adjunct.	Grade B, Level 2+	52

No.	Recommendation	Grade, Level of evidence	CPG Page No.
	Musculoskeletal tuberculosis		
24	The preferred treatment duration for musculoskeletal tuberculosis is 9 months with a rifampicin-containing regimen.	Grade A, Level 1+	53
	Miliary tuberculosis		
25	Miliary tuberculosis (in the absence of central nervous system or musculoskeletal involvement) may be treated with the standard 6-month treatment regimen.	Grade D, Level 4	53
	Pleural tuberculosis		
26	Pleural tuberculosis may be treated with the standard treatment regimen.	Grade B, Level 1+	53
	Pericardial tuberculosis		
27	Tuberculosis pericardial effusion can be treated with the standard tuberculosis regimen. Adjunctive steroids should be prescribed.	Grade C, Level 2+	54
	Lymph node tuberculosis		
28	The standard tuberculosis regimen can be used in tuberculous lymphadenitis.	Grade C, Level 2+	54
Treatment under special circumstances			
	Pregnancy and breastfeeding		
29	Standard tuberculosis treatment may be used during pregnancy and breastfeeding. Due to the small risk of relative pyridoxine deficiency, pyridoxine should be given to the breast-fed infant of a mother who is receiving standard anti-tuberculosis treatment.	Grade D, Level 4	55
	Renal insufficiency and end stage renal failure		
30	For tuberculosis patients on haemodialysis or with creatinine clearance of less than 30 ml/min, the recommended dose of pyrazinamide is 25 mg/kg three times a week. The dose should be given post-dialysis.	Grade D, Level 3	55

No.	Recommendation	Grade, Level of evidence	CPG Page No.
31	The recommended dose of ethambutol is 15 to 25 mg/kg three times a week in tuberculosis patients with end-stage renal disease or with creatinine clearance of ≤30 ml/min.	Grade D, Level 3	56
32	Streptomycin should be used with great care in tuberculosis patients with renal impairment. If it must be used, the recommended dose of streptomycin is 12 to 15 mg/kg 2 to 3 times a week post-dialysis.	Grade D, Level 3	56
	Hepatic disease		
33	Patients with hepatic disease should be monitored closely during treatment*. The 9-month regimen with rifampicin, isoniazid and ethambutol can be used if the tuberculosis patient with hepatic disease can tolerate this regimen. Pyrazinamide should generally be avoided in patients with hepatic disease†.	*GPP †Grade D, Level 4	57
	HIV co-infection		
34	The standard six-month treatment regimen is recommended for HIV co-infected patients with pulmonary tuberculosis. As with non-HIV-infected patients, the treatment should be extended to 9 months in patients with tuberculous osteomyelitis and to 12 month in patients with central nervous system tuberculosis.	Grade A, Level 1++	58
35	Patients with HIV-related tuberculosis should, as far as possible, be treated with a regimen containing a rifamycin for the full course of tuberculosis treatment.	Grade D, Level 4	58
36	Intermittent dosing regimen for tuberculosis treatment is not recommended for patients with advanced HIV disease (CD4 counts less than 100 cells/mm3) in view of the risk of acquiring rifamycin resistance.	Grade D, Level 4	58

No.	Recommendation	Grade, Level of evidence	CPG Page No.
	Monitoring of patients on tuberculosis treatment		
37	Directly observed therapy (DOT) should be the standard of care for all infectious tuberculosis cases. Tuberculosis patients who are assessed to have difficulty adhering to treatment or who pose greater public risk of transmission, e.g. sputum-smear positive or working in institutional settings or settings with susceptible populations, or those at risk of or diagnosed with drug-resistant tuberculosis, are high priority for DOT.	Grade C, Level 2+	63
38	Before commencing the treatment, patients must be counselled regarding the importance of adhering to and completing the full course of treatments, as well as medication adverse effects.	GPP	64
39	The patient's weight should be documented at each visit and the drug dosages adjusted accordingly. Adult patients on ethambutol must have their visual acuity and colour vision checked at each visit. Those with risk factors for drug-induced hepatitis must be closely monitored.	GPP	64
40	Patients should be reviewed monthly by the specialist to monitor their clinical condition, adherence to treatment and adverse effects of tuberculosis medications.	Grade D, Level 4	65
41	Bacteriological response to treatment should be monitored in patients who are initially sputum acid-fast bacillus (AFB) and/or culture-positive.	Grade D, Level 4	66
42	Cigarette smokers with tuberculosis should be strongly advised and supported to stop smoking.	Grade D, Level 3	67
	Management of multidrug-resistant/extensively drug-resistant tuberculosis		
43	A multidrug-resistant treatment regimen must contain at least four drugs, preferably more, (including a later-generation fluoroquinolone and a second-line injectable agent) to which the organism is shown to be susceptible and to which the patient has previously not been exposed.	Grade D, Level 3	68

