

Chemotherapy of tuberculosis in Hong Kong: a consensus statement

The Tuberculosis Control Coordinating Committee of the Hong Kong Department of Health and the Tuberculosis Subcommittee of the Coordinating Committee in Internal Medicine of the Hospital Authority, Hong Kong

This consensus statement is prepared primarily as a concise reference for tuberculosis chemotherapy in Hong Kong. Treatment should be tailored to patients individually, expert advice should be sought when necessary, and 'directly observed treatment' should be used where possible. A 6-month regimen is recommended as the initial treatment of uncomplicated pulmonary tuberculosis and a 9-month regimen is recommended for retreatment. Patients with disease that is resistant to isoniazid or rifampicin may require modified regimens. Multidrug-resistant tuberculosis should be managed in specialised centres, using multiple drugs as guided by in vitro susceptibility tests. Recommended regimens to treat extrapulmonary tuberculosis are based on limited current evidence, although shorter regimens may be acceptable when better evidence emerges. A longer duration of treatment is required for diabetic, immuno-compromised, or silicotic patients. During pregnancy, streptomycin should be avoided; the safety profiles of second-line drugs have not yet been ascertained. Hepatotoxic drugs should be used with caution in patients with liver dysfunction, and extra caution and dosage reductions are required if streptomycin and ethambutol are used in patients with renal impairment.

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Introduction

Tuberculosis (TB) remains a very important infectious disease in Hong Kong. In 1996, there were 6501 notifications of TB and 310 deaths, which corresponded to

crude notification and death rates of 103 per 100 000 and 5 per 100 000, respectively. As TB can affect organ systems other than the lungs, doctors practising in different fields may sometimes encounter patients with this disease. The Tuberculosis Control Coordinating Committee of the Hong Kong Department of Health and the Tuberculosis Subcommittee of the Coordinating Committee in Internal Medicine of the Hospital Authority, Hong Kong, have jointly prepared the following consensus statement, which primarily serves as a reference and which is not meant to be exhaustive. Indeed, the multitude of possible situations involving TB¹⁻⁹ preclude in-depth discussion of each in this concise statement. The various clinical situations are broadly classified into suitable categories. In each category, recommendations on the treatment regimens are made. However, because solid scientific data in a number of areas are still lacking, on-going evaluation and updating of such information will be required.

It is desirable for TB patients to be managed by or in consultation with doctors experienced in this field. Proper pretreatment assessment and careful monitoring

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Table. Dosages for first-line antituberculous drugs

	Daily dosage			Intermittent dosage (thrice weekly)		
	Adults and children (mg/kg)	Adults		Adults and children (mg/kg)	Adults	
		Weight (kg)	Dose		Weight (kg)	Dose
Isoniazid (H)	5	–	300 mg	15	–	–
Rifampicin (R)	10	<50 ≥50	450 mg 600 mg	15	–	600 mg
Pyrazinamide (Z)	25-35	<50 ≥50	1.5 g 2.0 g	50	<50 ≥50	2.0 g 2.5 g
Ethambutol (E)	25 for 2 months then 15*	–	–	30	–	–
Streptomycin (S)	15-20	<50 ≥50	500-750 mg [†] 750 mg [†]	15-20	<50 ≥50	750 mg 1 g [†]

* 15 mg/kg for the entire treatment duration acceptable if patient is aged >70 years

† If patient is aged >70 years, acceptable dosages are 500 mg daily and 750 mg thrice weekly

during treatment are necessary. The treatment plan should be tailored for each individual patient. Drug compliance is crucial for treatment success and prevention of drug resistance. As far as possible, all antituberculous drugs should be administered using 'directly observed treatment' to ensure patient compliance. Apart from giving antituberculous drugs, adjunctive measures such as the use of short courses of corticosteroids¹⁰ can be useful to treat TB pericarditis and the late stages of TB meningitis, as well as certain cases of TB lymphadenitis, TB pleural effusion, fulminant pulmonary TB, genitourinary TB, and some other forms of TB. Public health measures should also be taken. All cases of TB should be notified to the Department of Health using notification form DH1A(s)(Rev.96)—this is a statutory requirement. Proper completion of all items in the form is necessary to provide comprehensive data on the surveillance of the disease.

