# CHEMOTHERAPY OF TUBERCULOSIS IN HONG KONG

## UPDATE IN 2001

A consensus statement of
the Tuberculosis Control Coordinating Committee of
the Hong Kong Department of Health and
the Tuberculosis Subcommittee of
the Coordinating Committee in Internal Medicine of
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ABSTRACT

This is an update of the previous consensus statement on chemotherapy of tuberculosis published in 1998. More detailed recommendations have been provided to facilitate management of patients in a number of special settings like HIV infection, liver and renal dysfunction. A new section on geriatric tuberculosis has also been added to take into account of the increasing number of elderly tuberculosis patients within the local community. The usual dosages of second-line anti-tuberculosis drugs are incorporated, as are the common adverse reactions of both first and second-line drugs. It is hoped that this enriched statement may serve as a concise reference for chemotherapy of tuberculosis in Hong Kong.

Overall, directly observed treatment remains the mainstay of anti-tuberculosis chemotherapy. A 6-month standard combination regimen with four drugs in the initial phase is recommended for uncomplicated new cases of pulmonary tuberculosis, while a 9-month standard regimen starting with 5 drugs is recommended for retreatment cases. Multidrug-resistant tuberculosis requires individually tailored treatment regimens as guided by drug susceptibility testing. Recommendations for extrapulmonary tuberculosis are based on relatively limited data. Shorter regimens may be acceptable in some situations when better evidences accrue. A longer duration of treatment is generally required for patients with diabetes mellitus, silicosis and immunocompromization. During pregnancy, streptomycin should be avoided and the safety of most second-line agents has not yet been ascertained. Potentially hepatotoxic agents should be used with caution in patients with liver dysfunction. The renal route of elimination of streptomycin, ethambutol and some second-line agents necessitates caution and dosage reduction in case of renal impairment.

Key words: Antituberculosis agents; Pulmonary tuberculosis; Extra-pulmonary tuberculosis; Hong Kong

## INTRODUCTION

Tuberculosis (TB) remains a very important infectious disease in Hong Kong. In 2000, there were 7,578 notifications of TB and 299 deaths, which corresponded to crude notification and death rates of 111.7 per 100,000 and 4.4 per 100,000, respectively. As TB can affect organ systems other than the lungs, doctors practising in various specialties may sometimes need to manage patients with this disease. This is an update of the previous consensus statement on chemotherapy of TB published in 1998[1]. This updated statement has been prepared on behalf of 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 Hong Kong Hospital Authority. The multitude of possible situations involving TB precludes an in-depth discussion of each in this concise statement[2-8]. Though not exhaustive, it may still serve as a primary reference in antituberculosis chemotherapy. The clinical situations are broadly classified into several categories. In each category, recommendations on the treatment regimens are made. As accrual of new scientific data is always ongoing, periodic updating of such information will inevitably 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 during treatment are necessary. While a treatment protocol is mandatory for programme purpose, flexibility as tailored to individual patient's clinical status is often needed. Drug adherence is crucial for treatment success and prevention of drug resistance. As far as possible, all antituberculosis drugs should be administered using "directly observed treatment" to meet the purpose[6-8]. Apart from giving antituberculosis drugs, adjunctive measures such as short courses of corticosteroids can be useful in managing TB pericarditis, advanced stages of TB meningitis, certain cases of TB lymphadenitis, TB pleural effusion, TB pyrexia, genitourinary TB, and some other extrapulmonary forms of TB[9,10]. These can also be used to suppress severe hypersensitivity reactions to antituberculosis drugs. Public health measures should also be taken. All cases of TB must be notified to the Department of Health using notification form DH1A(s)(Rev.99). Proper completion of all items in the form is essential to provide comprehensive data on the surveillance of the disease.

Section I: pulmonary tuberculosis
Category A: uncomplicated tuberculosis
Category A1: new cases
Recommendation* 2HRZ+(E or S) / 4 HR

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* 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 (i.e. subscript "3" indicates thrice weekly administration) and absence of subscript indicates daily administration |

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Four drugs — isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin — are recommended for the initial 2-month phase of treatment[6-8], 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[6-8], which makes a total treatment duration of 6 months.

