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Summary

Management principles in treating TB
The objective of anti-tuberculous treatment is to achieve a lifetime of cure of the disease while preventing resistance.

Treatment regimens must contain multiple drugs to which the organisms are susceptible.

Single agents should not be added to an existing treatment regimen, and particularly not to a failing regimen. The addition of two or more drugs is required if treatment failure is suspected.

All patients with MDR-TB or XDR-TB must be treated with daily DOT.

Ciprofloxacin is no longer recommended to treat drug-susceptible or drug-resistant TB.

Standard treatment regimens for susceptible pulmonary TB isolates
Treatment of active TB usually includes two phases. The phases are the:

- intensive phase of treatment (when more drugs are used) – bactericidal phase
- continuation phase (with fewer drugs) – sterilisation phase.

Adults should be treated with a standard six-month regimen consisting of an intensive phase of isoniazid, rifampicin, ethambutol, and pyrazinamide for two months followed by isoniazid and rifampicin for four months (2HREZ/4HR). No other agents can be substituted in the intensive or continuation phase of treatment, as this would decrease the efficacy of the regimen and a longer duration of therapy would be required.

Ethambutol should be added to the initial regimen for the treatment of all TB patients until such time as drug susceptibility tests establish that it is not necessary. Once full susceptibility is confirmed, ethambutol can usually be stopped however in patients with a significant disease burden, some clinicians recommend continuing ethambutol for the entire first two months or until smear conversion has occurred. An injectable agent or moxifloxacin may be used instead when ethambutol is not an option provided drug resistance is not suspected, in which case multiple additional agents may be required in the initial regimen.

Directly observed therapy
Wherever possible the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy.

Patients may receive a daily intensive phase followed by a three times a weekly continuation phase (2RHEZ/4(RH)₃), provided that each dose is directly observed.

Alternatively three times weekly dosing throughout therapy (2RHEZ/4(RH)₃) may be used provided that every dose is directly observed and that the patient is not living with HIV infection. Thrice-weekly DOT is suitable from the outset of treatment during the intensive phase regimen, only if the patient is non-infectious and has a low burden of disease. Twice-weekly DOT regimens are no longer recommended.

In the presence of widespread disease or major cavitatory TB, daily therapy should be used initially. Good clinical progress and smear or culture conversion should be demonstrated before switching from daily treatment to thrice-weekly DOT.

Smoking cessation
All patients with TB who smoke should be advised and offered support to quit smoking.

**Standard treatment regimens for extra-pulmonary TB**

With three exceptions, central nervous system TB, miliary/disseminated TB and bone and joint TB, non respiratory TB is treated with the same regimens as pulmonary TB. Patients with some forms of extra-pulmonary TB may require a more prolonged treatment course. Patients with miliary/disseminated TB should be assessed for evidence of central nervous system TB.

**Drug-resistant TB**

The most important predictors of drug-resistant TB are:

- a previous episode of TB treatment
- progressive clinical and/or radiographic findings while on TB treatment
- origin from, history of residence in or frequent travel to a region/country with high rates of drug resistance
- exposure to an individual with infectious drug-resistant TB.

Suggested regimens for the treatment of patients with mono- and poly-drug resistance are shown in Table 5.1.

A daily dosing schedule should be used for all patients with drug-resistant TB. Intermittent dosing schedules must not be used.

All cases of MDR-TB or XDR-TB must be treated in consultation with a tertiary centre experienced in the care of such patients.

**Corticosteroid treatment in the management of TB**

Corticosteroids should only be given when adequate anti-tuberculosis treatment is also being given. Adjuvant corticosteroids treatment is recommended for both TB meningitis and TB pericarditis and may also provide benefit in life threatening cases of TB.

**Monitoring**

Patients who are sputum smear–positive before treatment should have repeat sputum tests at least monthly to confirm sterilization. If the specimen at the end of the third month is both smear and culture positive, repeat drug susceptibility testing should be performed. As early detection of drug resistant TB is important, repeat DST after two months of treatment may be appropriate in some patients where there are concerns that acquired drug resistance may have developed.

Baseline blood count, creatinine, alanine amino-transferase (ALT), hepatitis B surface antigen, and hepatitis C and HIV serology should be completed in all adults who are to be treated for TB disease or latent TB infection. Depending on the patients risk factors for hepatotoxicity, regular monitoring of either ALT or liver function tests should occur in all patients on treatment for TB.

**Drug adverse effects**

The prompt recognition and appropriate management of adverse drug reactions is essential. Patients should be advised of common and important side effects such as those associated with hepatitis and ocular toxicity, and to report these promptly.
Monthly monitoring of visual acuity and colour discrimination is recommended for all patients on ethambutol for longer than two months and for any patient with renal impairment.

Four weeks is an arbitrary maximum period for a patient to be off all drugs.

The maximum period for a patient to be on a partial regimen is 10 days.

Some patients will require a temporary treatment regimen to be started following a drug reaction until the difficulties have been resolved.

**Interactions with anti-TB drugs**

The interaction of TB drugs with other medications is not uncommon and must always be considered when starting TB treatment.

**Special situations**

The management of TB in patients with hepatic dysfunction and renal impairment is complex and treatment regimens may require dose adjustment with regular patient monitoring.
Introduction

This chapter includes information on the treatment of TB disease, the monitoring of patients on TB treatment and the treatment of TB in special situations including renal impairment, hepatic impairment and pregnancy. This chapter refers specifically to the treatment of TB in adults. The treatment of TB in children is discussed in Chapter 5. The treatment of TB in patients with HIV infection is discussed in Chapter 6.

Practitioners who are not familiar with TB and its management are advised to refer patients to a clinician experienced in the field. TB medications are specialist only.
1 Management Principles in Treating TB

The objective of anti-tuberculous treatment is to achieve a lifetime of cure of the disease while preventing resistance. Effective chemotherapy taken over an adequate period of time is the guiding principle of treatment for all forms of tuberculosis. Investigations should be undertaken that give the best possible chance of identifying the organism and its sensitivity pattern. This is particularly important when drug resistance is possible.

Treatment regimens must contain multiple drugs to which the organisms are susceptible. **Single agents should not be added to an existing treatment regimen**, and particularly not to a failing regimen. The addition of two or more drugs is required if treatment failure is suspected. Initial treatment should be modified if drug resistance is suspected (see section 5.2).

Clinicians should notify all patients who are treated for TB disease or infection. Relapse of TB, whether this occurs during treatment or not, must be re-notified. Infectious cases of TB must be isolated to prevent further spread of disease. Isolation (in hospital or at home) is discussed in Chapter 12.

Poor adherence to prescribed anti-TB treatment is the most common cause of treatment failure. Directly observed therapy (DOT) is an effective way to monitor adherence to treatment.

**All patients with MDR-TB or XDR-TB must be treated with daily DOT.** Universal provision of DOT is not currently feasible for all patients treated for TB in New Zealand however priority should also be given to the following circumstances (and see Chapter 4):

- suspected or proven drug-resistant organisms
- treatment failure /re-treatment
- social or medical circumstances that are likely to impair adherence to the treatment regimen
- suspected non-adherence or previous non-adherence
- cases that are sputum smear positive for acid-fast bacilli
- people on treatment for both TB and HIV infection
- children.

Completion of therapy is based on the total number of doses administered and not on the duration of therapy alone.1

1.1 Phases of treatment and abbreviations of treatment regimens

Commonly used abbreviations for the names of tuberculosis (TB) drugs in treatment regimens are:

- E ethambutol
- H isoniazid
Treatment of active TB usually includes two phases. The phases are the:
- intensive phase of treatment (when more drugs are used) – bactericidal phase
- continuation phase (with fewer drugs) – sterilisation phase.

In a treatment regimen such as ‘H₃R₃’, the subscript numbers indicate the number of doses per week in an intermittent regimen. For example, H₃R₃ means a treatment regimen of three doses per week of isoniazid and three doses per week of rifampicin.

In a treatment regimen such as ‘2RHEZ/4RH’, the number and letters before the slash refer to the initial phase and those after it refer to the continuation phase. In this example, the treatment regimen is two months of daily isoniazid, rifampicin and pyrazinamide during the initial phase followed by four months of daily isoniazid and rifampicin in the continuation phase. The absence of a subscript number means the drug is taken daily.
2 Drug Doses and Administration

2.1 Drug doses

Table 2.1 shows the dosage recommendations for anti-TB medicines. In obese patients, ideal body weight should be used to calculate doses of the first-line TB drugs. Drug doses in obesity are discussed in section 11.4.

**Ciprofloxacin is no longer recommended to treat drug-susceptible or drug-resistant TB.** The most potent available fluoroquinolones in descending order based on in vitro activity and animal models are: moxifloxacin=gatifloxacin > levofloxacin > ofloxacin. If a fluoroquinolone is required to treat a patient with TB, moxifloxacin is currently the preferred agent in New Zealand.

Table 2.1: Dosage recommendations for anti-tuberculosis agents for adults

<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily dose</th>
<th>Thrice-weekly dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid#</td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Maximum dose/kg</td>
<td>300 mg</td>
<td>900 mg</td>
</tr>
<tr>
<td>Maximum dose/day</td>
<td>5 mg</td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>5 mg*</td>
<td></td>
</tr>
<tr>
<td>Maximum dose/kg</td>
<td>300 mg</td>
<td></td>
</tr>
<tr>
<td>Maximum dose/day</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Maximum dose/kg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>Maximum dose/day</td>
<td>25 mg</td>
<td>35 mg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>2 g</td>
<td>3 g</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 mg</td>
<td>30 mg (25–35)</td>
</tr>
<tr>
<td>Maximum dose/kg</td>
<td>2.5 g</td>
<td></td>
</tr>
<tr>
<td>Maximum dose/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Second-line agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily dose</th>
<th>Thrice-weekly dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protionamide and ethionamide</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum dose/kg</td>
<td>15–20 mg</td>
<td></td>
</tr>
<tr>
<td>Maximum dose</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15–20 mg</td>
<td>1 g</td>
</tr>
<tr>
<td>Maximum dose, intramuscular, intravenous</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>15–20 mg</td>
<td></td>
</tr>
<tr>
<td>Maximum dose, intramuscular, intravenous</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>15–20 mg</td>
<td></td>
</tr>
<tr>
<td>Maximum dose, intramuscular, intravenous</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15–20 mg</td>
<td></td>
</tr>
<tr>
<td>Maximum dose intramuscular</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td>15–20 mg</td>
<td>750 mg–1 g</td>
</tr>
<tr>
<td>P-aminosalicylic acid (4 g sachets)</td>
<td>150 mg</td>
<td>8–12 g</td>
</tr>
</tbody>
</table>

* Sometimes doses up to 450 mg are used.