Section I: pulmonary tuberculosis

Category A: uncomplicated tuberculosis

Category A1: primary treatment (no treatment within the previous 5 years)

Recommendation*

2HRZ+(E or S) / 4HR

* Notations used for TB treatment regimens in this consensus statement: *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 (ie subscript '3' indicates thrice weekly; subscripts '5', '6', or '7' indicate 5, 6, or 7 times weekly, respectively); absence of subscript indicates either thrice weekly or daily—the commonly used convention where the absence of a subscript indicates only daily frequency is not used in this statement

Four drugs—isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin—are recommended for the 2-month initial phase of treatment, as the rate of initial resistance to isoniazid is more than 4% in Hong Kong. Two drugs—isoniazid and rifampicin—are recommended for the 4-month continuation phase, which makes a total treatment duration of 6 months.

The drugs may be given daily or intermittently (three times per week) in both the initial and the continuation phase. The recommended dosages are listed in the Table. The existing service programme in the chest clinics is intermittent throughout the 6 months and is suitable for patients who are receiving ambulatory treatment from the start of chemotherapy. This regimen can also be considered for those in-patients who have uncomplicated TB and are soon to be discharged to chest clinics for the continuation of ambulatory chemotherapy. The efficacy is under continuous evaluation.

For patients with extensive disease, the 2-month initial phase may be extended to 3 or 4 months, depending on clinical, bacteriological, and radiological responses, while the total duration of treatment may remain at 6 months. If there is suspicion of drug-resistant TB (eg contacts of patients with drug-resistant TB), the initial phase of treatment may be similarly extended, pending the drug sensitivity (ST) results.

Category A2: retreatment (for those who have received treatment within the previous 5 years)

Recommendation

3(4)HRZES / 6(5)HR±E

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 ST results, the smear results, extent of disease, and probability of drug-resistance. Isoniazid and rifampicin (also with ethambutol if the disease is extensive or the ST pattern is unknown) are recommended for the continuation phase; the total treatment duration is 9 months. If the ST results that are available subsequently are unfavourable, the above regimen may need to be modified (see Category B).

Category B: drug-resistant tuberculosis

There are no documented regimens for the treatment of drug-resistant TB.^{11,12} 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. To assist in the management of drug-resistant TB, the following regimens are suggested for reference.

Category B1: resistance to isoniazid alone Recommendations

(1) If the ST pattern is known before starting treatment:

2R₇Z₇E₇S₆ / 10R₇Z₇E₇

(2) If ST results are reported during primary treatment (as in Category A1):

(a) During primary treatment, the ST results may become available during the continuation phase when using the drug combination of isoniazid with rifampicin. If resistance to isoniazid is noted, the treatment regimen should be changed to the daily administration of rifampicin, pyrazinamide, and ethambutol as follows:

2HRZ+(E or S) / (1-2)[†]HR / (9-8)[†]R₇Z₇E₇

(b) For patients with:

- (i) limited parenchymal involvement (total area <15 cm² on chest radiogram) without cavitory disease; and
- (ii) no pleural effusion; and
- (iii) no histology showing positive acid-fast bacilli:

If the response (clinical, radiological, and/or bacteriological) to initial treatment is favourable,

the original 6-month regimen for uncomplicated TB can be followed even when isoniazid resistance is noted. After completion of treatment, the patient should be observed for possible relapse, the chance of which should be small. If relapse occurs, review with the updated ST pattern to guide the retreatment.

Apart from these regimens, clinical trials have also shown that other regimens, such as **6HRZ+(E or S)** are useful in isoniazid-resistant disease. Regimens such as **2HRZS / 4H₃R₃** and **2H₃R₃Z₃S₃ / 2H₃R₃**, are also reasonable regimens and have a relapse rate of less than 10%.

(3) If ST results are reported during retreatment, the following regimen is recommended:

(3-4)[†]HRZES / (9-8)[†]R₇Z₇E₇

Category B2: resistance to rifampicin alone Recommendations

(1) If the ST pattern is known before starting treatment, the following regimen can be given for a total duration of 18 months, or 12 months after negative culture:

(3-4)H₇Z₇E₇S₆ / H₇Z₇E₇

(2) If ST results are reported during primary treatment, the following can be given for a total duration of 18 months, or 12 months after negative culture:

2HRZ+(E or S) / (1-2)[†]HR / H₇Z₇E₇

However, if before changing to a combination of isoniazid, pyrazinamide, and ethambutol, an acquired resistance to isoniazid is also suspected or the treatment response is unsatisfactory (eg if the sputum remains positive for acid-fast bacilli), isoniazid, pyrazinamide, and ethambutol with streptomycin (or other drugs) can be given in the third phase, until the new ST results are available.