The drugs may be given on a daily or thrice-weekly basis in both the initial and the continuation phase[7]. Studies have shown that daily administration for 2 months followed by thrice-weekly treatment for 4 months can be equally efficacious[3,6,7]. The recommended dosages are listed in Table 1. The existing service programme in the chest clinics is intermittently administered chemotherapy throughout the 6 months[5,11] and is suitable for patients who are receiving ambulatory treatment right from the start of therapy. This regimen can also be considered for those in-patients who have uncomplicated TB and are soon ready for discharge to chest clinics for continuation of ambulatory chemotherapy.

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 still remain at 6 months. An occasional patient may need prolongation of therapy to beyond 6 months. If there is a suspicion of drug-resistant TB (e.g. in contacts of patients with drug-resistant TB), the initial phase of treatment may be similarly

extended, pending the conventional drug susceptibility test (ST) results, if rapid susceptibility studies are not available.

Category A2: retreatment cases
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[7], depending on the timing of the availability of ST results, the rate of smear conversion, 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

Comparative less supporting data are available for categorical recommendation of regimens for the treatment of drug-resistant TB[12]. It is important to avoid the "addition phenomenon"[13] — namely, adding a single drug to a failing regimen. Otherwise, acquired resistance to the newly added drug may develop. Instead, add at least 2, 3, 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[2-4,14,15]

(1) If the ST pattern is known before starting treatment:
   (a) 2 SRZE / 7 RZE or
   (b) 12 RZE

(2) If ST results are reported during treatment of new cases (as in category A1):
   During 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 ± E / (9-8) RZE
   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 / $4H_3R_3$ and $2H_3R_3Z_3S_3$ / $2H_3R_3S_3$ / $2H_3R_3$ are also acceptable regimens and have a relapse rate of ≤10%.

(3) If ST results are reported during retreatment, the following regimen is recommended:
   (3-4) HRZES / (9-8) RZE

Category B2: resistance to rifampicin alone
Recommendations[16]

(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 sputum culture conversion to negative:
   (a) (3-4) HZES / (15-14) HZE or
   (b) 18 HZE

(2) If ST results are reported during treatment for new cases, 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 ± E / (15-14) HZE
   However, if before changing to a combination of isoniazid, pyrazinamide, and ethambutol, additional acquired resistance to isoniazid is also suspected or the treatment response is unsatisfactory (e.g. 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 / (15-14) HZE

Category C: multidrug-resistant tuberculosis

For the treatment of multidrug-resistant TB (MDR-TB) — that is, TB caused by bacilli that are resistant to at least isoniazid and rifampicin in vitro, a combination of drugs to which the organism is, or is likely to be, susceptible should be used. This usually comprises 5 or 6 drugs for the initial 6 months and then 3 or 4 drugs subsequently[13]. Apart from the first-line anti-TB drugs (ethambutol and pyrazinamide), other drugs available include the fluoroquinolones (e.g. ofloxacin, levofloxacin, ciprofloxacin), aminoglycosides (kanamycin or amikacin), capreomycin, prothionamide / ethionamide, cycloserine, para-aminosalicylic acid, and clofazimine. The dosages of such drugs are shown in Table 2.

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 negativity[13]. However, local experience suggests that, with adequate multidrug-treatment regimens, and the inclusion of fluoroquinolones to which the bacilli are still susceptible, the total duration may be shortened to 12 to 15 months[17]. A longer duration may be required for patients with diabetes mellitus, silicosis, slow sputum culture conversion, or extensive disease.

Treatment should be conducted in specialized centres[13]. It is essential to monitor the clinical, radiological, and most importantly bacteriological progress[17]. Caution is to be exercised in the use of second-line drugs, as they are often associated with significant side effects[13,17].

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 as 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 further modified as better evidence for shorter regimens emerge, or as experience accumulates. Generally speaking, the initial phase should be advisably given on a daily basis. Adjunctive corticosteroid therapy can be useful as previously alluded.

