



Update on the Management of Pulmonary and Extrapulmonary Tuberculosis

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 January 2006.

Introduction

Tuberculosis is still a common disease locally. In the interest of the patients and our community, the attending physician has the responsibility to maximise the chance of successful treatment till completion, in collaboration with the public health programme.

Pulmonary tuberculosis

The six-month "short-course chemotherapy" is the current standard treatment for active pulmonary TB (Table 1)^{1,2}. Directly observed treatment is recommended as far as practicable. Four drugs - isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin - are recommended for the initial two-month phase, as the local rate of initial isoniazid resistance is more than 4%. Two drugs - isoniazid and rifampicin - are recommended for the four-month continuation phase. The drugs can be given either daily or thrice weekly at the appropriate dosages (Table 2). The drugs should, as far as possible, be taken together in one single dose and not in split doses. Combined drug preparations (e.g. rifater, rifinah) are useful alternatives but have to be given daily. While they help to avoid monotherapy with a single drug, there are possible disadvantages such as higher costs, lack of flexibility in dosing or circumventing intolerance and suboptimal bioavailability for poorly validated preparations.

For patients with extensive disease, the two-month initial phase may be extended to three or four months, depending on clinical, bacteriological, and radiological responses, with the total duration of treatment remaining at six months. In the updated statement from ATS/CDCP/IDSA, nine months of treatment (with an extended seven-month continuation phase) is recommended for patients with drug-susceptible pulmonary TB who have risk factors like cavitation on the initial chest X-ray and persistent sputum culture positivity at two months³. This recommendation is supported by other studies examining risk factors for relapse^{4,5}.

For retreatment cases, five drugs - isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin - are recommended for the initial 3 to 4 months, depending on

the timing of the availability of drug susceptibility testing (DST) results, the rate of smear conversion, extent of disease, and probability of drug resistance (Table 1). Isoniazid and rifampicin (also with ethambutol if the disease is extensive or the DST pattern is unknown) are recommended for the continuation phase; the total treatment duration is nine months. If the DST results that are available subsequently are unfavourable, the above regimen may need to be modified.

Drug-resistant tuberculosis

Comparative less supporting data are available for categorical recommendation for the treatment of drug-resistant TB (See Table 1). For isolated isoniazid resistance alone, which is relatively common locally, clinical trials have also shown that other alternative regimens, such as 6HRZ + (E or S), 2HRZS / 4H₃R₃ and 2H₃R₃Z₃S₃ / 2H₃R₃S₃ / 2H₃R₃, are also acceptable regimens having relapse rates of ≤ 10%. In all cases, it is important to avoid the "addition phenomenon" - namely, adding a single drug to a failing regimen. Otherwise, acquired resistance to the newly added drug may develop. Instead, add at least two, three, or more drugs to which the organisms are known to be susceptible, or which have not already been taken by the patient.

For multidrug-resistant TB (MDR-TB, with resistance to at least isoniazid and rifampicin), treatment should be conducted in specialised centres. A combination of first and second-line drugs (Tables 2 and 3) to which the bacilli are, or are likely to be, susceptible should be used. Drugs that have not been used to treat the patient before are preferred, and so are bactericidal drugs. Treatment usually comprises 5 or 6 drugs for the initial 6 months, followed by 3 or 4 drugs subsequently. The inclusion of an injectable agent for the initial months and a fluoroquinolone all through are generally recommended. Daily regime should be used, except perhaps for the injectables. Drugs showing in-vitro resistance are generally excluded, with the possible exception of isoniazid in cases of low-level resistance. The possibility of cross-resistance between drugs should be noted.

The optimum duration of therapy for MDR-TB has not yet been clearly identified. Some authorities



recommend a total duration of at least 18 months after culture conversion⁶. However, local experience suggests that, with adequate number of active drugs, and the inclusion of fluoroquinolones to which the bacilli are still susceptible, the total duration may be shortened to 12 to 15 months, or one year after sputum culture conversion. However, a longer duration is generally required for patients with diabetes mellitus, silicosis, slow sputum culture conversion, resistance to many drugs or extensive radiographic disease.