§ An intravenous form of rifampicin is available.

|| Protonamide and ethionamide are given in divided doses.

# Patients >50 kg should be prescribed Rifinah 300 x2 tablets daily (rifampicin 600 mg daily and isoniazid 300 mg daily); adult patients <50 kg are usually prescribed Rifinah 150 x3 tablets daily (rifampicin 450 mg and isoniazid 300 mg daily).

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**2.1.1 Ethambutol**

The daily dose of ethambutol should be 15 mg/kg, unless there is a good reasons for a higher dose. Ethambutol should be avoided in patients who have renal impairment (section 11.1). The risk of optic neuritis is greater with higher doses. Higher doses may be used for treatment with intermittent therapy.

**2.1.2 Pyridoxine with isoniazid and cycloserine**

In patients taking isoniazid, it is advisable to also give pyridoxine 10–25 mg/day. This is essential for people at risk of peripheral neuropathy from other causes such as diabetes, chronic renal failure, malnourishment, alcoholism, HIV infection and pregnancy. In patients on isoniazid, a pyridoxine dose of 25 mg is sufficient as higher doses may interfere with isoniazid activity.

In patients taking cycloserine, the pyridoxine dose should be 50 mg for every 250 mg of cycloserine prescribed.
2.2 Administration of amikacin

Aminoglycosides should be dosed once-daily or at extended intervals. This results in a high peak serum concentration, which declines over a 24-hour period and a drug-free period at the end of the dosing interval.

2.2.1 Dose adjustments for weight

The correct dose of amikacin is based on body weight. The weight used to calculate the dose should be the actual bodyweight for non-obese individuals. For these patients the usual daily dose is 15 mg/kg, given by intravenous infusion (or, albeit rarely, intramuscularly). The method of calculating the dosing weight with obese people is discussed in section 11.4.

2.2.2 Doses with (stable) renal impairment

Modifications are required to the dose and/or dosing interval when significant renal impairment is present. Prescribers are advised to consult their local guidelines, hospital pharmacist or a clinician experienced in the use of aminoglycosides.

2.2.3 Prolonged treatment with amikacin and normal renal function

Depending on the severity of TB, amikacin is generally given daily for five or six days per week. When necessary, amikacin can be continued at the same dose three times a week after an initial period of daily administration.3

Monitoring of patients on amikacin is discussed in section 7.3.

2.3 Pharmacological considerations with anti-tuberculosis drugs

The sections below discuss the pharmacological considerations with the anti-TB agents isoniazid, rifampicin, rifabutin, ethambutol, pyrazinamide, prothionamide and ethionamide, fluoroquinolones, streptomycin, amikacin, and whether directly observed therapy should occur before or after food.

2.3.1 Isoniazid

Isoniazid is best taken on an empty stomach with no antacids taken for at least two hours afterwards.7 Food and antacids may reduce the absorption of isoniazid.

2.3.2 Rifampicin

Rifampicin is best taken on an empty stomach. The peak serum concentration is reduced by one-third, if rifampicin is taken after a fatty meal. Smaller reductions are seen with carbohydrate meals. Antacids do not affect the absorption of rifampicin.8
Only free rifampicin (not plasma protein-bound rifampicin, which accounts for 75% of the total serum rifampicin level) is available to interact with mycobacteria. Therefore, to produce a concentration of ‘free’ rifampicin of 0.2–0.5 µg/ml (the MIC of rifampicin for *M. tuberculosis*) a total serum concentration of 0.8–2.0 µg/ml is required. This is usually attained and persists for several hours, even if the drug was administered postprandially.8,9

Rifampicin is excreted in urine, sweat, tears and other bodily fluids and colours those fluids orange. It may permanently discolor soft contact lenses.

2.3.3 Rifabutin
Rifabutin should be taken straight after food to enhance serum concentrations of rifabutin.10 This is opposite to the effect of food on rifampicin blood levels.

2.3.4 Ethambutol
Food does not affect the absorption of ethambutol.11

2.3.5 Pyrazinamide
Food does not impair the absorption of pyrazinamide.

2.3.6 Protionamide and ethionamide
Protionamide and ethionamide drugs have a narrow therapeutic side effect profile. They are well absorbed after food. The effect of antacids on absorption is uncertain.

2.3.7 Fluoroquinolones
The ingestion of fluoroquinolones with food delays the time to peak serum concentration by one to two hours, but does not change the extent of absorption. Antacids or ferrous sulphate may interfere with the absorption of fluoroquinolones.

2.3.8 Streptomycin
Streptomycin must be given parenterally. The peak serum level occurs one hour after an intramuscular dose. The half-life of streptomycin in the blood is about five hours. Excretion is almost entirely renal. Streptomycin enters the cerebrospinal fluid only in the presence of inflamed meninges.

2.3.9 Amikacin
Amikacin is usually given by intravenous infusion over half an hour. If given intramuscularly, the peak serum concentration occurs an hour later.
2.3.10 Directly observed therapy – whether drug taking should be before or after food

If feasible, a person undergoing directly observed therapy should take their drugs on an empty stomach. However, if this is not possible, the drugs can be taken without fasting, since the timing is often not critical. However, caution is required; rifampicin levels are lower when the drug is taken after food, especially after a fatty meal. Prescribers should give appropriate advice to people undergoing directly observed therapy.

Before a prescriber starts a person on directly observed therapy, they should ask the person about symptoms of malabsorption. The combination of malabsorption and postprandial administration of rifampicin during directly observed therapy may result in treatment failure or the selection of rifampicin-resistant organisms.13

2.4 Drugs in fixed-dose combinations

Fixed-dose combination (FDC) tablets contain two or more medicines within the same tablet or capsule. An advantage of FDCs is the reduced risk of resistance developing, because if a dose is missed, all the drugs are omitted and it is less easy to take an inadequate combination. Other advantages are that fewer medication errors occur with FDCs and fewer prescription items need to be ordered.

A disadvantage of many FDC formulations is reduced bioavailability of some drugs, in particular rifampicin, and the loss of flexibility in obtaining an optimal dose of some agents, such as pyrazinamide; the total number of tablets may not be reduced.

2.4.1 Rifinah

‘Rifinah 150’ and ‘Rifinah 300’ refer to the dose (mg) of the rifampicin component. The dose of isoniazid in these two preparations is 100 mg and 150 mg respectively. Therefore, to provide a satisfactory dose of isoniazid, use:

- Rifinah 150 (x3 tablets daily) in people weighing under 50 kg
- Rifinah 300 (x2 tablets daily) in people weighing over 50 kg.
3  Standard Treatment Regimens for Susceptible Pulmonary TB Isolates

The treatment of active TB usually includes two phases. The phases are the:

- intensive phase of treatment (when more drugs are used) – bactericidal phase
- continuation phase (with fewer drugs) – sterilisation phase.

Adults should be treated with a standard six month regimen consisting of an intensive phase of isoniazid, rifampicin, ethambutol, and pyrazinamide for two months followed by isoniazid and rifampicin for four months (2HREZ/4HR).\(^2\) No other agents can be substituted in the intensive or continuation phase of treatment, as this would decrease the efficacy of the regimen and a longer duration of therapy would be required.

Ethambutol should be added to the initial regimen for the treatment of all TB patients until such time as drug susceptibility tests establish that it is not necessary.\(^2\) Once full susceptibility is confirmed, ethambutol can usually be stopped however in patients with a significant disease burden, some clinicians recommend continuing ethambutol for the entire first two months or until smear conversion has occurred.\(^1,2\) An injectable agent or moxifloxacin may be used instead when ethambutol is not an option provided drug resistance is not suspected, in which case multiple additional agents may be required in the initial regimen.

2HREZ/4HR is the preferred treatment regimen for all cases of susceptible TB. 2HRE/7HR may also be used when pyrazinamide is not tolerated or if the organism is resistant to pyrazinamide.\(^14\) Mycobacterium bovis (or BCG related disease) is naturally resistant to pyrazinamide.

All treatment regimens suggested in this chapter give the minimum period of treatment required to achieve cure. Extensive TB, whether pulmonary or multi-system, requires a longer duration of treatment. In patients with cavitatory disease or positive cultures after two months of treatment, the continuation phase of the six-month treatment regimen should be extended so that the patient receives at least nine months of treatment in total. Clinicians should also consider increasing the duration of treatment for patients with extensive TB or slow radiological improvement.

3.1 Directly observed treatment

Wherever possible the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy. There are two alternatives to this recommendation (Table 3.1). Patients may receive a daily intensive phase followed by a three times a weekly continuation phase (2RHEZ/4R\(_3\)H\(_3\)), provided that each dose is directly observed. Alternatively three times weekly dosing throughout therapy (2R\(_3\)H\(_3\)E\(_3\)Z\(_3\)/4R\(_3\)H\(_3\)) may be used provided that every dose is directly observed and that the patient is not living with HIV infection. Thrice-weekly DOT is suitable from the outset of treatment during the intensive phase regimen, only if the patient is non-infectious and has a low burden of disease.\(^4\) Twice-weekly DOT regimens are no longer recommended.\(^4\)
In the presence of widespread disease or major cavitatory TB, daily therapy should be used initially. Good clinical progress and smear or culture conversion should be demonstrated before switching from daily treatment to thrice-weekly DOT. Intermittent regimens are unproven in the treatment of extra-pulmonary TB.