Category A: tuberculous meningitis (including central nervous system tuberculoma)
Recommendation[6,8,18,19] 3 HRZE ± S / 9 HR ± E

Depending on computed tomography findings and treatment response, some authorities may further prolong the total duration of treatment for central nervous system tuberculoma. Extended treatment may also be considered for those presenting at an advanced stage (e.g. stage III) of TB meningitis. On pharmacokinetic consideration in relation to cerebrospinal fluid penetration, there may be a role of giving pyrazinamide for more than 3 months, especially in those cases where the earlier response is not entirely satisfactory.

Category B: miliary tuberculosis [6,8]
Recommendation 3 HRZ + (E or S) / 9 HR ± E

Category C: tuberculosis of bone and joint [6,8]
Recommendation 2 HRZ + (E or S) / 10 HR

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

Category D: tuberculous lymphadenitis [6,8,20]
Recommendations

(1) For peripheral disease which commonly involves the cervical region and where there are only solitary / few affected lymph nodes together with normal chest X-ray, 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 chest X-ray, and confirmed histologically.

It has to be noted that the clinical response of TB 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[6,8,21,22], but the continuation phase is extended such that the total duration of treatment becomes 9 months. For some cases that involve limited gut and genitourinary disease, 6 months of treatment may be adequate. One study on tuberculous pericarditis has shown that 3 SHRZ / 3 HR is highly effective[21].

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 9 months[23,24], or at least 4 months after culture conversion to negative. Rifampicin should generally not be used when patient is receiving a HIV-protease inhibitor and/or a non-nucleoside reverse transcriptase inhibitor. Rifabutin can be substituted for use together with some HIV-protease inhibitors. Efavirenz can be used with rifampicin or rifabutin, though the latter requires some increase in dosage. Alternatively, non-rifampicin regimens (such as isoniazid + pyrazinamide + streptomycin ± ethambutol), albeit less potent, can be used for extended durations to avoid clinically significant drug interactions. For retreatment and drug-resistant cases in immunocompromised subjects, the regimens are essentially similar to those immunocompetent 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 by itself not an absolute contra-indication to breast feeding[6-8,25].The infectiousness of the mother, however, must be considered. The interested reader can refer to the new detailed guidelines from World Health Organization[26].

Category D: children

The treatment regimens are essentially similar to those for adults[6,8,25], except that ethambutol should be avoided in children until they are at least 6 years old[8,25] 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. The recommendations[27,28] are as follows:

(1) new cases
   (a) 8 $H_3R_3Z_3$ + ($E_3$ or $S_3$) or
   (b) 2 HRZ + (E or S) / 7 HR

(2) retreatment cases
   (a) 3 $H_3R_3Z_3E_3S_3$ / 5 $H_3R_3Z_3$ + ($E_3$ or $S_3$) or
   (b) 3 HRZES / 6 HR±E

The former regimen, (a) is likely associated with a higher success rate but the tolerance is questionable (≥20% intolerance especially to streptomycin and / or pyrazinamide).

Category F: geriatric tuberculosis

Basically, the treatment of tuberculosis in the elderly should not markedly differ from that in the younger population. However, due regard must be paid to the physiological, psychological and social changes as well as the increased prevalence of co-morbidity that may be associated with aging. As the risk of hepatotoxicity is much higher[29] especially in those with malnourishment, some individual tailoring of dosage, say by using isoniazid 200 mg instead of 300 mg once daily and pyrazinamide 1 gm instead of 1.5 gm once daily may appear warranted. Pyridoxine supplement should also be considered for those with poor nutritional intake or at increased risk of neuropathy. When the drug susceptibility pattern of the cultured bacilli is known to be favourable, use of rifampicin and isoniazid together may prove sufficient[30] for diseases with limited bacillary load. A total duration of 9 months is required for co-administration of these 2 drugs. Use of ethambutol can be problematic in many old patients with poor baseline visual function and / or difficulty in assessing visual acuity.