Extrapulmonary tuberculosis

Relatively few large-scale studies are available on the treatment of extrapulmonary TB, and consensus is often lacking, especially in relation to the duration of treatment. The recommendations in Table 1 are based on limited current evidence and local experience. Basically, a nine-month regimen is recommended, apart from meningitis, other central nervous system (CNS) involvement, miliary disease, and bone and joint TB, for which a one-year regimen is recommended instead. Some authorities may further prolong treatment for CNS tuberculoma and stage III meningitis. On pharmacokinetic consideration in relation to cerebrospinal fluid penetration, there may also be a role of giving pyrazinamide for more than 3 months, especially if the earlier response is not entirely satisfactory. For some cases that involve limited gut and genitourinary disease, 6 months of treatment may be adequate.

Generally speaking, the initial phase should preferably be given on a daily basis. Adjunctive corticosteroid therapy can be useful, e.g. for tuberculous pericarditis, or severe meningitis. Clinical response of TB lymph nodes during treatment may be quite unpredictable. Paradoxical increase in size is sometimes encountered, probably due to immunological reactions. Residual nodes may still be palpable after completion of treatment

Associated conditions

An extended nine-month regimen is similarly recommended in diabetic and immunocompromised patients. The treatment may have to be modified for patients on concurrent anti-retroviral medications. Possible options include:

- rifamycin-based (rifampicin or rifabutin) regimens, with anti-retroviral therapy (ART) suitably deferred.
- rifamycin-based regimens plus ART, with appropriate modification of the dosages of rifamycins / anti-retroviral agents;
- non-rifamycin-based regimens, plus ART.

With the pros and cons for each option, their choice should be tailored to individual circumstances. As new anti-retroviral agents are coming up from time to time, the interested reader should check the updated recommendations on their use⁷. Paradoxical reactions or immune reconstitution syndrome may occur, especially with concomitant ART. Corticosteroids may be indicated in such circumstances.

Special Clientele

Basically, rifampicin, isoniazid, ethambutol, and pyrazinamide can still be used during pregnancy.

Pyridoxine is sometimes recommended for pregnant women receiving isoniazid. Streptomycin should be avoided because of ototoxicity to the foetus. As the safety profiles of the second-line drugs have not been ascertained, they should also be avoided. For children, ethambutol should generally be avoided in children under 6 years old, and those not capable of reporting symptomatic visual changes accurately.

Assessment and Monitoring

Conditions requiring special attention during anti-TB therapy should be noted prior to commencement of therapy, in particular: liver and renal diseases, visual problems, hearing problems, drug allergy, and concomitant medications. Modifications to the regimens and / or close biochemical monitoring are often necessary if baseline assessment or blood tests reveal these abnormalities, especially among the elderly. More caution is also to be exercised in the use of second-line drugs, which are often associated with significant side effects. Above all, clinical and / or radiological progress should be monitored, together with bacteriological response as appropriate, for all patients on anti-TB treatment.

Conclusions

A six-month standard combination regimen with four drugs in the initial phase is recommended for uncomplicated new cases of pulmonary tuberculosis. Modification and /or extended duration may be necessary for extrapulmonary tuberculosis, retreatment, associated medical conditions, drug resistance and intolerance. Readers are encouraged to refer to updated local guidelines for further information.

Table 1: Summary of local recommendations on the treatment of tuberculosis^{1,2}

Categories of tuberculosis	Recommended Regimens*
Pulmonary	
<i>Uncomplicated</i>	
New Case	2HRZ+(E or S) / 4 HR [§]
Retreatment	3(4)HRZES / 6(5)HR±E [§]
<i>Drug-resistant #</i>	
Isoniazid alone	2SRZE/7RZE or 12RZE
Rifampicin alone [◇]	(3-4)HZES/(15-14)HZE or 18HZE
<i>Multidrug-resistant</i>	
	Individualized, preferably guided by drug susceptibility testing
Extrapulmonary @	
<i>Meningitis / CNS[△]</i>	3HRZE± S / 9 HR± E [¶]
<i>Miliary tuberculosis</i>	3HRZ + (E or S) / 9 HR± E [¶]
<i>Bone and joint[†]</i>	2HRZ + (E or S) / 10 HR [¶]
<i>Lymphadenitis</i>	
Isolated Cervical	2HRZ+(E or S) / 4 HR [¶]
Multiple / Mediastinal	2HRZ+(E or S) / 7 HR [¶]
<i>Pericarditis / Peritonitis</i>	Same as above
<i>Genitourinary / Gut[‡]</i>	Same as above
Associated Conditions @	
<i>Diabetes mellitus</i>	2HRZ+(E or S) / 7 HR [§]
<i>Immunocompromised</i>	
Non-HIV	Same as above
HIV	Same except modifications with anti-retrovirals
<i>Silicosis</i>	8H ₃ R ₃ Z ₃ + (E ₃ or S ₃) or 2HRZ + (E or S)/7 HR