**Table 3.1:** Dosing frequency for patients with drug-susceptible pulmonary TB

<table>
<thead>
<tr>
<th>Dosing frequency</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intensive phase</strong></td>
<td><strong>Continuation phase</strong></td>
</tr>
<tr>
<td>Daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Daily</td>
<td>Three times per week</td>
</tr>
<tr>
<td>Three times per week</td>
<td>Three times per week</td>
</tr>
</tbody>
</table>


A meta-analysis of the dosing frequency for HIV-negative patients on TB treatment outcomes found little evidence of differences in failure or relapse rates with daily or three times weekly regimens. However, rates of acquired resistance were higher among patients receiving three times weekly dosing throughout treatment.15

All patients with MDR-TB must receive daily DOT.

### 3.2 Smoking cessation

Recent reviews have shown that smoking is strongly associated with increased rate of both TB infection and the development of pulmonary TB.15A Smoking also leads to faster progression and poorer prognosis of TB. Smokers are less likely to adhere to TB treatment and are more likely to relapse after successfully completing treatment according to some studies.15B

All patients with TB who smoke should be advised and offered support to quit smoking.

With regard to smoking cessation, it is important to note that rifampicin increases the clearance of bupropion resulting in decreased levels of bupropion.
4 Standard Treatment Regimens for Extra-pulmonary TB

With three exceptions, central nervous system TB, miliary/disseminated TB and bone and joint TB, non respiratory TB is treated with the same regimens as pulmonary TB.

4.1 Duration of treatment for extra-pulmonary tuberculosis

Studies on the treatment of extra-pulmonary TB are more limited, but reports on pleural, lymphatic, renal, abdominal, meningeal and bone and joint TB show that outcomes are similar to those of pulmonary TB using similar regimens.\(^{16,17,18,19}\) However as the ideal therapy for meningitis, miliary/disseminated disease or spinal disease with neurological complications has not yet been defined with certainty, some authorities have recommended longer duration of treatment.

At least 12 months of treatment is usually recommended for meningeal TB and 12 months or longer of treatment for intra-cerebral TB.\(^{2,20}\) Patients with disseminated TB should be assessed for evidence of central nervous system involvement and treatment should be extended to 12 months if this is present.\(^{21}\) Some experts recommend at least 9–12 months of treatment for TB of bones and joints given the difficulties in assessing treatment response.\(^{2}\)

A longer duration of treatment is also recommended in the presence of severe or extensive disease, drug resistance or clinical or radiological progress that is slower than expected.

A daily dosing schedule is considered optimal for patients with central nervous system TB, miliary/disseminated TB and bone and joint TB.\(^{20}\)

4.2 Management of central nervous system tuberculosis

Table 4.1 shows that isoniazid and pyrazinamide penetrate best into the cerebrospinal fluid. Rifampicin is also an excellent agent if the meninges are inflamed. Rifampicin, isoniazid and pyrazinamide are therefore the most important drugs for the treatment of CNS tuberculosis.\(^{22}\) Some authorities recommend continuing pyrazinamide beyond two months in the setting of CNS TB.

An aminoglycoside can be used if the meninges are inflamed and can be an additional agent where drug resistance is suspected; isoniazid is the most common agent to which resistance is found. If there is no inflammation, protionamide may also be an option, as this does penetrate into the cerebrospinal fluid. Fluoroquinolones may represent an effective agent for the treatment of TB meningitis, however data concerning their cerebrospinal fluid pharmacokinetics and safety during prolonged therapy are limited.\(^{23,24}\)
Table 4.1: Treatment of tuberculous meningitis and intra-cranial tuberculosis

<table>
<thead>
<tr>
<th></th>
<th>Rifampicin R</th>
<th>Isoniazid H</th>
<th>Pyrazinamide Z</th>
<th>Ethambutol E</th>
<th>Streptomycin S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug penetration across the</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>blood/brain barrier:</td>
<td></td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>+/-</td>
</tr>
<tr>
<td>• inflamed meninges</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>+/-</td>
</tr>
<tr>
<td>• non-inflamed meninges</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>+/-</td>
</tr>
<tr>
<td>Drug efficacy in central</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>+/-</td>
</tr>
<tr>
<td>nervous system tuberculosis (TB)</td>
<td>10 mg/kg</td>
<td>5 mg/kg</td>
<td>25–35 mg/kg</td>
<td></td>
<td>20 mg/kg intramuscular (maximum 1 g)</td>
</tr>
<tr>
<td>Daily drug doses (for adults)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral steroid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Should be offered to all patients</td>
</tr>
<tr>
<td>Duration of TB medicines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9–12 months for adults</td>
</tr>
</tbody>
</table>

* For information about doses for children, see Chapter 5.
5 Drug Resistant Tuberculosis

5.1 Types of drug resistance

The three types of drug resistance are primary, secondary, and naturally occurring resistance.2

5.1.1 Primary resistance

Primary resistance occurs if the organisms transmitted are resistant to one or more TB drugs.

5.1.2 Secondary resistance

Secondary resistance occurs if new resistance develops during treatment.

5.1.3 Naturally occurring drug resistance

There is a degree of naturally occurring resistance to anti-TB drugs.25 This resistance varies from drug to drug. The approximate rates of development of resistant organisms in vitro are:

- $10^{-3}$ for ethionamide, capreomycin, cycloserine and thiocetazone
- $10^{-5}$–$10^{-7}$ for isoniazid, streptomycin, ethambutol, kanamycin and para-aminosalicylic acid
- $10^{-9}$ for rifampicin
- $10^{-14}$ for combined isoniazid and rifampicin.

Cavities contain approximately $10^8$–$10^9$ bacilli and there is a significantly higher risk of naturally resistant organisms being present in cavitating TB.23 Due to the occurrence of naturally occurring drug resistant TB it is essential that TB is treated with multiple drugs.

5.2 Suspected drug resistance

Additional drugs may be necessary in re-treating TB in people previously treated. If MDR-TB is a possibility and immediate treatment is clinically necessary, sufficient drugs should be used initially to avoid the development of further resistance should the isolate subsequently prove to be resistant to all first-line agents. In practice, this may necessitate use of an MDR regimen at the outset.

Treatment of TB caused by drug-resistant organisms should be done by or in close consultation with an expert in the management of these difficult cases. Second-line regimens often present the patient’s best hope for cure and thus inappropriate management of a drug-resistant case can have life threatening consequences.
The management of drug-resistant TB is often complicated by drug toxicities and long duration of therapy. Successful treatment outcomes for drug-resistant TB are often difficult to achieve compared with drug-susceptible disease, especially when multidrug-resistance is present.

The most important predictors of drug-resistant TB are:

- a previous episode of TB treatment
- progressive clinical and/or radiographic findings while on TB treatment
- origin from, history of residence in or frequent travel to a region/country with high rates of drug resistance
- exposure to an individual with infectious drug-resistant TB.

### 5.3 Treatment of drug-resistant TB

The duration of treatment needs to be re-evaluated when drug resistance is encountered. The following treatment periods are a guide and represent the minimum duration of treatment (Table 5.1). A daily dosing schedule should be used for all patients with drug-resistant TB. Intermittent dosing schedules must not be used.

It is essential that exemplary infection control practices are maintained in all case of drug resistant TB.
Table 5.1: Suggested regimens for mono- and poly-drug resistance (when further acquired resistance is not a factor and laboratory results are highly reliable)

<table>
<thead>
<tr>
<th>Pattern of drug resistance</th>
<th>Suggested regimen</th>
<th>Minimum duration of treatment (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (+/- S)</td>
<td>R, Z and E</td>
<td>6–9*</td>
<td>A fluoroquinolone may strengthen the regimen for patients with extensive disease</td>
</tr>
<tr>
<td>H and Z</td>
<td>R, E and moxifloxacin</td>
<td>9–12*</td>
<td>A longer duration of treatment should be used for patients with extensive disease</td>
</tr>
<tr>
<td>H and E</td>
<td>R, Z and moxifloxacin</td>
<td>9–12*</td>
<td>A longer duration of treatment should be used for patients with extensive disease</td>
</tr>
<tr>
<td>R</td>
<td>H, E, moxifloxacin plus at least two months of Z</td>
<td>12–18*</td>
<td>An injectable agent may strengthen the regimen for patients with extensive disease</td>
</tr>
<tr>
<td>R and E (+/- S)</td>
<td>H, Z, moxifloxacin plus an injectable agent for at least the first 2–3 months</td>
<td>18</td>
<td>A longer course (six months) of the injectable agent may strengthen the regimen for patients with extensive disease</td>
</tr>
<tr>
<td>R and Z (+/- S)</td>
<td>H, E, moxifloxacin plus an injectable agent for at least the first 2–3 months</td>
<td>18</td>
<td>A longer course (six months) of the injectable agent may strengthen the regimen for patients with extensive disease</td>
</tr>
<tr>
<td>H, E, Z (+/- S)</td>
<td>R, moxifloxacin plus an oral second-line agent, plus an injectable agent for the first 2–3 months</td>
<td>18</td>
<td>A longer course (six months) of the injectable agent may strengthen the regimen for patients with extensive disease</td>
</tr>
</tbody>
</table>

* In most cases of drug-resistant TB, the longer time period is the preferred minimum duration of treatment.


5.3.1 Isoniazid-resistant tuberculosis

Resistance to isoniazid is reported at 0.1 mcg/mL (low level) and 0.4 mcg/mL (high level). If low-level resistance is present, isoniazid should be continued as part of a regimen containing at least three other effective drugs. This is because the determination of isoniazid resistance is based on minimal inhibitory concentrations (MICs), and in practice the serum level could exceed the in vitro MIC.26

5.3.2 Rifampicin-resistant tuberculosis

Isolated resistance to rifampicin is uncommon and should raise the suspicion of MDR-TB. The loss of rifampicin from the treatment regimen requires a longer duration of treatment.

Resistance to rifampicin is associated in most cases with cross-resistance to rifabutin. It is not clear whether laboratory-reported rifabutin susceptibility in the presence of rifampicin resistance is sufficiently reliable to allow use of rifabutin as a substitute for rifampicin. It is recommended that a regimen similar to that used for rifampicin resistance be used.
5.3.3 Pyrazinamide-resistant tuberculosis

*Mycobacterium bovis* (or BCG related disease) is naturally resistant to pyrazinamide. 2RHE/7RH (or 9RH for minor extent of disease) is appropriate for treatment of patients with isolated pyrazinamide-resistant TB.