Category G: liver dysfunction

Transient changes in bilirubin and alanine transaminase levels are relatively common during antituberculosis chemotherapy and do not signify true hepatotoxicity. Drug-induced hepatitis which occurs more commonly in patients with compromised liver

reserve such as in chronic hepatitis B and C infection and alcoholic liver disease[6,31,32] necessitates cessation of therapy. Although it is somewhat controversial whether routine monitoring of liver function tests is required in patients receiving antituberculosis drugs, those at risk should be managed with vigilance both clinically and biochemically.

When the tuberculous disease is mild or has improved markedly, one can wait until the liver chemistry has normalized before retrial of the conventional antituberculosis drugs, by gradual re-institution. Whenever possible, isoniazid and rifampicin should be included in the regimen, so that treatment duration will not be unduly prolonged.

In the face of extensive disease when delay in therapy might be detrimental to the patient's health, ofloxacin can be used together with streptomycin and ethambutol as an interim regimen for treatment[33]. This has been found to be safe and efficacious 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 the co-administration of rifampicin and isoniazid. The optimum dosage of ofloxacin is unknown. Current experience shows that 400 - 600 mg once daily can be tolerated by most patients in this setting. For levofloxacin, the dosage of 400 mg once daily may be employed, pending accumulation of more experience. The fluoroquinolones' dosages should be tailored to age, body weight, renal function, extent of disease, and the number of accompanying drugs. The optimum duration of ofloxacin plus either rifampicin or isoniazid together with ethambutol as a definitive therapeutic regimen is unknown, and appears to be at least 1 year.

Category H: renal impairment

The development of antituberculosis drug-related renal impairment necessitates the withdrawal of the drug(s). Examples include streptomycin and rifampicin. In general, isoniazid, rifampicin and pyrazinamide can be used in normal dosages in the face of renal impairment.[7,8,25] In severe renal impairment, the dosage of isoniazid should be reduced to 200 mg once daily and pyridoxine supplementation is needed to prevent the development of peripheral neuropathy. Streptomycin and aminoglycosides should be avoided[7,8,25] or must have dosages adjusted in the presence of renal impairment. Ethambutol is also predominantly removed by the kidney. Dosage reduction is also mandatory[7,8,25]. In patients with creatinine clearances of 50 - 100 ml/min, ethambutol at 25 mg/kg thrice-weekly can be given; for patients with creatinine clearances of 30 - 50 ml/min, the same dose should be given twice a week. With lower creatinine clearance (10 - 30 ml/min), a dosage of 15 mg/kg at 48 - 36 hour intervals has been suggested. Therapeutic drug monitoring of streptomycin and ethambutol concentrations in serum may help to optimize therapy and minimize toxicity. Ofloxacin and ciprofloxacin are also dependent on renal clearance and dosage reduction in the presence of renal impairment must be made accordingly.

Isoniazid has previously been shown to be significantly removed by haemodialysis[34], but a recent study showed that the median isoniazid recovery in the dialysate was only 9.2%, suggesting that hepatic metabolism remains the primary mechanism of clearing isoniazid[35]. Rifampicin is not significantly removed by haemodialysis[34-36]. Both of them may be given in their usual daily dosage[35,37]. Haemodialysis removal of pyrazinamide is significant[35]. Its primary metabolite, pyrazinoic acid, has been shown to accumulate in

patients with renal failure. It is still not clear whether dosage reduction or spacing is required for patients on haemodialysis and receiving pyrazinamide[35,36]. A dosage of 25-30 mg/kg thrice per week has been recommended by some authorities[35], whereas 40 mg/kg thrice per week has been recommended by others[37]. Ethambutol can still be given at a dosage of 15-25 mg/kg thrice per week[25,35,37]. Regarding the timing of administration of drugs, some authorities have recommended dosing 6 to 24 hours prior to haemodialysis[37], while others have recommended post-dialysis treatment[35].