* Notations used for TB treatment regimens:

Drugs: E, ethambutol; H, isoniazid; R, rifampicin; S, streptomycin; Z, pyrazinamide

Duration: this is shown by the figures (in months) in front of the drug combinations; the slash "/" is used to separate different phases of treatment

Frequency: this is shown by the subscripts attached to the individual drugs (i.e. subscript "3" indicates thrice weekly administration) and absence of subscript indicates daily administration if not otherwise stated

§ May be given either daily or thrice weekly in both initial and continuation phases

¶ Daily treatment preferred in initial phase; daily or thrice weekly in continuation phase

Suitable modification of existing regimens may be employed if resistance is discovered during treatment

◇ Fluoroquinolones may be added to the regimen to shorten duration

@ Modifications may be required for retreatment / drug resistant cases

△ Pyrazinamide can be given for longer duration, based on disease severity and tolerance

† total duration may be reduced to 6 - 9 months in the case of TB spine and / or mild disease

‡ 6 months of treatment may be adequate for some cases of limited gut and genitourinary disease

Table 2. Usual dosages of conventional antituberculosis drugs

Drug	Daily dosage			Intermittent dosage		
	Adults and children (mg/kg)	Adults Weight (kg)	Adults Dose (kg)	Adults and children (mg/kg)	Adults Weight (kg)	Adults Dose (kg)
Isoniazid* [@]	5	-	300 mg [#]	10 (3 times/week)	-	-
Rifampicin *	10	<50	450 mg	10-12 (3 times/week)	-	600 mg
		≥50	600 mg			
Streptomycin * [^]		<50	500 mg		<50	500-750 mg
Age ≤50	12-15	≥50	750 mg (5 times/week)	12-15	≥50	750-1000 mg
Age 50-70			500 mg (5 times/week)			500-750 mg
Age ≥70			-			500-750 mg
Pyrazinamide	25-30	<50	1.0-1.5 g	30-40 (3 times/week)	<50	1.5-2.0 g
		≥50	1.5-2.0 g		≥50	2-2.5 g
Ethambutol	15	-	-	30 (3 times/week)	-	-
Thiacetazone *	2.5	-	150 mg	-	-	-
Rifater		per 10 kg	1 tablet			
		>50 kg	5 tablets			

* Some authorities recommend higher dosages (per kg body weight) of isoniazid, rifampicin, streptomycin, and thiacetazone for children.

Some elderly and/or malnourished patients can only tolerate isoniazid 200 mg daily.

@ Pyridoxine supplement should be considered for those with malnutrition or at risk of neuropathy, e.g. pregnancy, diabetes mellitus, alcoholism, chronic renal failure, and HIV infection.

^ Dosage of streptomycin is adjusted according to age.

Table 3. Usual dosages of second-line antituberculosis drugs in the treatment of multidrug-resistant tuberculosis

Drug	Daily dosage		
	Adults and children (mg/kg)	Adults Weight (kg)	Adults Dosage
Amikacin *	15		750 mg
Kanamycin *	15		750 mg
Capreomycin *	15		750 mg
Ofloxacin			600-800 mg
Levofloxacin			500-600 mg
Ciprofloxacin			750-1500 mg
Ethionamide	15 (adults)	<50	500 mg
Prothionamide		≥50	750 mg
Cycloserine	15 (adults)	<50	500 mg
		≥50	750 mg
Clofazimine			50-100 mg
Para-aminosalicylic acid	2 g / 10 kg		8-12 g

* Dosages may be adjusted downward to 500 mg for elderly subjects.