(3) If the ST results are reported during retreatment, the following can be given for a total duration of 18 months, or 12 months after negative culture:

(3-4)[†]HRZES / H₇Z₇E₇

Category C: multidrug-resistant tuberculosis

For the treatment of multidrug-resistant TB (MDR-TB)—that is, TB that is resistant to at least isoniazid

[†] Depending on the timing of availability of ST results

and rifampicin, a combination of drugs to which the organism is, or is likely to be, sensitive should be used, namely, a regimen that comprises five or six drugs for the initial 6 months and then three or four drugs subsequently. Apart from the first-line anti-TB drugs, other drugs available include the quinolones (eg ofloxacin, levofloxacin, ciprofloxacin), aminoglycosides (kanamycin, amikacin), prothionamide/ethionamide, cycloserine, para-aminosalicylic acid, and clofazimine.

The adequate duration of therapy for MDR-TB has not been clearly identified. Some authorities recommend a total duration of at least 18 to 24 months, or 24 months after negative culture. However, local experience suggests that, with multiple drug treatment and the inclusion of quinolones to which the bacilli are still susceptible, the total duration may be shortened to 12 to 18 months. The longer duration may be required for patients with diabetes mellitus, silicosis, slow sputum conversion, or extensive disease.

Treatment should be conducted in specialised centres. It is essential to monitor the clinical, radiological, and bacteriological progress, and to adjust the treatment regimen or duration accordingly. Caution is to be exercised in the use of second-line drugs, as they are often associated with significant side effects.

Section II: extrapulmonary tuberculosis

As there have been few large-scale studies on the treatment of extrapulmonary TB, consensus is often lacking, especially in relation to the duration of treatment. The following regimens are recommended for reference to assist in the management of extrapulmonary TB. These recommendations are based on limited current evidence and local experience, and may have to be modified as better evidence for shorter regimens emerge or as experience accumulates.^{3,5,6,8,13} Adjunctive corticosteroid therapy can be useful in tuberculous pericarditis, tuberculous meningitis, tuberculous lymphadenitis, tuberculous pleural effusion, fulminant pulmonary TB, and genitourinary TB.¹⁰

Category A: tuberculous meningitis (including central nervous system tuberculoma)

Recommendation
3HRZE / 9HRZ

Streptomycin may also be added for the initial 2 months. Depending on computed tomography findings and treatment response, some authorities may

extend the total duration of treatment up to 18 to 24 months for central nervous system tuberculoma. Prolonged treatment may also be considered for those who presented at a late stage (eg stage III) of TB meningitis.¹³

Category B: miliary tuberculosis

Recommendation
3HRZ+(E or S) / 9HR

Category C: tuberculosis of bone and joint

Recommendation
2HRZE / 10HR

The total duration of treatment may be reduced to 6 or 9 months in the case of TB of the spine or in other cases with mild disease.

Category D: tuberculous lymphadenitis

Recommendations

- (1) For peripheral cervical disease where there are only solitary/few affected lymph nodes in the upper cervical chain or posterior triangle and the chest X-ray is clear, the same treatment as stipulated in Section I, Category A1 should be given for a total duration of 6 months.
- (2) Other situations are treated using the same regimen as in Section I, Category A1, but with the continuation phase extended such that the total duration of treatment is 9 months. One such situation is peripheral cervical lymphadenopathy with the same setting as (1) above but involving many, enlarged lymph nodes, or supraclavicular lymph nodes (with or without the chest X-ray showing active TB). Another such situation is mediastinal lymphadenopathy as detected by computed tomography or plain X-rays, and confirmed histologically.

It has to be noted that the clinical response of TB of the lymph nodes during treatment may be quite unpredictable, sometimes with paradoxical increases in size probably due to immunological reactions. Residual nodes may still be palpable after completing the full course of treatment.