5.4 Multi-drug resistant TB

MDR-TB is defined as TB that is resistant to rifampicin and isoniazid. Resistance to other drugs may or may not be present.

Resistance to rifampicin and isoniazid eliminates the two most important TB drugs from the treatment regimen. **All cases of MDR-TB must be treated in consultation with a tertiary centre experienced in the care of such patients.**

Key recommendations for the treatment of MDR-TB include:

- drug-resistant TB should be promptly diagnosed and appropriate therapy initiated
- patients with MDR-TB should always be treated with a minimum of four or more drugs to which the patient has not been previously exposed and to which the isolate is susceptible
- drug susceptibility testing (DST) should generally be used to guide therapy, however do not depend on DST in individual regimen design for ethambutol, pyrazinamide and group 4 and 5 drugs
- ciprofloxacin should not be used as an anti-tuberculosis agent
- treatment should be continued for at least 18 months past culture conversion
- adverse effects should be treated immediately and adequately
- daily DOT is mandatory for all patients with MDR-TB.

WHO classifies five different groups of drugs available for use for the treatment of MDR-TB. These groups provide a systematic method for allocating drugs to an MDR treatment regimen (Table 5.2). Treatment regimens should be designed with a consistent approach based on the hierarchy of the five groups of anti-tuberculosis drugs.

### Table 5.2: WHO classification of anti-TB drugs

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 – first line agents (oral)</td>
<td>Isoniazid, rifampicin, ethambutol, pyrazinamide</td>
</tr>
<tr>
<td>Group 2 – injectable agents</td>
<td>Streptomycin, amikacin, kanamycin, capreomycin</td>
</tr>
<tr>
<td>Group 3 – Fluoroquinolone group</td>
<td>Moxifloxacin, ofloxacin, levofloxacin, gatifloxacin</td>
</tr>
<tr>
<td>Group 4 – Other, second line agents (bacteriostatic)</td>
<td>Ethionamide, prothionamide, cyloserine, PAS</td>
</tr>
<tr>
<td>Group 5 – Agents of uncertain efficacy (not routinely recommended)</td>
<td>Clofazamine, amoxicillin-clavulanate, clarithromycin, linezolid</td>
</tr>
</tbody>
</table>


---

*Guidelines for Tuberculosis Control in New Zealand 2010*
*Chapter 3: Treatment of Tuberculosis Disease*
Group 1: Ethambutol and pyrazinamide can be used if there is laboratory evidence of susceptibility but previous use potentially means that these drugs may be less effective. If the laboratory demonstrates low-level isoniazid resistance then high dose isoniazid may be beneficial.

Group 2: An injectable agent should be given to all MDR patients.

Group 3: A fluoroquinolone antibiotic should be included if susceptible. Moxifloxacin is the preferred fluoroquinolone. Ciprofloxacin is no longer recommended for the treatment of TB.

Group 4: Protonamide (or ethionamide) and cycloserine are the two most commonly used agents from this group. Para-aminosalicylic acid (PAS) is the next choice if a third drug is required.

Group 5: The effectiveness of drugs in this group is unclear. They should only be considered when drug options are limited.

In addition to expert consultation, current MDR guidelines published by WHO, Secretariat of the Pacific Community and Francis J Curry National Tuberculosis Center may be useful resources for clinicians involved with the management of patients with drug-resistant TB.3,27,28

5.5 Extensively drug-resistant TB
Extensively drug-resistant TB (XDR-TB) is defined as MDR-TB that is resistant to one or more of the fluoroquinolones and injectable agents.4

Treatment of XDR-TB will involve Group 5 agents and management should always be in consultation with an expert in the management of drug-resistant TB.

XDR-TB has a very high mortality rate, especially in the setting of HIV co-infection, and a low cure rate.
6 Corticosteroid Treatment in the Management of TB

Corticosteroids should only be given when adequate anti-tuberculosis treatment is also being given. Adjuvant corticosteroids treatment is recommended in the first eight weeks for both TB meningitis and TB pericarditis and may also provide benefit in life threatening cases of TB.

6.1 TB meningitis and intra-cerebral tuberculomas

Randomised controlled trials show improved survival with the use of corticosteroids in patients with all stages of severity of TB meningitis.\textsuperscript{29,30,31,32}

All patients with TB meningitis should receive adjunctive corticosteroids regardless of disease severity at presentation.\textsuperscript{20} The optimal corticosteroid dose is not certain but the following regimen was used in a recent controlled trial; adults were started on treatment with dexamethasone 0.4 mg/kg/24h with a reducing course over six to eight weeks.\textsuperscript{30}

6.2 Tuberculous pleural effusion

Oral corticosteroid is no longer routinely recommended for tuberculous pleural effusion, despite the fact pleural thickening with consequent impairment of ventilatory function can result from tuberculous pleuritis. A well-conducted placebo-controlled trial showed that oral corticosteroid, in conjunction with rifampicin, isoniazid and ethambutol, produced benefit in terms of rate of fever resolution and rate of resolution of pleural fluid, but not in the frequency of pleural adhesions.\textsuperscript{33}

A randomised trial of standard TB treatment, with or without corticosteroids, in the treatment of tuberculous pleurisy showed some benefits of steroid treatment (in terms of fluid resorption and pleural thickening) during the first two months. No difference was observed in these parameters after two months of treatment, regardless of whether steroid treatment was used.\textsuperscript{34}

Similarly, Wyser et al (1996)\textsuperscript{35} showed that earlier symptomatic improvement occurred in their prednisone-treated group, but had no benefit in this regard after the first two months or in the proportion of subjects with pleural thickening at six months. They stressed the importance of early complete drainage of effusions.
Recommendations for managing tuberculous pleural effusions

- Steroid treatment is not routinely indicated for tuberculous pleural effusions.
- Large, loculated effusions that cannot be adequately drained may benefit from steroid treatment. Any benefit is unlikely to occur after two months on steroid.
- Oral steroid may be required to obtain early control of symptoms (pain, fever or malaise).
- Full drainage of tuberculous effusions is desirable. Usually this can be achieved by repeated thoracentesis. In the past, intercostal tube drainage was avoided because of fears of causing a chronic fistula, but this is unlikely with concurrent modern chemotherapy.
- Follow-up is needed after drainage, as an effusion that has been fully drained may recur and need re-aspiration in the first two to three weeks of treatment.

6.3 Tuberculous ascites

No well-controlled studies are available. In the absence of evidence to support steroid treatment for tuberculous pleural effusion, it is not recommended for tuberculous ascites.

6.4 Tuberculous pericarditis

Although uncommon, pericarditis is a dire complication of TB. Tuberculous pericarditis is almost invariably fatal without treatment and has up to a 40% mortality rate even with treatment. Early diagnosis and early institution of anti-TB therapy are important in preventing the development of constriction.

Constrictive pericarditis usually occurs early, but can also be a late consequence, and is associated with high morbidity and mortality. Although there have been no controlled trials, early surgical intervention is said to be technically easier and is associated with lower operative mortality and a lower rate of subsequent constriction than late pericardectomy.

The efficacy of corticosteroid treatment in tuberculous pericarditis may vary in the different stages of the disease (effusive, effusive-constrictive and constrictive) and many reports do not distinguish these stages. Oral steroids are unlikely to stop the progression from any stage to constrictive pericarditis, but do improve survival and reduce the need for surgery.36,37

6.5 Miliary TB, advanced TB, and suspected hypo-adrenalism

There is evidence to support the use of steroid treatment in patients with miliary TB, very advanced TB, and suspected hypo-adrenalism.38 These situations are associated with unexpected death, the causes of which are often uncertain, but may include:

- adrenal insufficiency – potentially, this could be made worse by the introduction of rifampicin, which may reduce the available endogenous cortisol
- the Jarisch-Herxheimer reaction, occurring soon after the start of TB treatment
• sudden death from myocardial TB
• other common medical complications that may be additive and contribute to cardiac arrhythmias and death in people with advanced TB, including electrolyte disturbances (from TB or from other conditions or their treatment), hypoxaemia caused by pulmonary TB, or concurrent chronic air-flow obstruction or coronary artery disease.

Because of the small risk and the potential benefits from steroid treatment, steroid treatment of 20–60 mg/day should be considered:
• if the patient is very ill from TB
• if the CXR shows a miliary appearance
• to reduce the mass effects and obstructive complications from mediastinal lymphadenopathy.

Where clinical or laboratory features are compatible with hypo-adrenalism; a short synacthen test should be done before steroid treatment is started, or dexamethasone should be used until that test has been completed.

In severely ill patients or patients with radiologically advanced disease, steroid cover should start immediately. The duration of steroid treatment will be judged by the clinical circumstances, but may continue for several weeks.

6.6 Renal-tract TB

Oral steroid has been used with anti-TB drugs for the treatment of tuberculous renal-tract stenoses, especially if the stenosis was located at the pelvi-ureteric or uretero-vesical junction. The aim has been to avoid permanent stenoses from post-tuberculous scarring. Severe tuberculous cystitis has often been managed in the same way. However, benefits are unproven in both situations. Steroid treatment is likely to be helpful only if narrowing is due to acute inflammation caused by a hypersensitivity response to tuberculo-protein or to the infection.

6.7 Oral steroid in the management of drug side-effects

Only a clinician expert in the treatment of TB should manage drug side-effects with oral steroids.

There is little literature about the management of TB drug side-effects with oral steroid treatment. Steroid treatment is not usually needed as the offending drug(s) can be identified and stopped. When appropriate, testing for sensitivity by progressively adding drugs one at a time may be done (see Table 9.1).
7 Monitoring

7.1 Monitoring infectivity

Patients who are sputum smear–positive before treatment should have repeat sputum tests at least monthly to confirm sterilisation. Eighty-five percent of these patients are expected to be smear- and culture-negative after two months of treatment.\(^1\)

If the specimen at the end of the third month is both smear and culture positive, repeat drug susceptibility testing should be performed.\(^2\) As early detection of drug resistant TB is important, repeat DST after two months of treatment may be appropriate in some patients where there are concerns that acquired drug resistance may have developed.\(^2\)

7.2 Radiological monitoring

7.2.1 Chest X-ray monitoring

Chest X-ray (CXR) monitoring during treatment is required for all patients with X-ray abnormalities consistent with TB. The intervals between films will depend on the clinical circumstances.