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1. Tuberculosis Control Coordinating Committee of Department of Health and Tuberculosis Subcommittee of Hospital Authority. Chemotherapy of tuberculosis in Hong Kong - update in 2001. Annual Report 2001 of the TB & Chest Service of Department of Health, HKSAR. Accessible at http://www.info.gov.hk/tb_chest/index_5.htm
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4. Chang KC, Leung CC, Yew WW, Ho SC, Tam CM. A nested case-control study on treatment-related risk factors for early relapse of tuberculosis. *Am J Respir Crit Care Med* 2004;170:1124-30.
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6. World Health Organization. Treatment of tuberculosis : Guidelines for national programmes, 3rd edition. 2003 WHO/CDS/TB/2003.313."
7. CDC. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. MMWR 2004 Version 1.20.04. Accessible at http://www.cdc.gov/nchstp/tb/tb_hiv_drugs/toc.htm.

**MCHK CME Programme Self-assessment Questions**

Please read the article entitled "Update on the Management of Pulmonary and Extrapulmonary Tuberculosis" by Dr. Wing-wai Yew and Dr. Chi-chiu Leung and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheet via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 January 2006. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please choose the best answer.

1. The currently recommended treatment regimen(s) for an uncomplicated new case of active pulmonary TB is / are:

- a. 2HRZM / 4HR
- b. 2H₃R₃Z₃M₃ / 4H₃R₃
- c. 2HRZM / 4H₃R₃
- d. All of above
- e. None of above

2. In the updated statement from ATS/CDCP/IDSA, nine months of treatment is recommended for a new case of drug-susceptible pulmonary TB in presence of the following risk factor(s):

- a. Ethnic minorities
- b. Cavitation on the initial chest X-ray
- c. Persistent sputum culture positivity at two months
- d. Both a. and b.
- e. Both b. and c.

3. The currently recommended regimen(s) for retreatment of an uncomplicated but previously treated case of active pulmonary TB is / are:

- a. 2HRZES / 7HR±E, daily or thrice weekly
- b. 3HRZES / 6HR±E, daily or thrice weekly
- c. 4HRZES / 5HR±E, daily or thrice weekly
- d. Both a. and b.
- e. Both b. and c.

4. Which of the following regimen(s) is / are acceptable for treatment of an otherwise uncomplicated case of pulmonary TB with isolated isoniazid resistance

- a. 2SRZE/7RZE
- b. 12RZE
- c. 6HRZ + (E or S)
- d. 2HRZS / 4H₃R₃
- e. All of the above

5. In presence of isolated rifampicin resistance, the duration of treatment for a regimen based on isoniazid, pyrazinamide and ethambutol is:

- a. 6 months
- b. 9 months
- c. 12 months
- d. 18 months
- e. 24 months

6. In presence of isolated rifampicin resistance, which of the following drugs may be added to the regimen based on isoniazid, pyrazinamide and ethambutol to shorten the duration of treatment:

- a. Streptomycin
- b. Levofloxacin
- c. Rifabutin
- d. Rifapentine
- e. Ethionamide

7. "Addition phenomenon" refers to:

- a. Adding a single drug to replace another drug
- b. Adding two to three drugs to a failing regimen
- c. Adding a single drug to a failing regimen
- d. Adding a single drug to a working regimen
- e. Adding a new class of drug

8. Most of the second-line anti-TB drugs should be given:

- a. Daily
- b. Twice weekly
- c. Thrice weekly
- d. Daily or Thrice weekly
- e. Weekly



9. The locally recommended duration of treatment for TB meningitis is

- 6 months
- 9 months
- 12 months
- 18 months
- 24 months

10. Corticosteroids may be used:

- As adjunctive therapy for tuberculous pericarditis
- As adjunctive therapy for severe meningitis
- In the management of paradoxical reaction during anti-TB treatment
- All of above
- None of above

ANSWER SHEET FOR JANUARY 2006

Please return the completed answer sheet to the Federation Secretariat on or before 31 January 2006 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

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Answers to December 2005 issue

Irritable Bowel Syndrome - A Syndrome In Evolution

1. **C** 2. **B** 3. **E** 4. **E** 5. **C** 6. **E** 7. **B** 8. **E** 9. **C** 10. **E**

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