Section IV: use of fixed-dose combination tablets

Use of fixed-dose combination tablets (FDC) can provide a number of advantages. These include reduced chance of development of acquired drug resistance, simplification in prescribing effective regimens by physicians, improvement in patient adherence and lessened risk of inappropriate use of rifampicin[6-8,25]. However, there are also possible disadvantages such as compromised efficacy due to preparations with suboptimum bioavailability, higher cost and lack of flexibility in dosing[7]. More experience is required to recommend widespread use of FDC under programme setting[25]. Current and future preparations include combinations of rifampicin, isoniazid, pyrazinamide and ethambutol in various ways. However, the presently available combinations in Hong Kong include only rifater (R + H + Z) and rifinah (R + H).

Appendix I Adverse reactions to antituberculosis drugs

| Drug | Reactions | | |
|---|---|---|---|
| | Common | Uncommon | Rare |
| Isoniazid | | Hepatitis<br>Cutaneous hypersensitivity<br>Peripheral neuropathy | Giddiness<br>Convulsion<br>Optic neuritis<br>Mental symptoms<br>Haemolytic anaemia<br>Aplastic anaemia<br>Lupoid reactions<br>Arthralgia<br>Gynaecomastia |
| Rifampicin | | Hepatitis<br>Cutaneous hypersensitivity<br>Gastrointestinal reactions<br>Thrombocytopenic purpura<br>Febrile reactions<br>"Flu syndrome" | Shortness of breath<br>Shock<br>Haemolytic anaemia<br>Acute renal failure |
| Pyrazinamide | Anorexia<br>Nausea<br>Flushing | Hepatitis<br>Vomiting<br>Arthralgia<br>Cutaneous reaction | Sideroblastic anaemia |
| Ethambutol | | Retrobulbar neuritis<br>Arthralgia | Hepatitis<br>Cutaneous reaction<br>Peripheral neuropathy |
| Streptomycin | Cutaneous hypersensitivity<br>Giddiness<br>Numbness<br>Tinnitus | Vertigo<br>Ataxia<br>Deafness | Renal damage<br>Aplastic anaemia |
| Thiacetazone | Gastrointestinal reactions<br>Cutaneous hypersensitivity<br>Vertigo<br>Conjunctivitis | Hepatitis<br>Erythema multiforme<br>Exfoliative dermatitis<br>Haemolytic anaemia | Agranulocytosis |

| | | | |
|---|---|---|---|
| Amikacin<br>Kanamycin<br>Capreomycin | Ototoxicity: hearing damage, vestibular disturbance<br>Nephrotoxicity: deranged renal function test | Clinical renal failure | |
| Ofloxacin<br>Ciprofloxacin | Gastrointestinal reactions<br>Insomnia | Anxiety<br>Dizziness<br>Headache<br>Tremor | Convulsion |
| Ethionamide<br>Prothionamide | Gastrointestinal reactions | Hepatitis<br>Cutaneous reactions<br>Peripheral neuropathy | Convulsion<br>Mental symptoms<br>Impotence<br>Gynaecomastia |
| Cycloserine | Dizziness<br>Headache<br>Depression<br>Memory loss | Psychosis<br>Convulsion | Sideroblastic anaemia |
| Para-aminosalicylic acid | Gastrointestinal reactions | Hepatitis<br>Drug fever | Hypothyroidism<br>Haematological reactions |

Table 1 Usual dosages of conventional antituberculosis drugs

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

[*] Some authorities recommend higher dosages 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.

Table 2 Usual dosages of second-line antituberculosis drugs in the treatment of MDR-TB

| Drug | Daily dosage | | | |
|---|---|---|---|---|
| | Adults and children (mg/kg) | Adults | | |
| | | Weight (kg) | Dosage | |
| Amikacin | 15 | | 750 mg | three to five times/week |
| Kanamycin | 15 | | 750 mg | |
| Capreomycin | 15 | | 750 mg | |
| Ofloxacin | | | 600-800 mg | |
| Levofloxacin | | | 500-600 mg | |
| Ciprofloxacin | | | 750-1500 mg | |
| Ethionamide | 15 | <50 | 500-750 mg | |
| Prothionamide | (adults) | ≥50 | 750-1000 mg | |
| Cycloserine | 15 | <50 | 500-750 mg | |
| | (adults) | ≥50 | 750-1000 mg | |
| Para-aminosalicylic acid | 2 g/10 kg | | 10-12 g | |

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