No.	Recommendation	Grade, Level of evidence	CPG Page No.
44	Multidrug-resistant tuberculosis (MDR-TB) patients should be treated under strict programme conditions by physicians experienced in MDR-TB management. Directly observed therapy (DOT) should be utilised for the entire treatment duration.	Grade D, Level 4	68
45	Resectional surgery should be considered in high grade MDR-TB or XDR-TB patients with localised disease and adequate respiratory reserve, and for whom there are limited chemotherapeutic options, or who are not responding to chemotherapy.	Grade D, Level 4	69

6. Public health screening and infection control

No.	Recommendation	Grade, Level of evidence	CPG Page No.
Air travel and tuberculosis			
46	Physicians should inform persons with infectious or potentially infectious tuberculosis not to travel by commercial air transportation on a flight of any duration.	Grade D, Level 3	70
Public health screening			
47	Persons applying for long-term immigration passes should be screened for active tuberculosis to ensure early detection and access to treatment, and to reduce community risk of transmission. This is especially true for persons from high tuberculosis prevalence countries.	Grade D, Level 3	71
48	Chest radiograph examination should be used for the purpose of screening in long-term immigration pass applicants.	Grade C, Level 2+	71
49	Any chest radiograph abnormality compatible with tuberculosis (whether radiologically "active" or "inactive") should be evaluated further to rule out active tuberculosis.	Grade D, Level 4	72

No.	Recommendation	Grade, Level of evidence	CPG Page No.
50	Medical practitioners should have a high index of suspicion of drug-resistant tuberculosis in those who were previously treated, those who fail treatment, who are known contacts of multidrug-resistant tuberculosis (MDR-TB), or who come from countries with high prevalence of tuberculosis drug resistance.	Grade C, Level 3	72
Infection control for tuberculosis in healthcare settings			
51	Healthcare facilities that potentially receive tuberculosis patients should have an infection control plan for tuberculosis, comprising administrative controls, environmental controls and use of personal protective equipment to protect staff and patients from potential tuberculosis transmission.	Grade D, Level 4	75
52	Persons with tuberculosis symptoms should be promptly identified in healthcare settings and if necessary, separated from other patients.	Grade D, Level 4	76
53	A ventilation system (natural, mechanical or mixed mode) should be employed for health care facilities to ensure sufficient air exchange and control airflow direction to reduce the risk of tuberculosis exposure.	Grade D, Level 4	76
54	Where necessary, healthcare workers should use particulate respirators when caring for patients suspected or known to have infectious tuberculosis, especially drug-resistant tuberculosis patients and in situations where high-risk procedures are being performed.	Grade D, Level 4	76
Infection prevention in the home and the community			
55	Physicians should advise patients with suspected or confirmed tuberculosis to practise cough etiquette and respiratory hygiene (especially surgical mask use).	Grade D, Level 4	77

7. Tuberculosis contact investigations and screening

No.	Recommendation	Grade, Level of evidence	CPG Page No.
56	Contact investigations are carried out by the National Tuberculosis Programme. Persons with recent close exposure to infectious tuberculosis cases (i.e. bacteriologically positive cases of pulmonary tuberculosis, especially if acid-fast bacilli smear is positive) should be evaluated for active tuberculosis and Latent Tuberculosis Infection.	Grade B Level 2++	80
57	Testing for Latent Tuberculosis Infection should be targeted at high-risk groups and should only be performed if there is an intention to treat for Latent Tuberculosis Infection if detected.	Grade D, Level 4	81
58	Low risk groups (i.e. casual contacts) should not be screened as they are more likely to throw up false positive test results for Latent Tuberculosis Infection.	GPP	81
	Testing for Latent Tuberculosis Infection		
59	Either the tuberculin skin test or the interferon-gamma release assay may be used for the diagnosis of Latent Tuberculosis Infection in adults and children 5 years or older.	Grade A, Level 1+	83
60	The interferon-gamma release assay is the preferred test for adolescents and adults who have received Bacillus Calmette-Guerin (BCG) vaccination, while the tuberculin skin test is the preferred test for the diagnosis of latent tuberculosis in children <5 years of age.	Grade A, Level 1+	84
61	In significantly immunocompromised individuals, especially those with HIV/AIDS, the T-SPOT.TB may be preferable to the tuberculin skin test and QuantiFERON-TB Gold In-Tube (QFT-GIT) for the diagnosis of Latent Tuberculosis Infection.	Grade C, Level 2+	84
62	The interferon-gamma release assay (IGRA) should not be used to monitor response to preventive therapy.	Grade C Level 2+	84