A patient’s chest radiograph that does not show improvement after the patient has received three months’ treatment suggests:

- the diagnosis of TB may be wrong
- the TB may have produced scarring before treatment, so radiological improvement may not occur
- a mixed pathology may be present with TB co-existing with another condition
- the patient may not have followed their medication regimen and secondary drug resistance must be considered
- primary drug resistance may have been present from the outset

7.2.2 Chest CT scanning

Chest CT scanning is useful for monitoring extensive mediastinal lymph node TB. A comparison of an early CT with another done just before planned completion of treatment may lead to the treatment cessation date being revised. Longer treatment is indicated if lymph nodes continue to have a necrotic appearance or have not diminished greatly in size during treatment.

7.2.3 Serial imaging and extra-pulmonary sites

Serial imaging and extra-pulmonary sites: the need for repeat imaging will depend on:

- the site of involvement (for example, abdominal ultrasound for intra-abdominal disease; cerebral CT or MRI for intra-cerebral TB)
- the severity of involvement at the site(s) of disease.
7.3 Monitoring for drug toxicity

7.3.1 Hepatotoxicity

Pre-treatment
Baseline blood count, creatinine, alanine amino-transferase (ALT), hepatitis B surface antigen, and hepatitis C and HIV serology should be completed in all adults who are to be treated for TB disease or latent TB infection. A full panel of liver function tests should be completed for patients with an elevated ALT, and the case should be discussed with a clinical TB expert.

All patients should be advised to avoid drinking alcohol while taking TB drugs.

Monitoring during treatment
Some overseas experts recommend clinical monitoring without regular blood tests in people who are asymptomatic even older people who have a higher incidence of hepatotoxicity. However, we recommend regular clinical monitoring of liver function as:
- serious hepatic dysfunction can develop before patients develop symptoms and can happen at any time during the treatment
- hepatitis B carrier state or sero-positivity for hepatitis C or HIV increases the incidence of hepatotoxicity to TB drugs
- the prevalence of hepatitis B carriage is 2.5%; it is highest in Māori (5.6%), Asians (6.2%), and Pacific peoples (7.3%)
- risks are greater for those aged over 50 than for those aged 35–50, but for simplicity, 35 or over is the cut off for higher risk
- regular alcohol use is a risk factor for hepatotoxicity
- improvement occurs after removal of the drugs when liver dysfunction is noted
- even a rare death from TB-drug induced hepatitis is unacceptable
- iatrogenic hepatic failure sometimes requires liver transplantation.

7.3.2 Monitoring for hepatotoxicity
- After baseline screening, adults being treated for latent TB infection should have ALT monitoring at one month and then every two months.
- After baseline screening, adults being treated for TB disease who have no risk factors for hepatotoxicity, should have ALT monitoring at one month, two months, and then every two months thereafter.
- After baseline screening, adults being treated for TB disease who have risk factors for hepatotoxicity, should have complete liver function tests every month.
- If a patient’s ALT is more than three times the normal level, advice should be sought from a clinical TB expert promptly (see 8.2.5).
- Any patient with jaundice should be referred to a liver unit or gastroenterologist and all hepatotoxic drugs should be stopped immediately.
- Any patient whose TB treatment is stopped because of abnormal liver function should be notified to the Committee on Adverse Reactions to Drugs.

### 7.3.3 Ocular toxicity

Ocular toxicity is the most important side effect of ethambutol; it is less likely if the dose is 15 mg/kg than if the dose is higher. All patients starting ethambutol should have a baseline visual acuity test and a red–green colour vision assessment. Patients with abnormalities should be referred to an ophthalmologist.

All patients on ethambutol should be asked to report new visual symptoms and visual acuity effects. Monthly testing of visual acuity and colour discrimination is recommended for patients receiving ethambutol for longer than two months and for any patient with renal impairment. Ophthalmological review should occur if there are any abnormalities. Ethambutol should be avoided in people unable to report changes in vision and in people with moderate or severe renal insufficiency.

### 7.3.4 Monitoring of patients on amikacin

**Monitoring serum amikacin trough levels**

Serum amikacin trough levels should be measured regularly just before giving a dose.

The trough level should be less than 1 mcg/mL if toxicity is to be avoided. If the estimated creatinine clearance is less than 50 ml/min or serum creatinine is increasing, then trough levels should be monitored frequently. Serum peak levels may need to be assessed in some patients to confirm adequate dosing.

**Monitoring plasma creatinine concentration**

In patients with normal renal function requiring long-term dosing, fortnightly creatinine clearance monitoring is recommended to monitor plasma creatinine concentration.

**Monitoring ototoxicity and vestibular dysfunction**

With long-term dosing, audiometry testing should be completed fortnightly to monitor ototoxicity and vestibular dysfunction. Electronystagmography may be considered if vestibular symptoms develop.

### 7.3.5 Hypothyroidism

Patients on PAS and ethionamide may develop hypothyroidism. All patients on these medications should have thyroid function tests at baseline and then every three months.
7.3.6 Weight and nutrition

Many patients with TB are poorly nourished. Weight and nutrition status are important markers of disease status. Patient’s weight should be monitored throughout the course of treatment and nutrition should be optimised.

7.3.7 Monitoring by a nurse

All patients who are self-administering anti-tuberculosis treatment should be reviewed by a nurse every month and a pill count should be completed. Patients must be educated about TB and potential drug side effects and should be instructed to watch for common drug reactions.

7.3.8 Medical appointments

A medical review may be completed every two to three months provided there are no risk factors for poor compliance, the patient can be relied on to report symptoms, and a monthly review by a public health nurse is being carried out.

7.4 Therapeutic drug monitoring

7.4.1 Monitoring amikacin levels

See section 2.2.

7.4.2 Indications for therapeutic drug monitoring

Most patients with uncomplicated TB usually respond to standard treatment, however there are several situations in which the monitoring of serum drug concentrations might be helpful. Rifampicin and isoniazid therapeutic drug monitoring should be considered in the following circumstances:

- The disease does not show the expected improvement.
- Non-adherence or malabsorption is suspected. Malabsorption is particularly likely in patients with HIV infection, cystic fibrosis or diabetes mellitus. In patients with HIV there may be up to a 70% reduction in serum TB drug concentrations compared with control subjects. Sub-therapeutic drug concentrations carry a significant risk of drug resistance developing.
- The patient has ascites (see section 11.2.4).
- The patient experiences drug side effects, especially if the offending drug needs to be re-introduced.
- There are patients with isolates that are multidrug resistant or have acquired drug resistance.
- Risk factors for drug toxicity are present.
- The patient is severely obese (for example, a body mass index of 30 or more; see section 11.4).
7.5 Paradoxical reactions to TB treatment

A paradoxical reaction to TB treatment is defined as a ‘worsening of disease at a pre-existing site, or the development of new tuberculosis lesions following initiation of appropriate treatment’. These reactions generally occur about one to three months after the start of treatment, but can occur even after treatment is complete.

A paradoxical reaction is thought to result from an immunological host response to mycobacterial products that have been released as a result of treatment-induced bacterial cell death and dissolution and the restoration of part of the host immune response as a result of treatment.

Paradoxical reactions may have local or systemic components or both. Their nature is the same in HIV-infected and non-HIV-infected people, but they occur more frequently in HIV-infected people who are receiving TB treatment and then start taking anti-retroviral agents. TB-related paradoxical reactions in people with HIV infection are discussed in Chapter 6.

The differential diagnosis of apparent paradoxical reactions includes:

- incorrect or inadequate treatment, with worsening of the TB through non-adherence with drug treatment, malabsorption of TB drugs, the presence of primary drug resistance or the development of secondary drug resistance
- drug reaction
- concurrent infection or malignancy.

The diagnosis of paradoxical reactions may be difficult, depending on the site of involvement and the presence of immune-suppression. Investigations to detect other possible causes including tissue sampling and repeating TB cultures should be completed.
8 Drug Side-effects

Common adverse side-effects of TB drugs are listed in Table 8.1.