Category E: tuberculous pericarditis, tuberculous peritonitis, and genitourinary tuberculosis

The recommendation is the same as in Section I, Category A1, but the continuation phase is extended such that the total duration of treatment becomes 9 months. For some cases that involve mild genitourinary disease, 6 months of treatment may be adequate.

Section III: pulmonary tuberculosis associated with medical diseases or special settings

Category A: diabetes mellitus

The recommendation is the same as in Section I, Category A1, but the continuation phase is extended such that the total duration of treatment becomes 9 months.

Category B: immunocompromised patients

The recommendation is the same as in Section I, Category A1, but the continuation phase is extended such that the total duration of treatment becomes 9 months. For patients infected with the human immunodeficiency virus, the total duration of treatment should be at least 9 months, or for 6 months after negative culture.^{6,14} For retreatment and drug-resistant cases, the treatment regimens are essentially similar to those for the seronegative patients except that a longer duration of treatment is required. Universal precaution and infection control measures should be strictly observed if drugs are to be given by injection.

Category C: pregnancy

Basically, rifampicin, isoniazid, ethambutol, and pyrazinamide can still be used, although the manufacturers of rifampicin advise caution during pregnancy. Pyridoxine is sometimes recommended for pregnant women receiving isoniazid. Streptomycin should be avoided because of ototoxicity to the foetus. The safety profiles of the second-line drugs and ofloxacin have not been ascertained and thus these drugs should also be avoided. The taking of antituberculous drugs is itself not a contra-indication to breast feeding.

Category D: children

The treatment regimens are essentially similar to those for adults, except that ethambutol should be avoided in children until they are at least 6 years old and capable of reporting symptomatic visual changes accurately. The drug dosages need to be calculated according to the body weight and may have to be adjusted, especially during the period of adolescent growth spurt.

Category E: silico-tuberculosis

A longer duration of treatment is required for patients with silico-tuberculosis.^{15,16} The recommendations are as follows:

- (1) Initial treatment

2HRZ+(E or S) / 7HR or 8HRZ+(E or S)

- (2) If there is a history of previous treatment

3HRZES / 6HR±E or 3HRZES / 5HRZ+(E or S)

If streptomycin is to be given for a prolonged period, it is preferably given intermittently.

Category F: liver dysfunction

Transient bilirubin and alanine transaminase levels changes are relatively common and do not signify true hepatotoxicity. Drug-induced hepatitis, however, necessitates withholding of all drugs.

When the tuberculous disease is mild or has already improved markedly, wait until the results of the liver function tests return to normal before retrial of conventional antituberculous drugs. Whenever possible, isoniazid and rifampicin should be included in the regimen, so that treatment duration will not be unduly long.

During extensive disease and pending full recovery of liver function, ofloxacin can be used together with streptomycin and ethambutol as an interim regimen. This has been found to be successful for the majority of such patients. Incorporation of ofloxacin as a component of a definitive regimen should only be considered when the patient cannot tolerate rifampicin and isoniazid given concomitantly. The optimal dosage of ofloxacin is unknown. Currently, experience shows that 400 to 600 mg once daily can be tolerated by the majority of patients. The exact dosage to be given depends on age, body weight, renal function, extent of disease, and number of accompanying drugs. The optimal duration of ofloxacin together with either isoniazid or rifampicin and ethambutol as a definitive therapeutic regimen is unknown but should be at least 1 year.

Category G: renal impairment

The development of drug-induced renal impairment is an indication for withdrawal of the drug such as streptomycin or rifampicin. If there is pre-existing renal impairment, rifampicin, isoniazid, and pyrazinamide can be given in the normal dosages. However, in severe renal failure, it is recommended that isoniazid should be given at 200 mg once daily with pyridoxine to avoid peripheral neuropathy.

Streptomycin and ethambutol are the two main drugs that are dependent on the renal route for clearance. Extra caution should be exercised if these drugs are to be used for patients with renal impairment. Regular monitoring of renal function and adverse reactions is mandatory. Appropriate dosage reduction should be made.¹⁷ The guidelines in the literature are not unequivocal. In fact, certain nephrologists have

advised against the use of streptomycin for patients who have significant renal impairment. Adjustment of dosages would be required according to the degree of renal impairment. This is an extremely difficult area and the setting will be rendered more complicated by dialysis. A nephrologist should be consulted whenever doubt exists.

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