8. Tuberculosis in children - specific considerations

No.	Recommendation	Grade, Level of evidence	CPG Page No.
63	Children with persistent, unremitting cough for 2 weeks, plus objective weight loss, together with fatigue, should be evaluated for tuberculosis.	Grade C, Level 2+	85
64	All children being evaluated for latent or active tuberculosis (pulmonary or otherwise) should have a frontal chest radiograph. Where tuberculosis is strongly suspected, a lateral radiograph should be performed even if the frontal view is normal.	Grade C, Level 2+	86
65	Currently available scoring systems for predicting tuberculosis in children lack sensitivity and/ or specificity, and are not recommended to be used for diagnosis.	Grade B, Level 2++	87
66	In children younger than 5 years old suspected of having tuberculosis infection or disease, the tuberculin skin test (TST) is the preferred mode of initial immunological assessment.	Grade B, Level 2++	88
67	When interferon-gamma release assay (IGRA) testing is performed in children <4 years old, the T-SPOT.TB is preferred over the QFT-GIT due to a lower incidence of indeterminate results.	Grade C, Level 2+	88
68	Because of its excellent specificity, children with a positive interferon-gamma release assays (IGRA) are considered to have tuberculosis infection or disease, and should be offered treatment.	Grade B, Level 2++	88
69	For children with a clinical suspicion of tuberculosis disease with a negative tuberculin skin test (TST), the interferon-gamma release assay (IGRA) may be performed to increase sensitivity. However, treatment for tuberculosis should be considered when other factors are strongly supportive of tuberculosis (epidemiologic, radiologic, histologic, microbiologic), and neither a negative TST nor IGRA should delay treatment.	Grade D, Level 4	88

9. Clinical quality improvement (page 90)

The following clinical and audit parameters, based on recommendations in these guidelines, are proposed:

1. Percentage of patients with unexplained cough of more than 3 weeks, with tuberculosis diagnosis ruled out.
2. Percentage of tuberculosis patients who have a relevant clinical specimen(s) sent for mycobacterial cultures.
3. Percentage of patients who are assigned to DOT out of all index tuberculosis cases in a given year.
4. Percentage of tuberculosis patients who achieve 1-year treatment completion rate.
5. Cure rate* at one year for smear/culture positive pulmonary tuberculosis.
6. Percentage of delays in notification of suspect or confirmed tuberculosis cases (MD532), i.e. submitted more than 72 hours after diagnosis.
7. Percentage of delays in submission of treatment progress form (MD117), i.e. submitted more than two weeks after the declared follow-up appointment date.

***Cure rate** (for treatment cohort for smear/culture + pulmonary tuberculosis only) is defined as:

$$\frac{\text{No. of cured cases (initially smear or culture positive patients who have completed treatment and who had at least 2 negative sputum smear and /or culture during the continuation phase, one of which was at the end of treatment)}}{\text{Total no. of cases with smear and or culture positive started on treatment}}$$

Appendix 1: Recommendations for sputum collection (page 91)

1. General

a) Specimens should be collected before starting patients on anti-tuberculosis drug therapy.

b) Sputum specimens should be collected in a well-ventilated area and precautions should be taken to ensure that health care workers and others are not exposed to infectious aerosols and materials. Contaminated materials should be disposed of in accordance with standard biosafety procedures.

c) Specimens should be obtained under the direct supervision of a healthcare worker.

2. Procedure for sputum collection

a. Sputum must be collected in sterile, screw-capped, leak-proof, disposable, plastic containers. Containers must be free from paraffin and other waxes or oils. The container should be clear so the specimen can be visualise without opening the container

b. Sputum collection containers should be labelled with the patient's name, NRIC number, nature of specimen, date and time of collection. The label should be on the side of the container instead of the lid.

c. Patients should be instructed to:

   i. Collect the specimen in the morning before any oral intake.

   ii. Rinse his or her mouth with water before starting to collect the specimen to remove contamination such as food particles and bacteria. Patients with postnasal discharge should clear these passages before beginning sputum collection.

   iii. Cough from as deep inside the chest as possible as it is important to collect sputum and not saliva.

      1. Instruct patient to take a deep breath, hold his/her breath for a few seconds, and then exhale slowly.
      2. Do this twice.
      3. The third time, inhale deeply, hold his/her breath, and then forcefully exhale through the mouth.

Appendix 1: Recommendations for sputum collection (page 91) – Con't

4. The fourth time, inhale deeply and cough. Instruct patient to carefully direct the sputum into the container to maximise contamination of the outside of the container for safe handling.
5. Patient is to repeat the process until at least 5 ml of specimen has been obtained.

d. The healthcare worker supervising the sputum collection may rap gently and firmly on the applicant's back to help induce coughing and sputum production.

e. The supervising healthcare worker should inspect the specimen to ensure that it contains sputum and not saliva. Sputum is frequently thick and mucoid, but may consist of dull while or light green fluid with fine chunks of dead tissue that show up like solid flakes. Blood may or may not be present. In contrast, saliva appears thin and nearly clear; and should not be accepted.

f. The specimen container should be capped tightly to avoid leakage. Wipe off the outside of the container with a clean tissue before placing into a biohazard-labelled plastic specimen bag. Each specimen should be accompanied by a request with relevant patient and clinical data.

g. The healthcare worker and patient should practise hand hygiene after specimen collection to prevent transmission of microorganisms.

h. The specimen should be delivered to the laboratory as soon as possible after collection to maximise overgrowth of commensal bacteria or deterioration of the mycobacteria.

Grade D, Level 4