Table 8.1: Adverse effects of tuberculosis drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides (amikacin, capreomycin, kanamycin, streptomycin)</td>
<td>Ototoxicity (lowest incidence with streptomycin); renal damage, skin rashes, fevers, circum-oral paraesthesiae, neuromuscular blockade</td>
</tr>
<tr>
<td>Para-amino-salicylic acid</td>
<td>Gastrointestinal effects, hepatitis, fever, rash and hypothyroidism</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Dose-related central nervous system effects (drowsiness, vertigo, disorientation, confusion, coma and psychosis)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuropathy (dose-related); peripheral neuropathy, arthralgia or rash are rare</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Gastrointestinal effects, liver toxicity; rarely hypothyroidism, hypotension, hypoglycaemia, alopecia, convulsions and neuropathy</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Gastrointestinal disturbances, dizziness, anxiety, depression, confusion and convulsions; rarely, achilles tendon rupture, arthropathy and photosensitivity. For use in children, consult a paediatric tuberculosis expert.</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Isoniazid hepatotoxicity:</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity reactions are unusual.</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy, optic neuritis, fever, hepatitis, ataxia, euphoria, convulsions, tinnitus, insomnia, hyperglycaemia, gynaecomastia, dry mouth, epigastric discomfort, urinary retention, anaemia, arthralgia. Contraindicated in manic states and porphyria.</td>
</tr>
<tr>
<td></td>
<td>Idiosyncratic reactions may include a (usually reversible) lupus-like syndrome (fever, arthritis, pleuritis, pericarditis, positive rheumatoid factors, etc), and, very rarely, a rheumatoid arthritis-like syndrome, and agranulocytosis.</td>
</tr>
<tr>
<td></td>
<td>Very rare hypersensitivity reactions include eosinophilia, angiitis, toxic psychosis, and meningo-encephalitis.</td>
</tr>
<tr>
<td></td>
<td>Toxic doses decrease the synthesis of the inhibitory neurotransmitter gamma aminobutyric acid.</td>
</tr>
<tr>
<td></td>
<td>Central nervous system depression or stimulation may result.</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Gastrointestinal side effects, hyperuricaemia, hepatotoxicity, fever, anorexia, nausea and vomiting; precipitation of gout (see section 11.2); arthralgias, urticaria, sideroblastic anaemia.</td>
</tr>
<tr>
<td></td>
<td>Of the TB drugs, pyrazinamide is the most common cause of a rash.</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Rash, gastrointestinal disturbance, neutropaenia; uveitis, particularly in combination with macrolide antibiotics</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Gastrointestinal disturbance, cholestatic hepatic dysfunction, transient elevation of hepatic enzymes.</td>
</tr>
<tr>
<td></td>
<td>Danger with intermittent therapy: flu-like syndrome, shock, acute renal failure, death.</td>
</tr>
<tr>
<td></td>
<td>Acute haemolytic anaemia.</td>
</tr>
<tr>
<td></td>
<td>Rare reports of rifampicin-induced light chain proteinuria and renal failure, attributed to dehydration associated with fluid restriction for syndrome of inappropriate antidiuretic hormone.</td>
</tr>
<tr>
<td>Thiacetazone</td>
<td>Nausea, vomiting, diarrhoea, bone marrow depression, vertigo, ataxia, tinnitus, occasional liver toxicity, cutaneous hypersensitivity.</td>
</tr>
</tbody>
</table>

8.1 Dermatological side effects

Skin reactions can occur with any anti-TB drug. Pyrazinamide is the drug that most commonly causes skin reactions; in one study, it caused 26 out of 31 (84%) of all rashes in 1317 patients.\textsuperscript{50} Pyrazinamide also causes facial flushing or transient pruritis. Isolated skin rash occurs in about 2% of people taking isoniazid, but commonly occurs as part of a wider hypersensitivity reaction. Skin rash due to rifampicin is usually mild, but can take many forms. Photosensitivity can occur with pyrazinamide and the fluoroquinolones.

8.2 Hepatotoxicity from TB drug treatment

TB treatment includes several potentially hepatotoxic drugs, including isoniazid, rifampicin and pyrazinamide. Monitoring is discussed in section 9. Ethambutol rarely causes hepatic dysfunction.

8.3 Toxicity of aminoglycosides

The toxicity of aminoglycosides can be auditory and vestibular toxicity or nephrotoxicity.

8.3.1 Auditory and vestibular toxicity

Aminoglycosides can cause auditory and vestibular toxicity. Auditory damage begins in the basal end of the cochlea and progresses to the apical end. Symptomatic hearing loss begins with high frequency loss and, as administration continues, lower frequency loss occurs. At least half the cases of auditory toxicity are irreversible. Vestibular damage may be reversible. Early detection helps prevent hearing loss in the frequency range that can affect communication, so it is essential to test high-frequency ranges.

High trough serum levels and advanced age are the most important predisposing factors to ototoxicities. Other factors include the duration of administration, the total dosage, having a high fever and bacteraemia, dehydration, and prior renal or ear disease. Ototoxicity occurs independently of nephrotoxicity.

8.3.2 Nephrotoxicity

Nephrotoxicity relates to dose, duration of treatment, and age, and is more likely in patients with pre-existing renal impairment, dehydration or liver disease and in patients receiving loop diuretics or other nephrotoxic agents.
9 Management of Drug Reactions

9.1 Need for a new temporary regimen

The patient’s clinical situation determines the acceptable period for which the patient should stay off all TB treatment while awaiting resolution of TB-drug side-effects.

If it is necessary to stop anti-tuberculosis treatment (particularly to give a steroid to counteract treatment side effects), consider whether a new, temporary regimen would be helpful. This regimen should continue until full doses of all drugs in the definitive regimen have been started. A person who is acutely ill with TB or is infectious should be put on a temporary regimen immediately. For a non-infectious, well person, four weeks without treatment is an arbitrary maximum period to be off anti-tuberculous treatment. The development of infectiousness or the spread of disease to other sites is likely after this time.

9.1.1 Progressive but non-effective partial regimens

The period for which a progressive but non-effective partial regimen may be given without inducing drug resistance is not certain, but is in the order of days. In a person who is well despite TB, the period should not exceed 10 days. If the person is ill with TB, an alternative regimen should be started as soon as the original regimen is modified.

Repeated periods of partial or no treatment should be avoided. A second episode without treatment or partial treatment is an indication for a temporary regimen that should be continued for several weeks, until the difficulties have been fully resolved.

The development of resistance to moxifloxacin can appear relatively quickly and has been observed to occur in patients with TB who have been exposed to moxifloxacin monotherapy for as short a period as 10 days.\textsuperscript{51}

9.1.2 Agents in the temporary regimen

Agents in the temporary regimen could include amikacin (or streptomycin), moxifloxacin, ethambutol, and ethionamide (or protonamide).

Practice point – managing side effects of TB drugs

The maximum period for a patient to be off all drugs is four weeks.

The maximum period for a patient to be on a partial regimen is 10 days.

A typical temporary regimen is amikacin (or streptomycin), ethambutol and moxifloxacin.


9.2 **Management of drug challenges**

When troublesome side effects occur, stop treatment and allow the reaction to resolve. Then identify the agent or agents causing the reaction, by re-introducing the drugs sequentially.

Give the patient a few days on each dose of each agent; the more severe the reaction, the more caution is required. It may be necessary to start with small incremental doses and build up to the full dose over several days. It may be necessary to cover the patient with a temporary regime to prevent resistance emerging during the challenge period.

If the patient experiences no side effects, repeat the process with the next drug. With less-severe reactions, it may be possible to introduce full doses. The drug challenge doses for mild-to-moderate reactions are shown in Table 9.1.

If you are unfamiliar with conducting drug challenges, consultation with a clinical TB expert should occur.

| **Table 9.1:** Drug challenge doses for mild-to-moderate reactions |
|---|---|---|---|
| **Drug** | **Day 1 dose** | **Day 2 dose** | **Days 3 and 4 doses** |
| Isoniazid | 50 mg | 100 mg | 300 mg |
| Rifampicin | 75 mg | 150 mg | 450–600 mg |
| Pyrazinamide | 250 mg | 500 mg | Full dose |
| Ethambutol | 100 mg | 400 mg | Full dose |
| Streptomycin | 100 mg | 500 mg | Full dose |

Source: NHMRC (1989).52

9.3 **Management of drug de-sensitisation**

Desensitisation should be considered only when suitable replacement drugs are not available. Rapid desensitisation protocols can be used for patients that are sensitive to rifampicin, ethambutol53 and isoniazid.54 These guidelines are based on protocols for treating penicillin allergy. Desensitisation should always be carried out cautiously and with full resuscitation resources available.

9.4 **Management of skin side effects**

A minor rash and itchiness are common with anti-TB drugs. Sometimes the skin side effects are short-lived, so the drugs may not have to be stopped. If the drugs are stopped, it is sometimes possible to resume them successfully. Consider the following measures.

- Before assuming the anti-TB drugs are the cause of the symptoms, check the patient has not recently changed their brand of soap.
- Skin moisturisers may help dry, itchy skin.
- Pruritis may be helped by:
  - a non-sedating antihistamine such as loratidine, although older antihistamines may be tolerated and are cheaper
  - Pinetarsol gel or solution
  - BK bath oil or lotion.

Major skin rashes require all drugs to be stopped and the patient to be given test doses of each drug until the drug causing the reaction is identified.

9.5 Management of drug-induced hepatotoxicity

Generally, drugs that are closely related chemically should not be used if marked hepatotoxicity occurs with one of them. However, rifabutin may be tried cautiously after recovery from rifampicin hepatotoxicity.

If clinical hepatitis occurs (with anorexia, nausea, vomiting, hepatic tenderness and/or jaundice), stop all drugs and refer the patient to a liver unit or gastroenterologist.

Use your clinical judgement before reinstituting a drug that has caused hepatitis. In one series, reintroduction of rifampicin and isoniazid was possible in 41 out of 44 patients after resolution of marked biochemical and clinical hepatitis. Most experienced physicians would try cautiously reintroducing isoniazid and rifampicin after an asymptomatic abnormality of liver function. However, in all but very minor circumstances, consult a clinical TB expert.

9.6 Management of uncontrollable vomiting

Nausea is common with anti-TB drug treatment, but it can usually be managed with common agents. Theoretically, drugs such as metoclopramide, which stimulate gastric emptying, may have an effect on anti-TB drug levels, but there is no literature on this subject. If prolonged use of such drugs is needed, it may be preferable to use prochlorperazine (Stemetil) or cyclizine (Marzine).

9.7 Management of paradoxical reactions

Once a paradoxical reaction has been investigated and other causes excluded, the need for treatment depends on the location and severity of the reaction. Pulmonary reactions may precipitate acute respiratory failure, and an expanding intracranial abscess may result in serious neurological sequelae or death. In these and similar life-threatening situations, corticosteroid treatment may be needed to control cytokine-induced inflammation. Painful, grossly enlarged lymph nodes may need to be excised.
10 Interactions with Anti-TB drugs

The rifamycin–warfarin interaction and interactions with pyrazinamide are discussed below. For other drug interactions, see Table 10.1.

10.1 Rifamycin–warfarin interaction

The rifamycin–warfarin interaction is very important. This interaction can cause sub-therapeutic anticoagulation or a dangerous degree of over-anticoagulation when rifampicin is stopped.

Sub-therapeutic anticoagulation may occur when a patient on warfarin starts rifampicin.56 Patients who are taking both agents and who have an absolute indication for anticoagulation, need monitoring at least weekly. If warfarin anticoagulation is difficult, use low molecular weight heparin.

Dangerous over-anticoagulation may occur when rifampicin is stopped, thereby effectively reducing the hepatic metabolism of warfarin.

10.2 Interactions with pyrazinamide

Allopurinol may paradoxically increase serum urate levels if given with pyrazinamide.57 Pyrazinamide may need to be avoided in patients with troublesome gout, as it can precipitate acute attacks. Anecdotally, it may be possible to continue pyrazinamide after recovery from an attack of gout if the patient can tolerate colchicine in a dose of 0.5 mg BID. If successful, the colchicine should be continued, and stopped when the pyrazinamide is discontinued.

10.3 Oral contraceptive use

Rifamycins are inducers of certain hepatic cytochrome P450 enzymes. Both oestrogens and progesterones are metabolised through this pathway. As a result, their elimination is accelerated in women taking rifampicin or rifabutin, and contraceptive efficacy is lost for both combined oral contraceptives and progesterone-only pills.57A,57B Rifampicin is the more potent inducer and the induction of liver enzymes begins six days after commencement of rifampicin and can be observed for up to one month after cessation of the drug.57C

A second mechanism by which rifamycins lower circulating blood oestrogen levels is by reducing their entero-hepatic circulation. This has been shown to occur with ethinyloestradiol. This mechanism does not operate with progesterone hormones.

An alternative contraceptive method should be used during rifamycin therapy and for one month after stopping, even if rifamycin was for less than a week.57C,57D
Injectable progesterone, depot medroxyprogesterone acetate is considered an effective contraceptive. The standard recommendation is a 12-weekly injection. It is uncertain whether a greater frequency is needed when rifamycins are being taken. The usual recommendation is to reduce the dosing interval to 10 weeks (one source advises eight weeks) in women taking rifampicin or rifabutin.57E

10.4 Rifampicin-corticosteroid interaction

Induction of hepatic enzymes due to rifampicin can result in a profound reduction in corticosteroid levels. Patients on corticosteroids therefore should have the dose of corticosteroid increased by two to three fold when rifampicin is commenced. Clinicians should also be aware that enzyme induction may persist for two to three weeks after the discontinuation of rifampicin.

Table 10.1: Clinically important interactions with tuberculosis drugs

<table>
<thead>
<tr>
<th>Tuberculosis drug</th>
<th>Interacting agent</th>
<th>Effect</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Antacids, containing aluminium</td>
<td>Reduced absorption of isoniazid</td>
<td>As for fluoroquinolones + antacids</td>
</tr>
<tr>
<td></td>
<td>Anti-epileptics: • carbemazepine</td>
<td>Inhibition of carbemazepine hepatic metabolism has been described</td>
<td>Monitor carbemazepine blood levels</td>
</tr>
<tr>
<td></td>
<td>• phenytoin</td>
<td>Inhibition of phenytoin hepatic metabolism; phenytoin toxicity may develop over days to weeks</td>
<td>Monitor phenytoin levels and symptoms</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics</td>
<td>Possible increased plasma haloperidol</td>
<td>Adjust dose if needed</td>
</tr>
<tr>
<td></td>
<td>Anxiolytics and hypnotics</td>
<td>Possible delayed metabolic clearance of diazepam and triazolam, causing prolongation of their effects</td>
<td>Monitor effects; decrease dose if necessary</td>
</tr>
<tr>
<td></td>
<td>Anti-fungals</td>
<td>Possible decreased antifungal blood level</td>
<td>No problem using Fluconazole</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
<td>Marked rise in cyclosporin levels</td>
<td>Monitor cyclosporin blood levels</td>
</tr>
<tr>
<td></td>
<td>Cyclosporin</td>
<td>Central nervous system toxic effects of Disulfiram among 30% of people on both</td>
<td>Reduce dose or discontinue Disulfiram</td>
</tr>
<tr>
<td></td>
<td>Disulfiram</td>
<td>Enhanced defluorination of this anaesthetic agent may lead to accumulation of nephrotoxic fluoride (more likely in isoniazid rapid acetylators)</td>
<td>Avoid concurrent use of these two agents</td>
</tr>
<tr>
<td></td>
<td>Enfluorane</td>
<td>Flushing, chills, headache, wheeziness, palpitations, diarrhoea, vomiting, burning</td>
<td>Advise on diet; give antihistamine, if necessary</td>
</tr>
<tr>
<td>Tuberculosis drug</td>
<td>Interacting agent</td>
<td>Effect</td>
<td>Advice</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Tyramine-rich foods</td>
<td>Red wine, cheese, yeast extract (due to slight monoamine oxidase effect of isoniazid)</td>
<td>Advise on diet</td>
<td></td>
</tr>
<tr>
<td>Rifampicin and rifabutin</td>
<td>Reduced levels of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiarrythmics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• disopyramide</td>
<td></td>
<td>Monitor response</td>
<td>Avoid use</td>
</tr>
<tr>
<td>• mexilitine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• propafenone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• quinidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifungals</td>
<td></td>
<td>Monitor serum level; may increase antifungal dose</td>
<td>As for clarithromycin</td>
</tr>
<tr>
<td>• itraconazole</td>
<td>Raised rifabutin level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• fluconazole</td>
<td>Reduced absorption, halving the rifampicin level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ketoconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-retrovirals (see Chapter 8)</td>
<td>Significant interactions occur between the rifamycin drugs and the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors</td>
<td>See Chapter 6 for details</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin (and possibly other macrolides)</td>
<td>Raised rifabutin levels; risk of uveitis</td>
<td>Keep rifabutin dose at or below 300 mg/day; acute uveitis: stop rifabutin; ophthalmology review.</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Profound reduction in steroid levels</td>
<td>Increase steroid dose two- to three-fold; reduce when rifamycin is discontinued</td>
<td></td>
</tr>
<tr>
<td>• gluco- and mineralo-corticoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam, nitrazepam</td>
<td>Likely with renal impairment</td>
<td>Monitor levels; dose may need to be doubled.</td>
<td></td>
</tr>
<tr>
<td>Digitalis preparations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppressive agents</td>
<td>Levels reduced about 50%; significance uncertain</td>
<td>May need three- to five-fold increase in cyclosporin dose</td>
<td></td>
</tr>
<tr>
<td>• cyclosporin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• tacrolimus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-amino salicylic acid</td>
<td>Possible increase in serum rifampicin</td>
<td>Ensure these two agents are taken eight hours apart.</td>
<td></td>
</tr>
<tr>
<td>Phenyoitin concurrent isoniazid</td>
<td>Markedly reduced anti-epileptic effect, especially in fast acetylators</td>
<td>Isoniazid counteracts lowering of serum phenybin by rifampicin</td>
<td></td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• tolbutamide</td>
<td></td>
<td>Monitor diabetic control.</td>
<td></td>
</tr>
<tr>
<td>• possibly others (eg, glibenclamide)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis drug</td>
<td>Interacting agent</td>
<td>Effect</td>
<td>Advice</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Warfarin (see also section 10.1)</td>
<td>Markedly reduced anticoagulation</td>
<td>Warfarin dose may need to be doubled or tripled at the start, and be similarly reduced when the rifamycin is stopped (see also section 10.1).</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>No interactions of note</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Allopurinol (see also section 10.2)</td>
<td>Acute gout</td>
<td>Avoid allopurinol; try colchicine instead. May need to abandon use of pyrazinamide.</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Antacids, containing aluminium, calcium and magnesium</td>
<td>Reduced absorption of fluoroquinolones</td>
<td>Avoid antacids; or give fluoroquinolone two hours before or four hours after antacid</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Occasional, unpredictable prolonged prothrombin time</td>
<td>Monitor anticoagulation carefully, if starting or stopping fluoroquinolones.</td>
</tr>
<tr>
<td></td>
<td>Iron and zinc</td>
<td>As for fluoroquinolones + antacids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sucralfate</td>
<td>As for fluoroquinolones + antacids</td>
<td></td>
</tr>
<tr>
<td>Ethionamide and protionamide</td>
<td>Increased risk of hepatotoxicity with rifampicin, isoniazid and pyrazinamide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
11 Special Situations

11.1 Renal impairment and treatment of TB

Isoniazid, rifampicin, pyrazinamide, ethionamide and prothionamide are eliminated almost entirely by non-renal routes (i.e., by metabolism or biliary secretion). When prescribing TB drugs in a person with significant renal impairment, monitoring of blood levels may be required.

11.1.1 Renal impairment, without dialysis

Isoniazid

It has been estimated that isoniazid of 5–6 mg/kg/day given to a slow acetylator with severe renal impairment would be equivalent to a dose of 7–9 mg/kg/day in a normal subject. Therefore, standard doses of isoniazid should be given in people with renal failure. If side effects occur, therapeutic drug monitoring is indicated (see section 9).

Rifampicin

Up to 30% of rifampicin is excreted in urine (possibly as a result of the biliary route becoming saturated) but less than half of this is unaltered. Although the half-life of 600 mg rifampicin increases 30–40% in patients with renal insufficiency, it is well tolerated and no dosage adjustment is required.

Ethambutol

About two-thirds of the dose of ethambutol is excreted unchanged in urine. Ethambutol should be avoided if possible in the setting of renal impairment. However, if ethambutol is given, the frequency of dosage should be reduced according to the severity of renal impairment. Alternatively, the daily dosage adjustment can be based on the glomerular filtration rate (GFR) but note the following:

- With normal renal function, corrected creatinine clearance is the best indicator of GFR.
- In the early stages of glomerular failure the corrected creatinine clearance remains the most sensitive indicator of GFR. Because of the hyperbolic relationship between creatinine clearance and serum creatinine, the clearance will fall significantly during a period in which the serum creatinine remains normal.
- Once renal failure is established and the serum creatinine is significantly elevated (above 0.2–0.3 mmol/L, depending on muscle mass), the serum creatinine becomes a more sensitive indicator of any further deterioration of the GFR. The serum concentration will rise rapidly while the creatinine clearance will show little further change.
Pyrazinamide

Pyrazinamide is primarily metabolised by the liver to pyrazinoic acid and other metabolites, 3% appearing unchanged in the urine and 30–40% as pyrazinoic acid. Consequently, mild-to-moderate degrees of renal impairment do not require any adjustment of dose or frequency of administration.

Fluoroquinolones

The mode of excretion varies among the fluoroquinolone family, so drug management varies in the presence of renal impairment.

Moxifloxacin is excreted both by renal (20–30%) and biliary pathways, so no dose adjustment is needed, with or without haemodialysis.59,60

Aminoglycosides

Streptomycin, kanamycin, amikacin and capreomycin are excreted almost exclusively by the kidney, and dosages must be adjusted according to the degree of renal impairment. Serum concentrations of drugs should be monitored. However, these drugs are best avoided in renal impairment.

Table 11.1: Doses of major anti-tuberculosis agents and renal impairment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Chronic renal failure</th>
<th>Peritoneal dialysis</th>
<th>Haemodialysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Normal dose</td>
<td>Normal dose</td>
<td>Normal dose</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Normal dose</td>
<td>Normal dose</td>
<td>Normal dose</td>
</tr>
<tr>
<td>Ethambutol#</td>
<td>Avoid unless absolutely necessary</td>
<td>Avoid unless absolutely necessary</td>
<td>Avoid unless absolutely necessary</td>
</tr>
<tr>
<td></td>
<td>GFR 20–50: Dose as in normal renal function</td>
<td>15 mg/kg every 24–36 hours</td>
<td>25 mg/kg three times a week, after dialysis or 5–7.5 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>GFR 10–20: 15 mg/kg every 24–36 hours</td>
<td>15 mg/kg every 48 hours or 5–7.5 mg/kg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GFR &lt; 10 ml/min: 15 mg/kg every 48 hours or 5–7.5 mg/kg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>GFR &lt; 10 ml/min: 15–25 mg/kg daily (use 50–100% of dose)</td>
<td>25 mg/kg daily</td>
<td>25–30 mg/kg three times a week, after dialysis</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Avoid if possible; or single dose and monitor serum levels</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate (mL/min).
* TB medicines are given after haemodialysis.
# Ethambutol should be avoided in renal impairment unless absolutely necessary.


11.1.2 Peritoneal dialysis

It is acceptable to give the normal dose of rifampicin and isoniazid even in slow isoniazid acetylators.61 Ethambutol should be avoided unless absolutely necessary.
11.1.4 Haemodialysis

Isoniazid, rifampicin and ethambutol are not significantly removed by haemodialysis.\textsuperscript{62}

Isoniazid and rifampicin

Isoniazid and rifampicin can be given in their usual daily doses. Conventional doses are safe and effective.

Ethambutol

Ethambutol should be used with caution in renal impairment. Blood levels of ethambutol can vary from one patient to another due to variable absorption. This variation in levels may be the result of pre-dialysis fluid overload, and better absorption may be achieved with post-dialysis dosing.

The recommended dose of ethambutol with haemodialysis is 15–25 mg/kg given three times a week after dialysis, when dialysis is given at that same frequency.

If ethambutol is used, serum levels of ethambutol must be monitored and regular ophthalmology assessments are essential.

Pyrazinamide

Pyrazinamide is significantly removed by haemodialysis. Doses of 25–30 mg/kg must be given after haemodialysis, three times a week. Pyrazinoic acid, which is the primary metabolite of pyrazinamide, is partially removed by haemodialysis, but the extent of removal is uncertain.

Timing of doses

Rifampicin, isoniazid and ethambutol may be administered after haemodialysis, and this may facilitate directly observed therapy.

Other tuberculosis drugs

Ethionamide and para-aminosalicylic acid are not significantly dialysed.\textsuperscript{63}

Cycloserine is significantly removed by dialysis, so doses should be given after dialysis. Usual doses, given three times a week after dialysis, are recommended.

Ethionamide is rapidly metabolised by the liver, so dose adjustment for renal failure or dialysis is unnecessary. The absorption of ethionamide may be delayed in long-term dialysis patients.

Clofazimine should be given in its usual dose of 100–200 mg daily, administered after dialysis.

Moxifloxacin can be given in usual doses with haemodialysis.\textsuperscript{60}
11.2 Hepatic dysfunction (and ascites) and TB treatment

The monitoring of hepatotoxicity of TB drugs is discussed in section 8.2. Sometimes liver dysfunction is detected before treatment is started.

11.2.1 Causes of abnormal liver function tests

Hepatic dysfunction before TB treatment may be due to TB. If this is the cause of the hepatic dysfunction improvement should occur within the first few weeks of treatment.

Other drugs taken when TB is diagnosed may also cause abnormal liver function.

11.2.2 Tests before starting treatment

Section 7.3 discusses the investigations of liver function that should be obtained before starting treatment. If tests are abnormal, investigations should include appropriate clinical evaluation; an ultra-sound may be indicated if an obstructive pattern is present.

11.2.3 Regimens when major liver disease is present before treatment

In hepatic failure, there is decreased total body clearance of isoniazid and rifampicin, resulting in drug accumulation and higher serum levels. The elimination half-life may increase 30–100% in hepatic failure. Significant accumulation of pyrazinamide in icteric patients can occur. Although 50% of quinolone clearance occurs in the liver, its serum concentration is not substantially altered in hepatic disease.

In renal disease, indices of renal function correlate with estimates of residual renal function, but this is not true of hepatic dysfunction where transaminase levels usually do not correlate with the ability of the liver to metabolise drugs.

If a person with active TB has major hepatic dysfunction, treatment should start with an effective, non-hepatotoxic regimen such as amikacin, ethambutol and moxifloxacin. If these do not cause side effects in the first three to four days, the potentially hepatotoxic agents may be added one at a time. Rifampicin would be the next agent of choice to add. Consultation with a TB clinical expert and a hepatologist is strongly recommended. Therapeutic drug monitoring may be helpful.

11.2.4 Ascites

Ascites presents a problem with many anti-tuberculosis drugs, because those that distribute freely into water will display a larger volume of distribution and therefore a longer elimination half-life. Therapeutic drug monitoring is recommended for people with persistent ascites (see section 7.4).

11.2.5 Hepatitis B, hepatitis C and HIV infected patients

Patients with HIV infection or hepatitis B or C infection may have abnormal liver function when starting treatment and are also more likely to develop hepatotoxicity than other people.
11.3 Pregnancy and lactation

11.3.1 Pregnancy

The risk of untreated TB to a pregnant women is far greater than the risk of toxic effects from the drugs used in its treatment. When active TB is diagnosed in a pregnant women it is essential that prompt, effective treatment is administered.

If there are strong indications of active TB disease but bacteriological confirmation is lacking, treatment may often be deferred until after the first trimester.

In pregnant women with no symptoms, negative bacteriology, a lack of radiological change but evidence of past TB infection, initiation of preventive therapy for latent TB may be delayed until after the birth unless the infection has been recently acquired or the women has other medical conditions such as HIV infection that places her at higher risk of developing TB disease.

Little is known about the safety of second-line agents during pregnancy. These drugs should only be used in specific instances after consultation with a TB specialist.

11.3.2 Isoniazid, rifampicin and ethambutol

The use of isoniazid, rifampicin and ethambutol have been well studied and are considered safe in pregnancy. All pregnant women on isoniazid should receive pyridoxine to prevent neurotoxicity in the foetus.

11.3.3 Pyrazinamide

There is a lack of controlled data on the safety of pyrazinamide during pregnancy and international guidelines differ in their recommendations.

The World Health Organization and the International Union Against TB and Lung Disease both recommend the routine use of pyrazinamide during pregnancy and toxicity to the foetus has not been documented. The American Thoracic Society and Centers for Disease Control guidelines however do not recommend the general use of pyrazinamide with drug-susceptible TB due to a lack of controlled data in pregnancy. The Francis J Curry National Tuberculosis Center guidelines for Drug-resistant tuberculosis recommend that for women with HIV co-infection or drug-resistant disease, pyrazinamide should be included in the TB regimen if the isolate is susceptible. In cases with drug resistance, the risk of taking pyrazinamide is less than the risk of not curing TB.

Pregnant women with TB should be counselled appropriately and if pyrazinamide is not used the minimum duration of treatment is nine months.
11.3.4 Streptomycin, amikacin, capreomycin and kanamycin
Aminoglycosides are potentially ototoxic to the foetus. Streptomycin and kanamycin have been implicated as the cause of mild to severe bilateral congenital deafness in up to 17% of pregnancies. For that reason, amikacin and capreomycin are also not recommended during pregnancy but have been used safely in some reports for the treatment of drug-resistant TB.

11.3.5 Ethionamide and protionamide
Ethionamide and protionamide are considered potentially teratogenic, so should not be used during pregnancy.

11.3.6 Rifabutin, cycloserine and PAS
Rifabutin, cycloserine and PAS have not been studied extensively but animal models and anecdotal human reports have not shown toxicity.

11.3.7 Lactation
Treatment with first line agents for TB is not a contraindication for breast-feeding as the small concentrations of these drugs in breast milk do not produce toxic affects in the newborn.72

It is therefore important to note that because of the low concentrations of anti-tuberculosis drugs in breast milk, they do not provide an effective treatment for disease or latent TB infection in a breastfed infant.

11.4 Obesity and TB drug doses
Antimicrobial dosing in obese patients is complex and poorly understood, but some issues are discussed in a review by Wurtz et al (1997).73 Obesity leads to physiological changes with effects on antimicrobial pharmacokinetics; these factors may be interactive. Important considerations include:

- increased body mass (including lean body mass and adipose mass)
- increased cardiac output and blood volume
- increased renal clearance (equations to estimate creatinine clearance do not accurately predict the higher creatinine clearance observed in obesity)
- hepatic metabolic changes
- changes in serum protein levels.
11.4.1 Doses of first-line TB medicines in obesity

Maximum doses of the standard TB medicines are discussed in section 2.

With short obese adult, standard maximum doses may be excessive. Here the ideal body weight (IBW) should be obtained, and the dose of the first-line agents should be based on this.

The calculation of IBW (or lean body weight) for:
- women is 45 kg + 0.9 kg per cm of height above 150 cm
- men is 50 kg + 0.9 kg per cm of height above 150 cm.
References


